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Forensic Neuropathology and Associated Neurology

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With a Foreword by Kurt A. Jellinger

With 264 Figures and 69 Tables

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Foreword

Partly as a result of major recent advances in neurobiology and molecular sciences, but also as a consequence of improving methods in clinical neurosciences, general and forensic pathology, forensic neuropathology has become a highly specialized field of modern medicine, which deals with disorders of the nervous system under non-natural, traumatic, exogenous or criminal conditions. Although forensic neuropathology has a long tradition, leading from C.B. Courville (1964) via Leestma (1988), and Unterharnscheidt (1992–94) to Manfred Oehmichen, and is of eminent importance within the field of forensic sciences, this particular and complicated subject has received only little attention within the scientific community. With greater and more precise understanding of the pathological, physical, biochemical, and molecular genetic processes involved in disorders of the nervous system and their relations with causes of death under natural and non-natural circumstances, the prospects of new forms of investigation into fatal processes are becoming more practicable. Based on lifelong experience in the field of general forensic medicine and, in particular, forensic pathology and neuropathology, Forensic Neuropathology and Associated Neurology, written by Manfred Oehmichen, Roland N. Auer, and Hans Günter König presents a timely overview of the state-of-the-art of examination and clarification of diseases of the nervous system under general and forensic circumstances. Like general pathology and neuropathology, its forensic part serves not only to clarify the causes of death due to nervous system disorders, but it is an important method for quality control excluding natural causes of death. Thus, forensic neuropathology, based on recent results, guidelines and standards of modern pathology and neurosciences, has become an integral part of forensic medicine and practice.

The concept and the structure of the book is based on the principles of forensic neuropathology, modern cytology, cell and tissue reactions, modern biophysics, and molecular biology of the nervous system. It is an important and difficult task for the forensic neuropathologist to differentiate naturally occurring disorders from non-natural and exogenous ones, and he needs extensive experience in order to avoid misinterpretation of cerebral lesions, which becomes more and more difficult with our increasing knowledge of the pathology and pathogenesis of nervous system disorders, the etiology of which remains to be elucidated. On the other hand, basic and clinical neuropathologists not experienced in forensic problems often may not be able to differentiate naturally developing disorders from forensic ones, while many forensic pathologists are not acquainted with the current neuropathological literature. The present book, the first one on forensic neuropathology after almost two decades, and the first written by German scientists after Unterharnscheidt's handbooks of traumatic lesions of the brain and spinal cord, closes a broad gap between clinical and forensic neuropathology. The coverage of the topics listed in the table of contents is comprehensive and complete. After dealing with general aspects and basic mechanisms of molecular neuroscience, it reviews the major disorders of the central and peripheral nervous system with impact on lesions most frequently observed in forensic medicine, i.e., physical, ischemic/hypoxic, and toxic damage to the nervous system of adults, and especially of infants and children, but also naturally occurring disorders of the nervous system, including vascular, metabolic, toxic, degenerative, and age-related diseases, all handled in a well-written, concise, and didactic way. The book is based on the senior author's vast experience in his particular profession, and will provide the reader with a state-of-the-art overview of forensic neuropathology. The illustrations, as one would expect in a Springer book, are outstanding, and the reference lists added to each chapter are informative.

Speaking as one who has spent much of his lifetime in neuropathology and applied neurosciences and as a close friend to the senior author of this seminal book, I am glad to note that it covers practically the whole field of neuropathology with impact on

forensic problems. I am happy to recommend this outstanding volume as a first-rate reference book to a wide audience of forensic scientists, general pathologists, clinical neuropathologists as well as to neurologists, neuropediatrists, and psychiatrists, and other health professionals interested and engaged in forensic problems of disorders of the nervous system. Indeed, many physicians and health professionals will find much information within its pages. I am confident that this outstanding and distinguished textbook is assured of full success.

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Preface

The present textbook was written with the same intentions as Leestma introduced his excellent monograph (Forensic Neuropathology. Raven, New York, 1988), "to deal with those areas which have the most importance in forensic settings, are typical problem areas, or seem to be poorly understood by most forensic pathologists…." The authors have attempted not only to describe the pathomorphology of insults of the human nervous system, but also the underlying pathophysiological, molecular, and biomechanical principles that can help forensic pathologists to understand the pathological changes induced by a traumatic event and enable the expert witness to reconstruct the criminal act; they have tried to integrate the forensic and criminalistic problems and questions as well as – to a certain degree – the clinical features and sequelae. The aim of this volume is to bridge the gap between the ways of thinking of the basic neuroscientist, the researcher, the practicing medicolegal neuropathologist, and the clinical physician. We hope the reader will find this approach unique and useful, as well as intriguingly broadening the horizons of what is usually discussed under medicolegal headings and topics.

The clinical aspects are discussed since forensic pathologists are increasingly asked to aid in medicolegal questions in connection with medical lawsuits. On the other hand we have lost sight of the needs of clinical neurologists, neurosurgeons, neuropediatricians, neurotraumatologists, and neuroradiologists, who may also be called to serve as expert witnesses in court. Thus we offer essential information on the pathological processes encountered in survivors of different brain injuries. The present book may therefore be a useful tool for both pathologists and clinicians confronted with forensically relevant injuries and disorders of the human nervous system.

M. Oehmichen, R.N. Auer, H.G. König

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M. Oehmichen owes a great debt of gratitude to his fellow scientists and wishes to express additional acknowledgements, as follows:

- Dr. Ivana Gerling/Lübeck, Germany
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- Dr. Arthur Reiter/Lübeck, Germany

who over many years of joint effort performed autopsies and issued expert opinions from which in part the present volume's extensive documentation and work-up of case material was cooperatively derived.

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- Professor Dr. Ingo Pedal/Heidelberg, Germany
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Contents

Abbreviations

AAP	American Academy of Pediatrics
AC	alcohol concentration
ACh	acetylcholine
ACTH	adrenocorticotrophic hormone
AD	Alzheimer's disease
AD	Anno Domini
ADC	apparent diffusion coefficient
ADCC	antibody-dependent cell-mediated cytotoxicity
ADH	alcohol dehydrogenase
ADP	adenosine diphosphate
AI	axonal injury
AIDS	acquired immune deficiency syndrome
ALDH	aldehyde dehydrogenase
AMS	acute mountain sickness
apoE	apolipoprotein E
β-APP	beta-amyloid precursor protein
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
BAC	blood alcohol concentration
BBB	blood – brain barrier
BC	before Christ
BCNU	cytostatic agent: carmustine
BMT	bone marrow transplantation
BrdU	bromodeoxy uridine
BSE	bovine spongiforme encephalopathy
BZE	benzoylecognine
C1, 2, etc.	vertebral body of the cervical spine
CA	cornu Ammonis = hippocampus
CA1, CA2, etc.	anatomical subfields of the hippocampal area
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CAII	carbonic anhydrase II
CBF	cerebral blood flow
CCNU	cytostatic agent: lomustine
CCS	children's coma score
CCT	cerebral computer tomography
CD	cytoplasmic dynein
CDC	Centers for Disease Control and Prevention
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CHE	dichlorvos
CJD	Creutzfeldt–Jakob disease
CMRglc	glucose metabolic rate
CNS	central nervous system
CO–Hb	carboxyhemoglobin
COS	children's outcome scale
COX	cyclooxygenase
CPP	cerebral perfusion pressure
CRH	corticotrophin-releasing hormone
CS	cervical spine
CSF	cerebrospinal fluid
CT	computer tomography
CVT	cerebral venous thrombosis
D-1, 2, etc.	vertebral body of the thoracic spine
DAE	dialysis-associated encephalopathy
DAI	diffuse axonal injury
DCS	decompression sickness
DFP	diisopropyl fluorophosphate
DHC	dihydrocodeine
DIC	disseminated intravascular coagulation
DNA	deoxyribonucleic acid
DOM	2,5-dimethoxy-4-methylamphetamine
DW-MRI	diffusion-weighted MRI
E_o	kinetic muzzle energy of projectile
E_5	kinetic energy of projectile at a distance of 5 m from muzzle
E-605	parathion
EAE	experimental autoimmune encephalitis
ECPE	encephaloclastic porencephaly
EDH	epidural hemorrhage
EEG	electroencephalogram
EME	ecgonine methylester
EOM	extraocular muscles
E-selectin	endothelial-leukocyte adhesion molecule-1
Fc	fragment crystalline; c-terminal part of both the H-chains of immunoglobulin G
fiO_2	fractional inspiratory concentration of oxygen
FRG	Federal Republic of Germany

GABA	gamma-aminobutyric acid
GFAP	glial fibrillary acidic protein
H&E	hematoxylin and eosin
HACE	high-altitude cerebral edema
HAPE	high-altitude pulmonary edema
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high density lipoprotein
hGH	human growth hormone
HIV	human immunodeficiency virus
HSES	hemorrhagic shock and encephalopathy syndrome
ICAM	intracellular adhesion molecule
ICH	intracerebral hemorrhage
ICP	intracranial pressure
IEG	immediate early gene
IFN-γ	interferon-gamma
IL	interleukin
iNOS	inducible nitric oxide synthase
IPSP	inhibitory postsynaptic potential
IQ	intelligence quotient
IVF	in vitro fertilization
IVH	intraventricular hemorrhage
JNK	c-jun N-terminal kinase
LAMMA	laser microprobe mass analysis
LD_{50}	dosis letalis media
LDL	low density lipoprotein
LFA	lymphocyte function-associated antigen
LSD	lysergic acid diethylamide
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide
MABP	mean arterial blood pressure
6-MAM	6-monoacetylmorphine
MAO	monoamine oxidase
MAP	microtubule-associated protein
MAPK	mitogen-activated protein kinase
MBI	mechanical brain injury
MBK	methyl-n-butyl ketone
MBP	myelin basic protein
MDEA	3,4-methylenedioxyethamphetamine
MDMA	3,4-methylenedioxymethamphetamine
MELAS	mitochondrial encephalopathy with lactic acidosis and stroke
MEOS	microsomal oxidizing systems
MERRF	mitochondrial encephalopathy with ragged red fibers
MHC	major histocompatibility complex
MPTP	N-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine
MRI	magnetic resonance imaging
MW	molecular weight
NASD-ClAE	naphthol AS-D chloroacetate esterase
NFP	neurofilament protein
NFT	neurofibrillary tangle
NIA	National Institute of Aging
NMDA	N-methyl-D-aspartate
NO	nitric oxide
NOS	nitric oxide synthase
NS	nervous system
nvCJD	new variant Creutzfeldt–Jakob disease
PACNS	primary angiitis of the CNS
PAS	periodic acid-Schiff reaction
PCP	phencyclidine
PD	Parkinson's disease
PDGF-β	platelet-derived growth factor β
PLP	proteo-lipid protein
PNS	peripheral nervous system
pO_2	oxygen pressure
ppm	‰
PrP	prion protein
RNA	ribonucleic acid
ROS	reactive oxygen species
SAH	subarachnoid hemorrhage
SAS	subarachnoid space
SCI	spinal cord injury
SCUBA	self containing underwater breathing apparatus
SDH	subdural hemorrhage
SI	International System of Units
SiCH	spontaneous intracranial hemorrhage
SIDS	sudden infant death syndrome
SMON	subacute myelo-optic neuropathy
SOD	superoxide dismutase
STAT 3	signal transducer and activator of transcription 3
SUDEP	sudden unexpected death in epilepsy
$T_{C,F,K,R}$	temperature measured in °C, °F, K, °R
TET	triethyltin
TGFβ	transforming growth factor β
Th	thoracic spine
THC	Δ9-tetrahydrocannabinol
TIA	transient ischemic attack
TNF	tumor necrosis factor
TPP	thiamine pyrophosphate
v_5	velocity at 5 m from muzzle
VCAM	vascular cell adhesion molecule
v_o	muzzle velocity of projectile
WBC	white blood cells

Quantities and Units

In this book physical quantities on principle will be measured in "SI-Units," laid down in the "Système International d'Unités" (SI) by the "Conférence Générale des Poids et Mesures" (CGPM), abbreviated according to agreement, and expanded by the following prefixes as decimal magnitude factors.

Prefix	Abbreviation	Decimal	Factor
hecto-	h	10^2	100
kilo-	k	10^3	1,000
mega-	M	10^6	1,000,000
giga-	G	10^9	1,000,000,000
deci-	d	10^{-1}	0.1
centi-	c	10^{-2}	0.01
milli-	m	10^{-3}	0.001
micro-	µ	10^{-6}	0.000001
nano-	n	10^{-9}	0.000000001

Example: 1 kilometer = 1 km = 10^3 m = 1,000 m
1 micrometer = 1 µm = 10^{-6} m = 10^{-3} mm = 0.001 mm

Quantity		SI-Unit		Conversions
Name	**Abbreviation**	**Name**	**Abbreviation**	
Length	*l*	Meter	m	1 mm=0.039 in; 1 cm=0.394 in 1 dm=0.328 ft; 1 m=1.094 yd 1 km=0.621 miles 1 in=25.4 mm=2.54 cm 1 ft=30.48 cm; 1 yd=0.914 m 1 mile=1.609 km
Area	*A*	Square meter	m^2	1 m^2=10^4 cm^2; 1 cm^2=100 mm^2 1 in^2=6.45 cm^2=645.2 mm^2 1 ft^2=0.0929 m^2=929.03 cm^2
Volume	*V*	Cubic meter (Liter)	m^3 l	1 m^3=10^3 dm^3=10^6 cm^3 1 l=1 dm^3=10^{-3} m^3 1 ml=1 cm^3, 1 dl=100 cm^3 1 in^3=16.387 cm^3 1 ft^3=28.23 dm^3=0.028 m^3 1 yd^3=764.53 dm^3=0.765 m^3
Mass	*m*	Kilogram	kg	1 kg=1000 g=2.205 lb 1 g=1000 mg=15.432 gr 1 g=0.0648 gr 1 lb=0.454 kg
Mass density	ϱ		kg/m^3	1 kg/m^3=1 g/dm^3=1 g/l=1 mg/ml 1 g/m^3=1 mg/dm^3=1 mg/l 1 mg/m^3=1 µg/l=1 ng/ml 1 lb/ft^3=16.019 kg/m^3=16.019 g/dm^3=16.019 g/l
Time	*t*	Second (Minute) (Hour) (Day) (Year)	s min h d	 1 min=60 s 1 h=60 min=3600 s 1 d=24 h 1 year=365 d

Quantity		SI-Unit		Conversions
Name	**Abbreviation**	**Name**	**Abbreviation**	
Frequency	*f*	Hertz	Hz	1 Hz=1/s 1 cycle/s=1 Hz
Angle		Radian	rad	1 degree (1°)=(π/180) rad=0.01745 rad 1 rad=57,296°
Temperature	*T*	Kelvin (Degree Celsius)	K °C	1°C=1 K=9/5°R=9/5°F $T_C=(T_K-273.15)°C$ $=5/9\ (T_R-491.67)°C$ $=5/9\ (T_F-32)°C$
Velocity	*v*		m/s	1 m/s=3.6 km/h=5.793 miles/h=3.281 ft/s 1 km/h=0.278 m/s=0.911 ft/s=0.621 miles/h 1 ft/s=0.305 m/s=1.097 km/h 1 mile/h=1.609 km/h=0.447 m/s
Angular velocity	ω		rad/s	1 rad/s=57.296 °/s 1 °/s=0.0175 rad/s
Acceleration	*a*		m/s^2	$1\ m/s^2=3.281\ ft/s^2$ $1\ ft/s^2=0.3048\ m/s^2$ Gravitational acceleration (g) $=9.807\ m/s^2=32.174\ ft/s^2$
Angular acceleration	α		rad/s^2	$1\ rad/s^2=57.296\ °/s^2$ $1\ °/s^2=0.0175\ rad/s^2$
Force	*F*	Newton	N	$1\ N=1\ kg\ m/s^2$ 1 N=0.102 kp a; 1 kp a=9.807 N 1 pdl=0.138 N 1 lbf=4.448 N 1 kgf=9.807 N

Quantity		SI-Unit		Conversions
Name	**Abbreviation**	**Name**	**Abbreviation**	
Pressure	*p*	Pascal	Pa	1 Pa=1 N/m^2 1 bar=100 kPa 1 mbar=100 Pa=1 hPa 1 mmHg=1 torr=133 Pa 1 atm=760 torr=101.325 kPa 1 pdl/ft^2=1.488 Pa 1 lbf/in^2=0.068 atm=6.895 kPa 1 lbf/ft^2=47.88 Pa
Energy	*E*	Joule	J	1 J=1 N m=1 kg m^2/s^2=1 W s=1 Gy kg
Potential			N m	
Kinetic			kg m^2/s^2	
Electric			V A s=W s	
Radiation			1 Gy kg	
Thermal		(Calorie)	cal	1 cal=4.184 J
Power	*P*	Watt	W	1 W=1 J/s=1 N m/s=1 V A 1 ft pdl/s=42.14 mW
Electric quantities				
Voltage	*U*	Volt	V	
Intensity of current	*I*	Ampere	A	
Resistance (impedance)	*R*	Ohm	Ω	1 Ω=1 V/A
Charge	*Q*	Coulomb	C	1 C=1 A s
Capacity	*C*	Farad	F	1 F=1 A s/V
Field strength	*E*		V/m	
Radiation dose		Gray	Gy	1 Gy=1 J/kg 1 Rad (rd)=10 mGy
Amount of substance	*n*	Mole	mol	
Concentration of amount of substance			mol/m^3	1 mol/m^3=1 mmol/l
Molality			mol/kg	

Introduction 1

The information obtained at autopsy is important in clinical and forensic practice at four different levels (Keeling 1993):

1. The light it sheds on the cause of death is of interest to the family of the deceased and the treating clinicians. It can serve as a quality control of the diagnostic and therapeutic measures taken.
2. It is indispensable for adequate audit of a department's policies and practices.
3. It will contribute to regional or national statistics by classifying data derived from postmortem examination.
4. It is important for students and doctors studying the morphology of disease processes and trauma.

Neuropathologists deal with disorders of the nervous system (NS), i.e., the brain, the spinal cord, the peripheral nerves, and, sometimes, the muscles. The NS extends to all other organ systems of the body as a network, connecting, coordinating, and regulating their functions. The pathology of the NS is therefore also an integral part of the pathology of all organ and tissue systems of the body. At autopsy the neuropathologist applies the same criteria that apply to general autopsy. Yet, in contrast to the clinical neuropathologist, the forensic neuropathologist must not only diagnose disease processes of the NS, including tumors, inflammation, and degenerative diseases, but he must also – and predominantly – investigate non-natural, exogenous events leading to injuries and/or death. The forensic neuropathologist is especially confronted with injuries of the head and brain as well as the spine and spinal cord and peripheral nerves, or secondary alterations of the NS which are caused by hypoxia, ischemia, toxic agents, etc.

The present volume deals with the problems of neuropathology for both the forensic and clinical neuropathologist, particularly emphasizing the relevance for routine practice. It incorporates recent findings in anatomy, physiology, pathophysiology, molecular biology, nosology, clinical features and sequelae, epidemiology, biomechanics, immunology, and pathology. Part I provides basic information on the tasks of the forensic expert, the cytology of the NS, techniques for dissection of the brain and spinal cord, and on staining methods. Parts II–IV discuss the various types of physical loadings to the head and central nervous system (CNS), asphyxia-related effects on the brain such as hypoxia and ischemia, and toxic effects on the brain. Part V deals with injuries in infants and children caused by prenatal and childhood traumatic events. Part VI is devoted to aspects of clinical neuropathology with cases of NS diseases leading suddenly and unexpectedly to death, that have to be considered in differential diagnosis or that are often additionally observed in cases of unnatural death.

Forensic neuropathology does not intend to substitute for clinical neuropathology. In contrast, the knowledge of general and special clinical neuropathology will be a precondition for understanding the present textbook, though the authors have strived to give basic information as well. Incorporating the most recent literature and up-to-date methods, the present textbook covers the main aspects of neuropathology with regard to the needs of forensic pathologists and specialists in associated fields, such as clinical pathology and neuropathology, neurology, neurosurgery, pediatrics, law, and criminology. The authors have attempted to impart basic information that can be fundamental to further scientific investigations. The concise, direct style is intended to provide the reader with succinct and easy-to-find answers to forensic-pathological and forensic-neurological problems.

The forensic neuropathologist is expected to provide answers regarding: (1) the cause of death, i.e., whether the neuropathological findings are sufficient to explain why the death occurred; (2) information on whether neuropathological changes could have influenced the fatal mechanism, i.e., whether the death was hastened by NS injury or diseases; (3) the victim's capacity or incapacity to act at a given time point, i.e., whether he was capable of resistance or flight, or could still perceive anything such as pain or danger; (4) the mode of death, i.e., whether death was caused by accident, disease, or was a suicide or homicide (murder, manslaughter, or due to negligence). These questions can usually be answered by (5) a plausible and detailed reconstruction of the process and/or events leading to the death inclusive

dating (time course) based on eyewitness accounts, evidence at the scene, analysis of the injuries, medical records, etc.

But why should the nervous system be examined by a forensic neuropathologist at all? Is a textbook dealing with the forensic aspects of only one organ system really necessary?

More than 50% of all *cases of death* encountered at forensic autopsy are *associated with primary or secondary involvement of the NS*, especially of the brain. The forensic pathologist must be able to judge or comment on NS injuries and/or diseases in dead as well as sometimes in living subjects. Often pathological examinations of the NS are sufficient to determine the "mode of death," sometimes only by ruling out a natural process within the NS as the cause of death. The neuropathological investigation can therefore also serve as a form of quality assessment and quality control, and can help to explain discrepant diagnoses presented at trial. Peiffer (1996) and Black and Graham (2002) have surveyed the types of cases dealt with by forensic neuropathologists and the sort of problems they pose.

According to the American Trauma Society (in Trauma Facts 1992) an estimated 500,000 Americans are admitted to hospitals as a result of mechanical brain injuries and more than one million children in the world sustain head injuries each year. Such cases should be assessed to determine whether the injuries could have been avoided in order to enhance prevention in future. The complexity of such cases and the methods used to examine them consequently warrant special, more in-depth consideration, possibly in the form of a monograph or textbook.

In-depth coverage can also aid in *quality control* and accreditation of laboratories. Guidelines and standards for neuropathological examinations must be set, which can be of special value to forensic neuropathologists confronted with questions of their own legal liability (Pounder 2002; Tingle 2002).

Equally important are *questions of research* as they relate to forensic practice. This holds particularly true for cases that are encountered only in legal medical institutions, rather than in clinicopathological or cliniconeuropathological institutes. In this regard it is a much appreciated development that forensic neuropathologists are being increasingly provided with their own distinct forums at congresses. This is happening both at meetings devoted solely to clinical neuropathology (*Neuropath Appl Neurobiol* 25:27–28, 1999; Kalimo et al. 2004) and at international congresses on forensic pathology and related fields (Oehmichen 2001).

One of the prime reasons for publishing a textbook on forensic neuropathology and associated neurology is reflected in the statement by Courville (1964) describing his own: "… *unhappy experience to learn that all too often a misinterpretation or an erroneous evaluation of a cerebral lesion has led to a gross miscarriage of justice*." The present textbook also has its roots in many forensic pathologists' practice of dissecting and then disposing of the brain after autopsy, without considering minor, though potentially important, findings. In such cases the brain is treated like a diffuse parenchymatous organ comparable to the liver, specimens being taken at random, fixed in formalin, and examined microscopically. Because the remaining brain tissue is discarded, it is no longer available for further investigations, precluding any retrospective examinations.

Conscientious forensic pathologists lacking either the knowledge or experience to deal with a particular problem themselves will fix the brain and spinal cord in formalin and hand them over to a clinical neuropathologist for evaluation. Sometimes though, the clinical neuropathologist may have no particular interest in forensic problems, and thus may find it difficult to unravel the true nature of the problem at hand. Moreover, the clinical neuropathologist is often not acquainted with the current forensic literature, or may not be able to differentiate autolytic changes and putrefaction from pathological findings and, when examining the autolytic material, to detect forensically relevant changes. The authors therefore regard expertise training and education in forensic neuropathology as highly desirable. Even though not every institute will need such special investigative techniques and experience, central research laboratories could be established that would make the neuroscientists, technicians, and methods needed for such investigations readily available.

The last comprehensive survey of forensic neuropathology in a textbook format was published by Leestma in 1988. The volume followed the example of Courville (1964), who was the first to write a textbook in this field. In the early 1990s Unterharnscheidt (1992–1994) published a handbook comprised of four monumental volumes in German devoted to mechanical injury of the head and spinal cord giving a review on the investigations, findings, and the literature of the previous 50 years. The numerous important findings that have been published since 1990, especially in the fields of molecular biology and biochemistry of the CNS, make the present volume both justified and necessary.

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Principles of Forensic Neuropathology

Risks, Responsibilities and Liabilities 2

The formal tasks that forensic pathologists and neuropathologists are asked to perform in the courts vary from country to country according to convention and statute, and will therefore not be dealt with in detail here. For details on the role of expert forensic witnesses in U.S. courts, the reader is referred to Leestma and Magee (1988), and for the English system to Knight (1996). In all different countries the forensic pathologist/neuropathologist is accountable primarily to legal authorities, i.e., the judiciary, lawyers, and/or public prosecutors. But they cannot avoid an additional, specifically medical/ethical responsibility, which extends to questions of experimental neuropathology and neurology, i.e., the use of certain experimental diagnostic and therapeutic methods, and to civil and political actions such as maltreatment and torture.

To our knowledge, no legal system in the world places physicians as physicians under the threat of civil liability. Physicians, therefore, are subject to the general rules of liability, with the effect that modern laws of medical liability are a part of case law created by the courts in most countries.

Beyond this formal task, a second justification forms the basis of the forensic physician's conception of his efforts: the prevention of unnatural death as well as the prevention of injury as a result of maltreatment and torture. Unnatural deaths are preventable and therefore – of course – of eminent interest in the field of (forensic) medicine. Recognition of violence, maltreatment, and torture is an especially important task of the forensic physician (Oehmichen 1999; Hall 2000; Barnett 2001), who is duty-bound to undertake all measures necessary to prevent these forms of violent injury before they result in death. Even if such a case has ended in death, measures must be taken to prevent others from becoming further victims. The appropriate civil and/or law enforcement agencies must be informed, and, in certain circumstances, the public itself. This duty must be fulfilled not only in cases of violence and maltreatment within a family or specific social group, but also in cases of maltreatment on the part of the police, prison guards, and/or the public prosecutor's office. Such a task is of particular importance – and entails real risks – in countries where torture is still officially tolerated. If violence, maltreatment or torture is observed or suspected, the physician – even the forensic neuropathologist – is obliged to register a protest from the medical point of view.

2.1 Basic Principles

The forensic neuropathologist is asked to examine cases classified as "unnatural death." In the United States and Germany, medically attended patients dying of natural causes can be autopsied only with permission of the next of kin. Official autopsies can be performed at the discretion of a forensic pathologist under the following circumstances (cf. Helpern 1977):

1. Sudden and unexpected death of persons in apparently good health
2. Cases involving evidence or suspicion of violent death, especially of accident, suicide or homicide
3. Deaths resulting from suspected medical malpractice and/or negligence
4. Deaths occurring during incarceration or while in police or institutional custody

5. Death at the workplace or due to toxic agents
6. Cases of death involving victims of unknown identity
7. Cases in which tissue loss due to decay and animal activity is so extensive that the victim's identity is unknown and neither the cause nor type of death can be established without autopsy

Many countries allow forensic autopsies if there is reason to believe that violence or poisoning has played a role in the death, or if there is evidence or suspicion of a criminal event. In most countries however autopsies are not allowed even in cases of violent death known to be purely accidental.

In autopsies of such cases the forensic pathologist, neuropathologist, toxicologist, molecular biologist or physicist must address the following issues depending on the nature of the case:

- Identity of the victim
- Manner of death (natural or unnatural death)
- Cause of death
- Process of dying (reconstruction of the process)
- Causality linking an event with death

The forensic neuropathologist can be asked to give an opinion on at least some of these issues. The individual points can be commented on as follows.

2.1.1 Identity of the Victim

The forensic neuropathologist is not often asked to establish identity, a task usually left to the expertise of the medical examiner or forensic pathologist. The forensic neuropathologist can however be asked to determine whether a mix-up has occurred in surgical or biopsy material from a neurological or neurosurgical clinic or from an institute of pathology. The identity of a biopsy specimen can be established by DNA analysis of the specimen by a molecular biologist. Only rarely must brain tissue be identified, following train accidents for example, or massive explosions with multiple casualties (the result of industrial accidents or terrorist attacks). Sometimes brain tissue can provide evidence that violent injury has indeed occurred (Oehmichen et al. 1984). In all such cases DNA analysis is now the investigative method of choice.

2.1.2 Manner of Death

A strict distinction must be made between the manner and the cause of a death. The manner of death differentiates between natural and unnatural death, and will give further information on the mechanisms of deaths: accident, suicide or homicide. The cause of death also defines the cause of the irreversible cardiac and respiratory arrest or of the respirator brain. As already mentioned, the accused and their legal council (and the civil authorities) are often only interested in an autopsy when an unnatural death has been certified or is suspected. In most cases, however, an autopsy – at least in Germany – is only performed if a criminal act by a third party is suspected or known to have led to the death. Even if the manner of death is usually determined by a pathologist at autopsy, in up to 10% of cases a forensic neuropathologist has to make this determination.

A distinction must always be made between the following manners of death:

1. Accidental death. The most common cause of accidental death in affluent Western societies is traffic accidents, the fatality often caused by mechanical brain injury; accidental deaths in the workplace are comparatively rare. Such deaths usually involve the sequelae of traumatic blunt impact, the death sometimes occurring after lengthy hospitalization and resulting from secondary complications.
2. Suicide. Death from suicide can result from brain injury caused by mechanical violence, due to a gunshot or fall for example, intoxication/poisoning (parathion, heroin, arsenic), electric shock, ischemic effects, etc.
3. Homicide. A distinction is made between murder and manslaughter. Depending on the type of weapon and cause of death, the victim can die of primary cerebral functional failure due to a blow to the head for example, of ischemia of the brain, of poisoning by centrally active drugs, or of secondary functional failure, such as acute blood loss, fat embolism, etc.

In some cases not even an autopsy can establish with certainty that the death was a suicide, accident, or homicide; this is especially common in drug-related deaths, or deaths associated with autoerotic manipulation.

2.1.3 Cause of Death

After performing an autopsy the neuropathologist, in cooperation with the pathologist, must certify the cause of death (for review see Black and Graham 2000). Among the neuropathologically relevant causes of death are **intracranial processes** such as poisoning that can lead to **primary functional failure** of the brain. An intracranial process can also be a **secondary cause** of fatal respiratory and cardiac arrest. Not every intracranial process (bleeding, inflammation, tumor, etc.), of course, is itself sufficient to exp-

lain a "central" death. The extent of the changes undoubtedly plays a major role. An irreversible cardiac arrest may be explained by brain edema with disturbances of brain stem function, the disturbances occurring secondary to "herniation" or brain stem hemorrhages, edema-induced generalized hypoxia or ischemia, etc. And lastly, **extracranial processes** can influence brain function and lead to death (cf. also Leestma 1988). The following is to be added in detail:

1. Primary functional failure of the brain associated with intracranial processes is generally the result of the following mechanisms:
   - Primary toxic effects (e.g., cyanide's effect on the central nervous system).
   - Primary ischemic effects.
   - Mass effects (intracranial hemorrhage, edema, etc.).
   - Primary mechanical effects causing diffuse axonal injury (DAI) and/or injury of multiple blood vessels and/or acute disturbance of the blood–brain barrier (acute edema).
2. Neurally mediated death is associated with the following events:
   - Brain stem hemorrhage secondary to herniation.
   - Neural discharges may reach the heart via the hypothalamus and autonomic centers of the brain stem. Parasympathetic impulses may briefly stop *the heart* while sympathetic discharges increase heart blood volume and blood pressure, with supervening arrhythmia, the most serious type being ventricular fibrillation, which can lead to a fatal outcome. The effect of environmental stress on cardiac dysfunction was reviewed by Natelson (1985). A more recent survey is given by Cechetto (2000) who listed three regions of the forebrain that are intimately involved in central control of the cardiovascular system. These regions are the mediators of the cardiovascular consequences of stroke and stress, and likely play a significant role in pathologies such as sudden cardiac death. The insular cortex, the infralimbic cortex, and the amygdala are the anatomical structures that influence the cardiac function. Moreover, a sudden catecholamine release is obviously able to induce a sudden unexpected cardiac arrest (Pedal et al. 1999; Kernbach-Wighton et al. 2003).
   - Disruption of *respiratory control* may induce Cheyne–Stokes breathing (alternating hyperpnea and apnea) and respiratory arrest. Among the possible causes are intoxication (heroin), DAI associated with closed head injury, and disruptive or destructive lesions deep to the cortex as in large basal ganglia or subcortical regions. Finally, total respiratory failure can result from downregulation of the respiratory centers secondary to brain stem trauma, brain stem herniation or neural shock.
   - *Neurogenic pulmonary edema* and congestion are observed especially following head trauma and can develop extremely rapidly.
   - Patients in a *vegetative state* often suffer sudden unexpected death. Such deaths can be caused by neural (electric) discharges or secondary diseases such as aspiration pneumonia or sepsis.
   - A *spinal shock* can lead to dilation of peripheral vessels and thus to low blood volume, which in turn can result in inadequate blood supply to the brain and heart. This phenomenon is associated with acute spinal trauma for example.
3. Extracranial processes can lead to functional failure of the brain as follows:
   - Low blood volume and/or blood loss resulting in insufficient oxygen supply to the brain.
   - Hypoglycemia associated with diabetes mellitus or insulin overdose.
   - Hyperthermia due to fever or excessive ambient heat can lead to death via brain edema and congestion.
   - Toxins. Potentiation of the mechanisms described here may occur if the brain is simultaneously assaulted by toxins from, for example, an infection.

2.1.4 Process of Dying

If the death is not sudden and readily explained by massive blood loss or brain stem destruction due, for example, to gunshot injury, reconstruction of the lethal process can be difficult. The following questions arise and may require a forensic-neuropathological answer:

1. How long did the victim survive the traumatic event? This can often provide clues regarding the cause – and thus, the course – of the traumatic event. Estimation of the survival time (dating) is therefore of major importance for the forensic neuropathologist.
2. If the survival time is known and if the victim was treated in hospital, the question arises as to how the "lethal" course can be explained despite the medical treatment. If, as often happens, the victim has survived for months or years, it can be difficult to demonstrate an unbroken causal chain connecting the traumatic event with the death (see below) or, conversely, to demonstrate a clear break in the causal chain. The latter eventuality can be assumed if it can be shown, for example, that the death was the result of serious malpractice or neglect on the part of the attending physicians or nursing staff.

3. If the cerebral injuries are comparatively minor, the same questions arise as discussed under "Cause of Death." What event led ultimately to death, and what is the pathophysiological explanation of the lethal process? Did the injury induced by the external event contribute to the lethal course at all?
4. In deaths following long survival times, the question always arises as to whether death might have occurred even in the absence of the traumatic event. This question, however, anticipates the next topic, Causation.

2.1.5 Causation

The following determinations must be made right at the start (Dawidoff 1977; Leithoff 1992).

The assessment of a possible relationship between a particular event and its effect has to begin with a definition of causation. The legal definition of "cause" differs from the scientific definition (factual cause vs. actual cause), the latter encompassing a much broader spectrum not restricted by legal theories of justice and expediency. The medical definition of causation is based on "natural" correlations and is deduced from the knowledge of a physical effect of an external event on the human body and its resulting organic or functional disorders (Zülch 1969). The juridical definition depends upon "artificial" correlations set by people through regulations and laws. In this case, the event must be the "main and essential" cause of the effects. To define one cause as main and essential presupposes that its action must be so prominent that without its effects the lesion ought not to have arisen at all nor else with the same speed of development nor to the same degree. There can be a wide-ranging debate as to whether a particular event produced or contributed to a particular result.

Like all legal concepts, the term "causation" is applied with an aim to guiding activity and redressing grievance by representing a consequence of factual activity in terms of a doctrine supporting the law's purposes. Even when there is factual and legal cause of action, the other elements of a cause of action – breach of duty and damages – must coexist for the defendant to be liable to the plaintiff. Moreover, the cause must be of the type that has been recognized within the confines of the particular legal theory that forms the basis of the plaintiff's complaint. Law, like other disciplines, deals with behavior in accordance with its own purposes and objectives, which are specifically reflected in its theory of causation. The same state of affairs can be subject to the differing standards of proof in civil law or criminal law.

Different types of causation can be cited depending on the type of legal proceeding, the theories underlying German legal practice differing from those of other countries. The expert has to avoid "putative" causes of diseases and injuries. Like the general public, judges and juries learn of the purported facts surrounding a case from broadcast and published news sources, the internet, etc. Such sources also report the results of scientific studies and may highlight public concerns regarding environmental exposure to toxic material from hazardous waste sites, chemical spills, or from electromagnetic fields created by power lines, or reported high cancer rates in specific places (Erdreich 1999). In German law the statement of different degrees of likelihood of causal relation may be "certain" (indubitable), "likely" or "possible" (see below, p. 12).

The American as well as the German legal system makes a clear distinction between civil and criminal malfeasance by providing separate legal proceedings and distinct legal responses to the two types of wrongdoing (Finkelstein 2002). In practice, the distinction looks something like this: in *civil law*, a private party brings a civil action against another party to seek compensation for an unintentional harm caused unlawfully by another party, whereas in *criminal law* the State brings a criminal action against a person for a deliberate offense against the community. Civil actions are pursued in civil courts and are governed by rules of civil procedure and constitutional provisions relating to civil cases. Criminal actions are tried in criminal courts and are governed by rules of criminal procedure and by a larger number of constitutional provisions. Civil actions seek civil remedies (pecuniary damages or injunctions), whereas criminal actions seek distinctive criminal punishments (imprisonment or the death penalty).

2.1.5.1 German Theories of Causation

Theory of necessary condition in *criminal law*: necessary conditions are those conditions (e.g., a blow) without which a given event (e.g., death or injury) cannot have happened (*conditio sine qua non*). The standard of evidence demands certainty or "probability bordering on certainty" that the death or injury, for example, was the result of the purported act.

Theory of adequate cause in *tort law*: only that condition which it is reasonable to assume was in itself sufficient to cause a given event is regarded as causal. A person cannot be held liable for an entirely unusual, unpredictable course of events.

2.1.5.2 American Theories of Causation (Moore 2002)

The *criminal law* contains several thousand prohibitions and requirements embodied in statutes that either prohibit citizens from *causing* certain results

or require them to *cause* certain results. Causation enters into both the prohibitions and the requirements and is thus central to criminal liability.

The so-called proximate cause, acting as it may have in combination with many other causes, is in essence something without which the event would not have happened (Palsgraf v. Long Island R.R. 248 N.Y. 339–356. 162 NE 99–105, 1928). Proximate cause refers to nearness in the order of responsible causation. Thus, the law establishes a point of causal proximity to the event in question that reflects legal concepts of responsibility, retribution, and deterrence. Proximate cause favors plaintiffs because it leaves ample room for acts to be causally linked to injury. In establishing proximate cause, the issue of negligence or wrongdoing is decided first, the question of responsible cause is then addressed as a perceptibly separate issue. In qualifying causation, the term "proximate cause" is used alternatively with the term "direct cause."

In essence, *tort law* has but one injunction: do not act so as to cause harm to another. Such an injunction places greater weight on causation while at the same time leaving open a broader range of questions regarding causality than does criminal law, such as "Do not intentionally hit another [person]."

2.2 Role of Expertise and Expert Witness

2.2.1 Definition: Expert Witness

Matson (1999) defines the expert witness as follows: the evidence given by the medical expert should be objective, the independent product of expertise uninfluenced by the exigencies of the litigation.

This definition is accepted in both the Anglo-American tradition and in Germany. The task of the expert witness in Germany is described in detail by Martens (1999), who also briefly describes the differences of definition between Germany and other countries. On the other hand, however, there are distinct differences in the expert witness' tasks in court.

2.2.2 Standards in (the American) Court

A basic tenet of American legal practice is its insistence that information is sought from the most reliable sources at trial. American law however has also long recognized that many human undertakings involve complex disciplines which the lay person can scarcely hope to understand without guidance from experts. Courts require that such expert witnesses have sufficient expertise in the field in question that their opinion will help the fact finder to arrive at a decision. While courts may rule that a member of a given profession (such as medicine or pharmacology) should serve as an expert witness, they do not always require a specialist from a particular field, however much such expertise may be desired.

Expert opinion regarding mechanical brain injury (MBI) is generally based on postmortem morphology or on intravital computed tomography (CT) scans, x-rays, electroencephalographs (EEG), and magnetic resonance imaging (MRI). Cognitive deficits in a victim of MBI are often revealed by neuropsychological testing where more traditional testing, such as routine neurological examination, x-rays, CT scans, and MRIs, failed to document organic impairment. Neuropathological evidence of impairment can be presented in court to demonstrate the morphological consequences of a lethal traumatic event.

If the medical evidence poses apparent difficulties, the pre-trial period is the proper time to clarify and define scientific matters of direct forensic interest (Shepherd 1993). This may prove difficult in practice, however, and the following discusses some of the issues that may arise (Roberts 1999):

- Before the case reaches court, undue reliance may be placed on medical evidence that is not in fact as strong as prosecutors or the defense believe (or have been led to believe by experts).
- Once in court, these deficiencies in the medical evidence may be exposed; for example, if a physician relies too dogmatically on evidence adduced from an examination while failing to acknowledge other, equally likely, explanations of the findings.
- After the court proceedings, problems can arise, not least for the victims.

The medical expert's main task is to provide guidance and assistance to the court in rendering a scientifically tenable decision (Weinstein 1999).

Among the surveys of the tasks of the expert witness in court are those of Myers (2001) and Shevell (2001). In most cases, the candidate expert is put in the witness stand to answer questions about his educational accomplishments, specialized training, and relevant experience. The judge must be convinced that the candidate possesses sufficient expertise to *qualify as an expert*.

If counsel requests, the expert must set out the basis for his opinion in an *expert's written report*. This report must include:

1. Explicit identification of the purposes for which the report has been prepared
2. A statement of the expert's own expertise and credentials that warrant expert status

3. A list of the materials and documents upon which the opinion is based
4. A review and chronology of the facts of the case under question
5. The expert's assessment and conclusions regarding the relevant questions at issue in the case

Assessment of the expert's competence must include the question of whether the expert has paid due regard to all relevant facts in formulating the opinion; whether the expert's understanding of pertinent clinical and scientific principles was adequate; whether the expert used appropriate, reliable, and valid methods of inquiry; whether the expert offered reasonable assumptions and conclusions based on the facts; whether the expert was reasonably objective. The main issue is whether the expert's reasoning is consistent, logical, and reasonably objective.

2.2.3 Function of Expert Witness

Expert testimony fulfils four separate functions, but the expert witness can only testify with regard to areas in which he is qualified (Matson 1999):

1. *Factual witness.* The expert witness is asked to testify regarding what could be observed at first hand. The witness may, for example, study the documentation in the case and testify as to what portions bear directly on the issue in question.
2. *Interpretation of the facts.* The expert witness is asked to explain the cause-and-effect relationships tying the data and/or facts of the case together. Correlating an apparent cause and effect link without theoretical justification is not recommended.
3. *Comments on the opposing expert's facts and opinions.* This aspect commonly does not arise in German courts, but is a part of the Anglo-American legal traditions.
4. *Definition of the professional standards in the particular area of his expertise.* In oral testimony the judge or jury are provided with information on the standards to which professio*nals i*n the field of expertise are held.

Giving an opinion is the most common form of expert testimony.

2.2.4 Probability of Expert Opinion

In American criminal law, expert witnesses must be reasonably confident of the opinions they give. The term lawyers use to describe the requisite degree of confidence is "reasonable certainty." The degree of certainty subsumed within this term lies somewhere between guesswork and absolute certainty.

Forensic neuropathologists do not need to possess any special legal knowledge. They must, however, be aware of differences in the evidentiary requirements of the various courts. An expert opinion must always explain the degree of probability with which a causal connection can be claimed to link two events and/or a particular diagnosis made. In German criminal law, the following five degrees of probability have become established in recognition of the fact that a clear "yes" or "no" is not possible in the majority of cases:

1. "Probability bordering on certainty": this corresponds to a probability of 99.8%; a reasonable doubt does not exist.
2. Probable: the evidence favoring a causal connection between two events is weightier than that against.
3. Undecided: the evidence for a causal connection and that against such a connection are equally plausible (50:50), i.e., the issue cannot be decided one way or the other.
4. Improbability: the evidence against a causal connection between two events is weightier than that for such a connection.
5. Least possibility: if a situation is theoretically possible, but the evidence clearly shows it was not the case, then it can be ruled out with a "probability bordering on certainty."

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Cytology of the CNS 3

Most standard textbooks of neurohistology and neurophysiology (e.g., Brodal 1998) contain both a general survey and detailed description of the morphology and function of the various cell types that make up the nervous system. Here we will only touch briefly on the essential points without attempting to provide a thorough overview. The term ”pathology” will be used here to denote the morphological changes exhibited by cells under pathological conditions and the reactions of various cell types to pathological changes within the nervous system.

3.1 Neurons

3.1.1 Morphology

Neurons are simultaneously genetic, structural, functional, and trophic units. Characteristically large *nuclei* of neurons are spherical or oval, with clear nucleoplasm containing one or two distinct *nucleoli* (Fig. 3.1a). The state of neuronal activity is reflected in the structure of its nucleoli. Human brains contain about 1×10^{12} neurons and each cortical neuron receives up to 30,000 presynaptic terminals (Tanner 1978). With increasing age the lipofuscin content of the neurons increases (Fig. 3.1b). If there is disruption of peripheral axons, the perikaryon will swell and the Nissl substance will disappear centrally, a process termed central chromatolysis (Fig. 3.1c).

The cell body of the neuron, the *perikaryon*, is typically pyramidal in shape (Fig. 3.1a) and has long processes varying in number and length extending outward from it. There are usually several branched *dendrites* but only a single *axon* with terminal ramifications. Dendrites often possess spines or spikes that are sites of specialized, adjustable contact with other neurons. Intact dendrites are demonstrable by microtubule-associated protein (MAP) immunohistochemistry (Fig. 3.2a) and may be disrupted and destroyed by mechanical and ischemic influences (Fig. 3.2b). The axons are demonstrable by silver

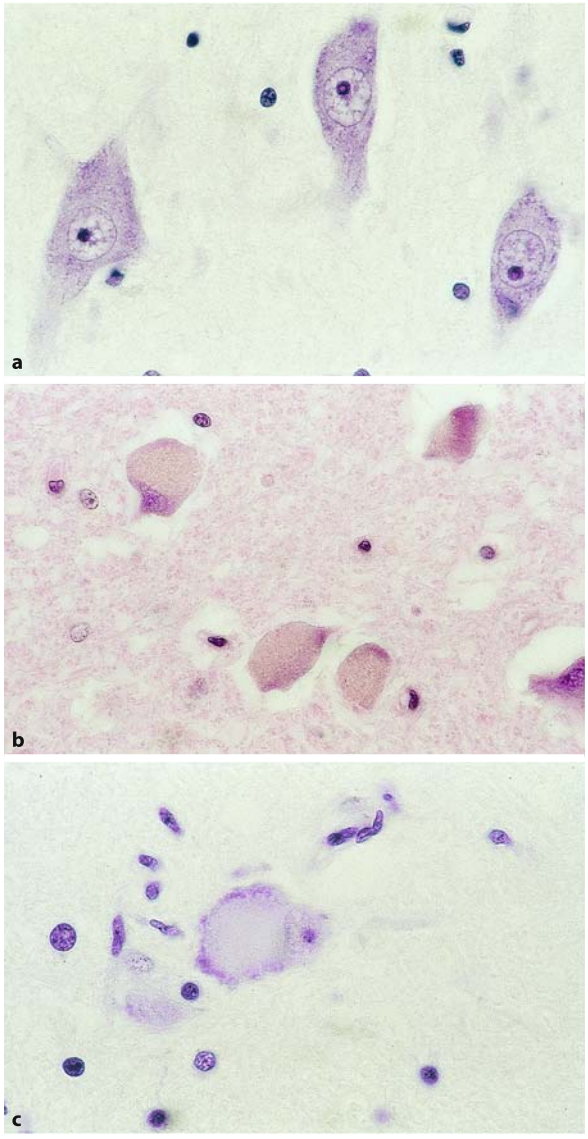

Fig. 3.1a–c. Nerve cells. **a** Normal pyramidal nerve cells in the cerebral cortex; **b** lipofuscin-containing neurons of an aged man; **c** central chromatolysis. **a, c** Nissl stain; **b** H&E; magnification **a–c** ×1,000

staining (intact axons: Fig. 3.2c; disrupted axons: Fig. 3.2d). Axonal injury leads to a ball-like swelling of the disrupted axon which is seen in silver staining specimens (Fig. 3.2e) and after β-amyloid precursor protein (β-APP) immunohistochemistry (Fig. 3.2f).

The *cytoplasm* of neurons is rich in organelles for oxidative metabolism and protein synthesis. The numerous mitochondria attest to the intense aerobic adenosine triphosphate (ATP) production using glucose as a substrate. The neuronal cytoplasm contains free ribosomes, lysosomes, Golgi complexes, and rough endoplasmic reticulum – organized in so-called Nissl bodies – for protein synthesis.

The perikaryon also has a special *cytoskeleton* consisting of fibrillary proteins, especially actin filaments, microtubules, and intermediate filaments (neurofilaments) that manage cytoplasmic transport within the axons and dendrites. Such a system is necessary to transport proteins along the axons and to sustain the synapses. Stains used to demonstrate neurons are the Nissl method (Aniline dye) and silver staining techniques for demonstration of axons, dendrites, and/or spines (Golgi methods). Golgi methods usually stain only about 5% of neurons, which is to great advantage since the sections would be uniformly black, and uninterpretable if the silver precipitated through every neuron in a section.

Axons are either myelinated or "unmyelinated." The myelin sheath of myelinated axons (Fig. 3.3a) reduces the current loss between nodes of Ranvier, from the axons to ambient tissue fluid during impulse conduction, allowing the current to jump faster from node to node (see below). The velocity at which an impulse travels along the axon is proportional to the diameter of the axon and of the myelin sheath: axons with the thickest myelin sheaths conduct at about 120 m/s, while unmyelinated axons conduct at less than 1 m/s. The (pathological) demyelination follows ischemic or inflammatory insults and is marked by a loss of myelinated axons (Fig. 3.3b, c) and phagocytosis of myelin fragments (Fig. 3.3d).

Peripheral nerves are surrounded by three layers of connective tissue that protect them from mechanical trauma: an external thick layer, the *epineurium*, an internal layer, the *perineurium*, and a layer of thin collagen fibers and fibroblasts, the *endoneurium*.

A nerve impulse is conducted along the axon to its *synaptic end*, where chemically mediated transfer of signals between neurons takes place. *Neurotransmitters* (e.g., glutamate, norepinephrine or acetylcholine) reside in synaptic vesicles located near the presynaptic membrane of boutons and are released by exocytosis. From each packet released by the presynaptic bouton, only a few thousand molecules find a receptor before they disperse or are removed enzymatically or by re-uptake. Depolarization of the presynaptic membrane usually precedes transmitter release, which itself requires Ca^{2+} to enter the bouton. The number of quanta of transmitters released is directly proportional to the amount of Ca^{2+} entering the bouton.

Neurons have three major *cytoskeletal elements*: neurofilaments, which are neuron-specific intermediate filaments that fill most of the axoplasm; microtubules, which are formed in the perikaryon and axon and serve the axonal transport system; and purified microtubuli, which consist mainly of α- and β-tubulin plus several polypeptides known collectively as microtubule-associated proteins (MAPs). The chief MAPs, MAP1 (350 kDa) and MAP2 (280 kDa) (see Fig. 3.2a), contribute to the assembly and stabi-

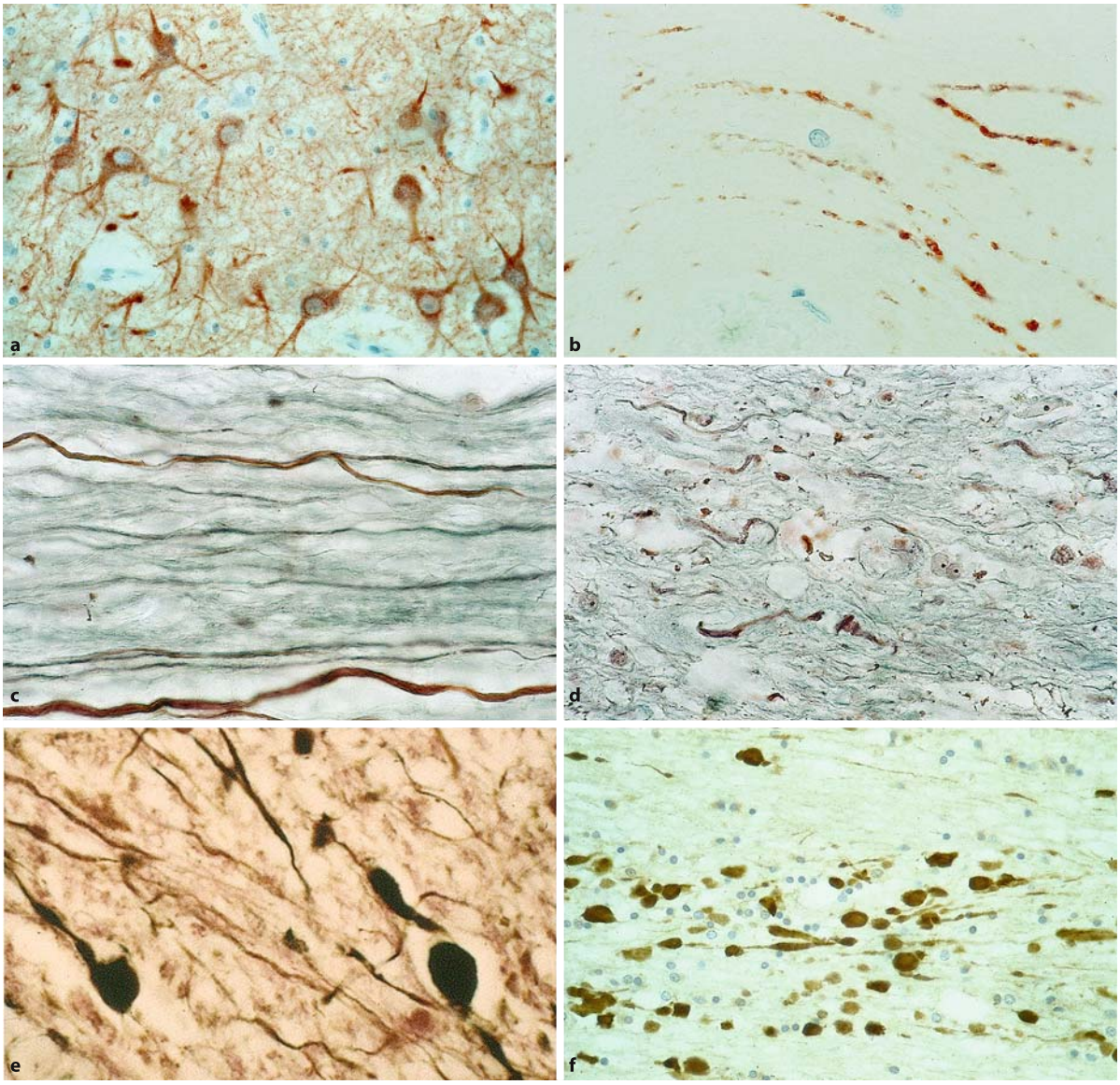

Fig. 3.2a–f. Neuronal processes. **a** Intact dendrites and **b** destroyed dendrites in the cerebral cortex (MAP2; magnification **a** ×500, **b** ×1,000); **c** intact axons and **d** disrupted axons (silver stain; magnification **c, d** ×1,000); **e** axon swelling/balls (silver stain; magnification ×1,000); **f** axon swelling/balls [β-amyloid precursor protein (β-APP) reactivity; magnification ×500]

lization of microtubules. MAP2 is a dendritic cytoskeletal molecule.

Because no protein synthesis occurs in either axons or distal dendrites, the transport system allows anterograde and retrograde transport of proteins within axons and dendrites (Sotelo and Triller 1997).

Although neurons are generally regarded as postmitotic cells, recent investigations have demonstrated "adult neurogenesis," especially in the hippocampal dentate and olfactory bulb (for details, see p. 66).

3.1.2 Function

Neurons are the principal transducing cells of both the central and peripheral nervous systems. Though they exhibit great structural variation, they all serve the same purpose: to receive, process, and transmit information via bioelectric signals (Kreutzberg et al. 1997). Neurons are characterized by their excitability and ability to conduct impulses, i.e., if sufficiently stimulated they release a brief electrical discharge, termed an action potential, which is conducted along the axon. The action potential is a major constituent

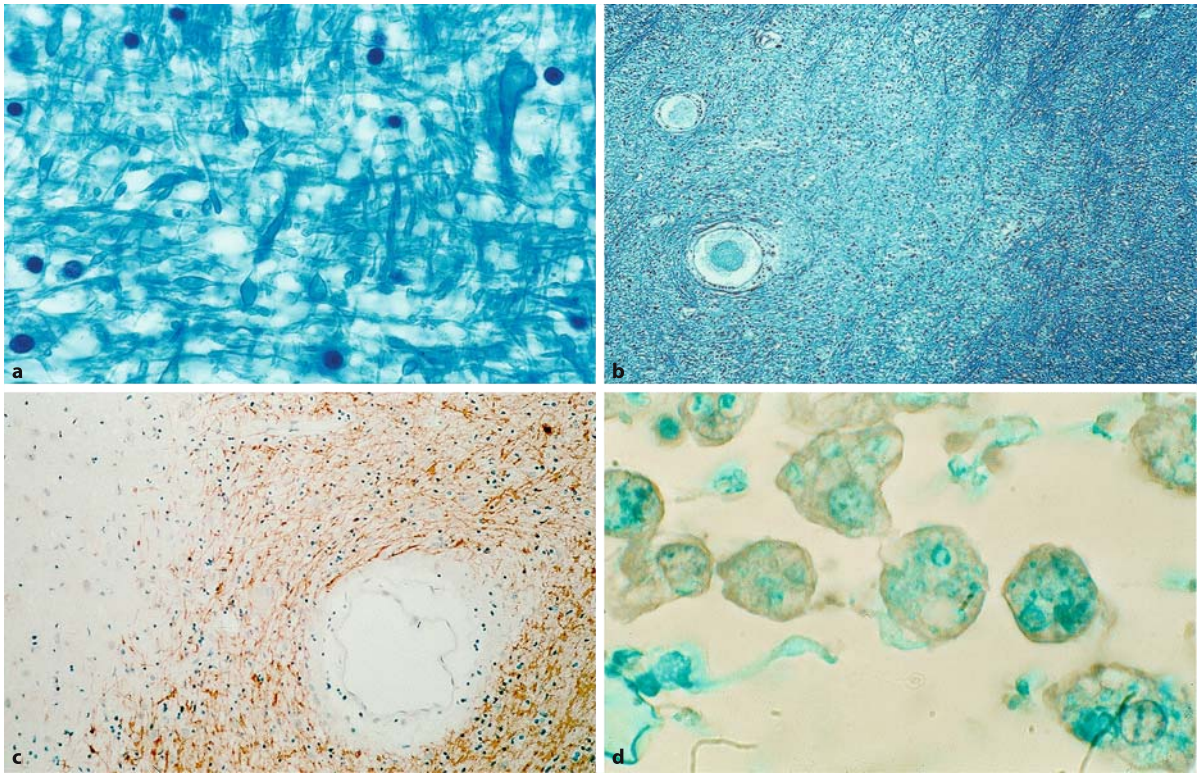

Fig. 3.3a–d. Myelin. **a** Normal myelin-staining pattern and **b** focal demyelinated structures in white matter of the cerebrum (Luxol fast blue; magnification **a** ×1,000; **b** ×100); **c** local demyelination in white matter as seen by application of antibodies against myelin basic protein (= MBP; magnification ×200); **d** the demyelination is characterized by phagocytosing cells (activated microglia) which contain myelin fragments (Luxol fast blue; magnification ×1,000)

of communication among nerve cells and between nerve cells and the body; it is an indispensable link between the central nervous system (CNS) and the world around us.

An action potential is created by the movement of ions through the cell membrane, which requires an electrical potential between the interior and exterior of the cell, the membrane potential. The electrical current is transformed at the synaptic level into a chemical signal: the released transmitters bind briefly to receptors on the postsynaptic membrane.

The action potential is based on the presence of *voltage-gated Na^+ channels* that open when the membrane is depolarized. Depolarization can result from electrical stimulation or opening of transmitter-gated Na^+ channels. The latter induces a flow of Na^+ into the cell driven by the concentration gradient and membrane potential. The inflow of Na^+ ions ceases once the membrane depolarizes to +55 mV.

The action potential is the result of an invariable all-or-nothing phenomenon. Messages can only be varied by a variation in the rate of action potentials, which in turn depends on the degree of depolarization. Some neurons are capable of a maximum frequency of action potentials exceeding 100 per second (100 Hz).

The *velocity at which an impulse is conducted* depends on the axon's diameter and myelin thickness and in meters per second is roughly 6 times the axonal diameter in microns. An action potential is generated when positive charges penetrate to the proximal part of the axon, which at that point becomes positive relative to more distal parts along its length. A corresponding current of positive charges moves in the opposite direction outside the axon, thus establishing an electrical circuit. The action potential in *myelinated axons* spreads passively (electronically) to the first node of Ranvier and is regenerated at each further node, where the axon membrane lacks a myelin sheath. The action potential moves by "jumping" from one node of Ranvier to the next.

Several authors have studied the role of neurons in the *immune response* process (Sedgwick and Hickey 1997). It is thought that healthy neurons probably do not respond even to cytokines, such as interferon-ɣ (IFN-ɣ), which are associated with the major histocompatibility complex (MHC). On the other hand, following infection, MHC expression has been found in neurons in vivo.

In the healthy CNS, MHC class I and II molecules are virtually absent. Under pathological conditions, however, MHC molecules are known to be upregu-

lated by various cells within the CNS (see below). Under normal circumstances neurons are able to prevent and/or limit inflammatory responses (for review see Neumann 2000, 2001). Under pathological conditions such as mechanical brain injury, genes are turned on, inducing a proinflammatory milieu with upregulation of MHC molecules, local production of proinflammatory cytokines, and recruitment of inflammatory cells (Streit et al. 1989; Olsson et al. 1992).

3.1.3 Pathology

Two apparently related types of cell death are to be distinguished: necrosis and apoptosis (pp. 62f). In addition to these degenerative changes of the cells themselves, pathological processes can be initiated by non-specific damage to axons and dendrites, as well as by regenerative processes. Since these negative and positive types of reactions affect all nervous tissue, not just neurons, they will be discussed in Chap. 4, "Cell and Tissue Reactions" (pp. 42ff).

Ischemic cell necrosis is a specific pathological reaction of the neuron and is described in detail in Chap. 13. For details on the morphology and pathogenesis of the other specific pathological changes of neurons, the reader is referred to the relevant neuropathology textbooks (especially Haymaker and Adams 1982; Graham and Lantos 2002; Peiffer et al. 2002). Let it be noted here, however, that in most cases diagnosis is based not on changes of the neurons alone, but on those changes in relation to all other trauma-induced tissue changes, i.e., in microglial cells, neuroglia, blood vessels, etc.

Neurons undergo certain physiological changes, notably the accumulation of lipofuscin in neurons (Fig. 3.1b) of the dentate nucleus of the cerebellum and inferior olive, and in motor neurons in the anterior horn of the spinal cord. Such changes are especially common in brains of the elderly. Neurons also react to axonal injury in the form of retrograde degeneration, i.e., a central chromatolysis or ballooned neurons (Fig. 3.1c). A chronic cell change is characterized by a shrunken, intense, dark staining neuron.

Further degeneration processes will be described below. But the following phenomena should be mentioned at the beginning:

- Loss of dendrites (and their MAP reactivity – see Li et al. 1995, 1997) by ischemic or mechanical loading (Fig. 3.2b).
- Destruction of axonal fibers as demonstrated by silver technique (Fig. 3.2d).
- Axonal swelling as a result of an axonal lesion – as demonstrated by the silver technique (Fig. 3.2e) and reactivity to β-amyloid precursor protein (β-APP) (Fig. 3.2f).
- Destruction and loss of myelin is demonstrable both by loss of myelin staining and an increase in scavenger cells (macrophages), the latter indicating active demyelination (Fig. 3.3d).

Intracytoplasmic Storage. Neurons can store other substances besides lipofuscin. A new classification of the storage diseases was recently introduced based on the intracytoplasmic increase in gangliosides or ceroid lipofuscin in neurons (for details: see textbooks on clinical neuropathology).

Basophilic Inclusions (Lafora Bodies – In Familial Myoclonic Epilepsy). Basophilic inclusions are globular bodies located within the cytoplasm. They vary in size from 1 µm to 20 µm, pushing the nucleus and Nissl bodies to the periphery of the perikaryon. The body is homogeneous in places, structured in others, and liable to splintering. If present in large numbers, they are indicative of a familial disease (myoclonic seizures, cerebellar ataxia). In rare cases, solitary Lafora bodies are present in normal postmortem material.

Inclusion Bodies in Viral Diseases. Inclusion bodies associated with viral diseases are usually intranuclear. In rabies, however, *cytoplasmic inclusions* are seen, termed *Negri bodies*, virus factories located in the cytoplasm of nerve cells of rabies victims (pyramidal cells of the hippocampus, Purkinje cells, and large motor cells of the brain stem and spinal cord). These are roughly spherical or oval bodies that range from 0.5 to 4.0 µm in diameter. *Intranuclear inclusion bodies* are the norm in viral illness, and are encountered in neurons and glial cells (oligodendrocytes, ependymal cells) of patients with cytomegalovirus infection, progressive multifocal leukoencephalopathy, subacute sclerosing panencephalitis, or herpes simplex virus encephalitis. They possess an amorphous spherical structure that is homogeneous or granular and surrounded by a small clear zone of nucleoplasm.

Neuronal Vacuolation (Bovine Spongiform Encephalopathy = BSE). The large neuronal vacuoles have thin walls and appear to coalesce. They almost completely displace the perikaryon.

3.2 Astrocytes

Astrocytes are the most common cellular elements of the brain, outnumbering neurons by ten to one and taking up about one-third of the volume of the cerebral cortex (Pope 1978). Astrocytes, like oligodendrocytes, are "neuroglial cells" or "macroglial cells." The two cell types derive from different precursors. These precursors, however, are the progeny of a common ancestor, the glioblast. Before birth the glioblast resides in the ventricular layer, after birth in the subependymal layer (Levison and Goldman 1993).

3.2.1 Morphology, Classification, and Immunoreactivity

A specific cell structure, immunoreactivity, and function characterize "astrocytes" as a distinct cell type. Morphologically they are distinguished by long, sometimes branched processes found in gray and white matter. Astrocytes are interconnected with each other via gap junctions that create a syncytium allowing ionic and metabolic coupling (Norenberg 1997). Endowed with receptors to most neurotransmitters and neuropeptides (Murphy and Pearce 1987), astrocytes possess messenger systems that maintain essential communication between themselves and neurons. Among the chief biological markers of astrocytes, besides glial fibrillary acidic protein (GFAP), are glutamine synthetase, S-100 protein, and pyruvate carboxylase.

All those cell types possess 10-μm intermediate filaments. Those in astrocytes express nestin, vimentin, and GFAP (49-kDa protein) (Eng et al. 1971; Galou et al. 1996; Colucci-Guyon et al. 1999). Thus vimentin and GFAP, for example, coexist in immature and in reactive astrocytes (Eng and Lee 1995). As stated above, astrocytes also express glutamine synthetase and S-100 protein.

Some astrocytes are GFAP negative (GFAP-negative astrocytes), chiefly in the fetal nervous system and in gray matter of the adult brain (Kitamura et al. 1987). In normal gray matter, these protoplasmic astrocytes contain only sparse GFAP and do not stain for GFAP in routine paraffin material.

Astrocytes are of three basic types: fibrous and protoplasmic astrocytes, and radial astrocytes. The former two types are demonstrable in adult CNS; the first type is most frequently found in the white matter (fibrous type), the second in the gray matter (protoplasmic type). Radial astrocytes are found in the walls of cerebral vessels and the neural tube mainly during embryonic development.

The three types of astrocyte can be classified, and exhibit the following features (Privat et al. 1995):

1. *Fibrous astrocytes* (white matter astrocytes – Fig. 3.4a,b). Markedly fewer in number than radial astrocytes, they are stellate in structure with long, thin, poorly ramified processes that are smoothly surfaced. The nucleus is spherical or oval shaped. Fibrous astrocytes react with GFAP antibody, but the cell body stains incompletely.
2. *Protoplasmic astrocytes* (gray matter astrocytes – Fig. 3.4c). Protoplasmic astrocytes have ramified processes of variable caliber. Most astrocytes residing in normal gray matter are GFAP negative, and this is the basis for determining reactive gliosis. GFAP-positive astrocytes in the gray matter are small and possess many short processes radiating from the cell body, which is usually poorly marked by GFAP immunoreactivity.
3. *Radial astrocytes* (white matter astrocytes). These cells, disposed in a plane perpendicular to the axis of the ventricles, are of particular importance during CNS embryology (Rakic 1995; Parnavelas and Nadarajahn 2001). The nucleus and perikaryon of radial astrocytes are located in close proximity to the pia mater, especially in the cerebellum and spinal cord. The processes lack ramification and at least one process touches the pia mater, the others coursing through the gray matter. GFAP-positive fibrous processes are distributed in the white matter of the lateral and ventral fasciculi of the spinal cord.

3.2.2 Function

Astrocytes are essential not only for keeping the highly differentiated neurons in their proper place within the brain, but also for maintaining their physiological environment (Lugaro 1907). It is known (Newman 1995) that a highly regulated intercellular environment is required for neuronal function and that astrocytes regulate the crucial environmental homeostasis of electrolytes, water, and pH and which eliminate amino acids and proteins from the extracellular space. Although primarily the role of endothelial tight junctions, astrocytes also uphold the blood–brain barrier (BBB) from extracerebral influences by controlling and regulating the intercellular transport of molecules from the vessel to the neuron.

Astrocytes perform the following functions:

1. *Developmental function* (*neurotrophic action)*. Astrocytes are indispensable for neuronal survival, migration, and neurite outgrowth. GFAP-negative astrocytes constitute a better substrate for such functions than GFAP-positive astrocytes. This phenomenon may explain why astrocytes do

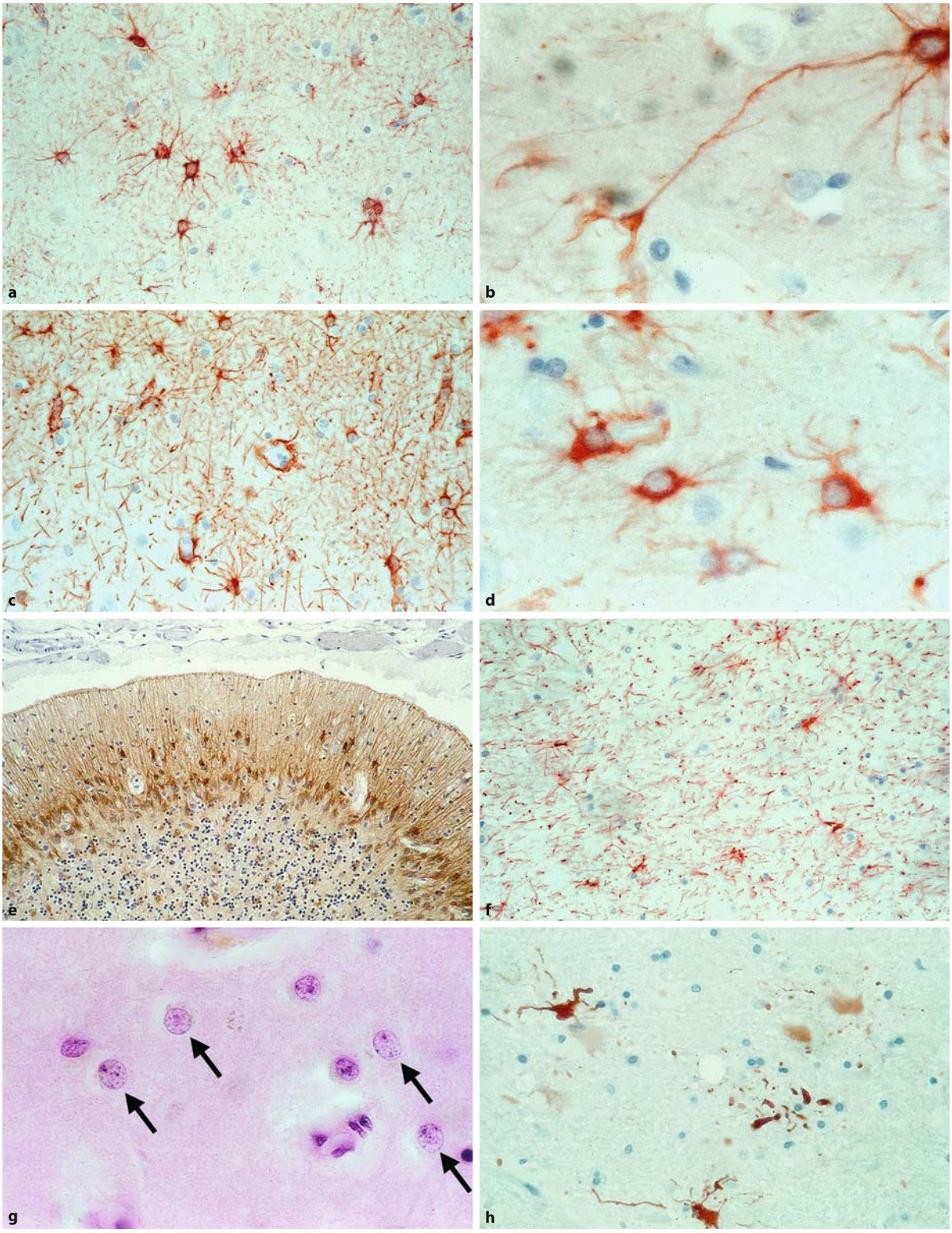

Fig. 3.4a–h. Astrocytes. **a, b** White matter astrocytes, i.e., fibrous astrocytes (GFAP; magnification **a** ×500; **b** ×1,000); **c** gray matter astrocytes, i.e., protoplasmic astrocytes (GFAP; magnification ×300); **d** activated, plump (hypertrophic) astrocytes (GFAP; magnification ×1,000); **e** isomorphic gliosis (GFAP; magnification ×300); **f** anisomorphic gliosis (GFAP; magnification ×300); **g** Alzheimer type II astrocytes marked by arrows (H&E; magnification ×1,000); **h** clasmatodendrosis of GFAP-positive astrocytes (GFAP; magnification ×1,000)

not express GFAP until relatively late in CNS development after the early phase of neurogenesis has been completed (Menet et al. 2000). Astrocytes also promote myelin synthesis and remyelination (Franklin et al. 1993).

2. *Electrolyte and water homeostasis and osmoregulation*. Depolarization of neurons is achieved by a cellular efflux of K^+ from active neurons with a consequent increase in extracellular K^+. Astrocytes possess mechanisms for active and passive accumulation of K^+ in the intercellular space and the transfer of K^+ by spatial buffer currents to the capillaries and/or cerebrospinal fluid (CSF) space (Newman 1995). As stated above, astrocytes regulate not only K^+ homeostasis, but also the homeostasis of Cl^- and bicarbonate (Walz 1995), Na^+ (Ballanyi 1995), Ca^{2+} (Finkbeiner 1995), and the pH (Deitmer 1995).
   Astrocytic swelling, known as cytotoxic edema (see below, p. 47), occurs almost immediately following the incidence of CNS injury and has been described in experimental allergic encephalitis (Eng et al. 1989). Axonal swelling probably arises from a trauma or disease-induced increase in levels of potassium, glutamate, fatty acids, arachidonic acid, lactic acid, and free radicals.
3. *Astrocyte-neuron lactate shuttle*. According to a recent published hypothesis (Hertz 2004), neuronal activity-induced uptake of glucose takes place predominantly in astrocytes, which metabolize glucose anaerobically while lacate produced from anaerobic glycolysis in astrocytes is then released from astrocytes and provides the primary metabolic fuel for neurons (Chih and Roberts 2003, Hertz and Dienel 2005).
4. *Control of vascular tone*. Zonta et al. (2003) suggest that neuron-to-astrocyte signaling in the cerebral cortex is central to the dynamic control of vascular tone, and that astrocytes play a crucial role in this process. This conclusion is based on the fact that following electrode stimulation of neuronal afferents Ca^{2+} levels increase in the somata and endfeet of astrocytes linked to arterioles. Thus there is a bridge between the response of astrocytes to neural activity and the observed dilation of arterioles (cf. Reilly 2003).
5. *Transmitter inactivation mechanism*. Henn and Hamberger (1971) demonstrated the uptake of γ-aminobutyric acid (GABA), norepinephrine, dopamine, and serotonin by a cell fraction rich in glial cells, suggesting that glia can eliminate, i.e., take up and metabolize, transmitters that overflow from the synaptic cleft. It is now known that protoplasmic astrocytes in the gray matter perform this function for the aforementioned amino acids and for the excitatory amino acid glutamate, inhibitory adenosine and adenosine triphosphate, histamine and *N*-acetylaspartylglutamate (Martin 1995).
6. *Plasma protein uptake*. Astrocytes immunostain for albumin (Klatzo et al. 1980), a phenomenon which has prompted some authors to propose that astroglial ingestion of plasma protein might aid in the resolution of brain edema (Oehmichen et al. 1979a; Tomimoto et al. 1996; Del Bigio et al. 2000).
7. *Reactivity in CNS injuries*. Following mechanical violence to the CNS, astrocytes undergo specific proliferative, morphological, and biochemical changes termed astrogliosis or reactive gliosis (see below, pp. 23f).
8. *Immunological activity* (for review see Dietrich et al. 2003). Astrocytes are stimulated by the cytokines interleukin-1 (IL-1), IFN-γ and tumor necrosis factor-α (TNF-α), as well as by multiple other growth factors (Norenberg 1997). Enlarged (reactive) astrocytes harbor an enhanced number of cytoplasmic organelles plus increased levels of GFAP, Ia antigen, IL-1, α-1-anti-chymotrypsin, and acute phase reactive protein (Eddleston and Mucke 1993).
   Under pathological conditions (infiltration by activated T-cells, blood–brain barrier disruption), the CNS shows an increased expression of the class I/II MHC, the adhesion molecule ICAM-1, the TNF-α receptor and complement component C3 (see Morgan 1999) plus production of TNF-α and IL-6 (Benveniste 1997).
   Astrocytes release various neuroactive compounds when stimulated by neurotransmitters, compounds such as taurine in response to β-adrenergic stimulation or GABA after glutamate receptor stimulation. A survey of the immune factors synthesized and released by astrocytes – and their effects – was published by Norenberg (1997).
9. *Regenerative CNS processes*. Gliosis clearly has an inhibitory effect on regeneration of the adult mammalian CNS (Fitch et al. 1999). However, there is also evidence that astrocytes play an active role in both embryonic and adult neurogenesis (Reilly 2002; Song et al. 2002; Svendsen 2002; – for details see p. 66).
10. *Neuron-like function*. Recent evidence suggests that glial cells play more sophisticated, neuron-like roles; they integrate neuronal input, modulate synaptic activity, and process signals related to learning and memory (Kurosinski and Götz 2002).

3.2.3 Pathology

Astrocytes react differently to different neuropathological conditions, including trauma, infection, seizure, infarct, metabolic processes, and tumor infiltration. GFAP upregulation and fibrillogenesis are the principal factors underlying the formation of the glial scar.

3.2.3.1 Reactive Astrogliosis

Reactive astrocytes typically undergo enlargement of the (homogeneously stained) cell body and filaments. Cells and processes both increase strikingly in number. The increase of the processes may culminate in sclerosing gliosis.

Astrogliosis is primarily characterized by swelling of the cell body and upregulation of glial filament expression (GFAP, vimentin). If cytoplasm is abundant and the cell rounded, such cells are variously termed "plump" astrocytes, "fattened" astrocytes or "gemistocytic" astrocytes (Fig. 3.4d). This cell type exhibits a homogeneous cytoplasm and a slightly enlarged nucleus with angular projections from which the processes arise. The nucleus is lateralized to one side of the cell body and may be irregularly rounded. Astrogliosis is induced by transmembrane signals (e.g., growth factors and neuropeptides) via extracellular signal-regulated kinase and mitogen-activated protein kinase (Mandell 2001).

In certain respects, reactive astrocytes resemble neurons undergoing central chromatolysis, which is a basic reaction to axonal transection (Bignami and Dahl 1995 – see below, p. 66). Moreover, at sites of brain tissue destruction, astrocytes form a scar in which they begin to shrink after some time and finally disappear, leaving behind a dense *meshwork of glial fibers* (Weil 1933). Clean excision of the brain parenchyma will leave a fluid-filled space the surrounding wall of which contains astrocytes that have undergone only a slight reactive change. Laceration as well as hypoxic changes (see below) of the brain parenchyma produce a powerful glial response and also proliferation of connective tissue.

Gliosis may be isomorphic or anisomorphic. *Isomorphic gliosis* (see also piloid gliosis – Fig. 3.4e) typically occurs in cases of selective damage to neurons and their processes in which the glial fibers maintain their normal orientation. *Anisomorphic gliosis* (Fig. 3.4f) is seen in cases of severe brain damage with major disruption of the brain and glial architectonics with consequent disruption of the blood–brain barrier.

Under pathological conditions glial cells form accessory *glial limiting membranes*. Reactive astrocytes, for example, may surround the necrotic tissue created by an infarct with a thick mesh of fibrils, thus demarcating it from viable brain tissue and helping to thwart the spread of edema. This glial scar (Figs. 9.10–9.12) will eventually be covered by a basal lamina and form a new surface of the brain. The cyst produced as macrophages absorb the necrotic tissue becomes part of the subarachnoid space. Astrocytes contribute to the synthesis of chondroitin sulfate proteoglycan (Gallo and Bertolotto 1990) and of the basal membrane proteins laminin and fibronectin (Price and Hynes 1985; Liesi and Risteli 1989).

Reactive astrocytes are characterized by a *rapid synthesis of GFAP* and – to a lesser degree – *vimentin* and by hypertrophy of the astrocyte cytoplasmic processes. The astrocytes in certain areas of healthy adult brain tissue, including the cerebellum, retina, and large tracts of myelinated fibers and optic nerve, continue to co-express vimentin and GFAP (Pixley and De Vellis 1984; Calvo et al. 1990; Schmidt-Kastner et al. 1990).

Numerous studies have shown in a variety of lesions that reactive astrocytes upregulate GFAP (Bignami and Dahl 1976; Tetzlaff et al. 1988). Although normal astrocytes lose their ability to express vimentin during normal development, reactive astrocytes appear to recover this capacity, especially in close proximity to the site of injury (Pixley and De Vellis 1984; Schiffer et al. 1988). Various experimental models [brain wounds in neonatal (Pixley and De Vellis 1984) and adult (Calvo et al. 1991) rats, for example] have demonstrated the co-expression of GFAP and vimentin by reactive astrocytes.

Hozumi et al. (1990) used comparative quantitative immunoblots and immunohistochemistry to show the presence of GFAP-positive cells around the wound 3 h after wounding, unaccompanied however by an increase in total GFAP. By 6 h after wounding, GFAP had decreased to 80% of the sham-operated control value, but began to increase again by 24 h. Reactive glia in the vicinity of the wound increased steadily in number and intensity, peaking at about 7 days, then declining significantly by 21 days.

A number of experimental models have shown increased immunostaining of GFAP in gliosis, after stab wounding for example (Miyake et al. 1988). *Astrocytes proliferate* dramatically from day 0.5 to day 3 after experimental stab wounding (Miyake et al. 1992 – see also Janeczko 1989). Maximum numbers of proliferating cells (an increase of GFAP-positive astrocytes) were observed on days 2.5 and 3. The phenomenon of astrocyte proliferation is however relatively limited, being confined mainly to the injury site (Miyake et al. 1992).

3.2.3.2 Piloid Gliosis

Piloid gliosis (also termed pilocytic or isomorphic gliosis) is associated with long-standing degeneration of nerve fibers in, among other sites, the spinal cord. The unusually long fibrils course in pathways parallel to the degenerating nerve fibers.

3.2.3.3 Metabolic (Protoplasmic) Gliosis

Metabolic gliosis (Norenberg 1996) develops mainly in the basal ganglia and cerebral cortex of patients in hepatic or uremic coma or in a precoma lasting several days, especially in victims of hyperammonemia. The astrocytes associated with metabolic gliosis are called "Alzheimer's type II astrocytes" (Fig. 3.4g). In metabolic diseases (Adams and Foley 1953) they exhibit a tendency to aggregation (giving rise to so-called Gliarasen) with an increase in number and size of their nuclei, which occur in clusters or pairs as a sign of the proliferation process. The nuclei are vesicular and may show a twofold increase in size. They have a prominent nuclear membrane and an optically empty nucleoplasm whose scant chromatin particles resemble nucleoli. Some of the astrocytes are located in close proximity to neurons (neuronal satellitosis) as a sign of neuronal damage. Intranuclear inclusions may be found upon staining for glycogen [e.g., Periodic Acid Schiff (PAS) stain]. Some but not all of the astrocytes express GFAP. Metabolic gliosis does not exhibit glial fiber formation.

3.2.3.4 Regressive Alterations

Astrocytes do not undergo progressive alterations alone, but also regressive changes such as atrophy, pyknosis, and clasmatodendrosis (Fig. 3.4h). In the early phase following mechanical loading or ischemic injury, the cell body swells and becomes rounded. Later lipid granules and vacuoles appear in the cell body and the surface becomes irregular. The cytoplasmic processes break off (clasmatodendrosis) and disintegrate into granular debris. Astroglia possessing pseudopodia-like appendages alone are called ameboid glial cells.

3.3 Oligodendrocytes

3.3.1 Morphology, Classification, and Immunoreactivity

Oligodendrocytes are small cells with a round or oval, relatively dense nucleus and a small rim of cytoplasm with a cell diameter of 6–8 μm. Oligodendrocytes possess ramified processes that can be demonstrated by silver techniques. They also exhibit a structural polymorphism that reflects differences in function. Three to five types of oligodendrocyte can be distinguished based on localization, which may also be related to differences in function.

1. *Perineuronal oligodendrocytes* (gray matter oligodendrocytes – Fig. 3.5a, b). This type of oligodendrocyte is commonly located near the larger pyramidal cells of the cerebral cortex and the nerve cells of the basal ganglia. Perineuronal oligodendrocytes are considered to be analogous to capsule cells of the dorsal root ganglia. They constitute 51% of the total perineuronal glial population (Bunge 1968).
2. *Perivascular oligodendrocytes* (gray matter oligodendrocytes). Fairly numerous, these cells are seen mainly around cerebral cortical vessels.
3. *Interfascicular oligodendrocytes* (white matter oligodendrocytes – Fig. 3.3c, d). This is by far the most common type of cell in the white matter. These have processes that run parallel to nerve fibers and partly or completely encircle nerve fibers; the cell nuclei are disposed in rows. In the corpus callosum of the rat 69.8% of glial cells in these rows are oligodendrocytes (Mori and Leblond 1970).
4. Szuchet (1995) describes a fourth type of oligodendroglia according to Rio Hortega (1956) which is associated with large axons and located near the entrance of nerve roots into the CNS.
5. An *oligodendrocyte precursor cell* is described as a fifth type, which comprises 5–8% of the glial cell population in the CNS (Levine et al. 2001). These cells have small cell bodies with multiple branched processes. In gray matter, the processes tend to be oriented radially, in white matter they are more longitudinally arranged and aligned with nerve fibers. Under normal circumstances the processes are in contact with synapses and nodes of Ranvier, a possible indication that these structures play a regulatory role in the axonal impulse conduction.
6. Meanwhile the oligodendrocyte has served as a model for lineage development in part due to the identification of specific additional phenotypic

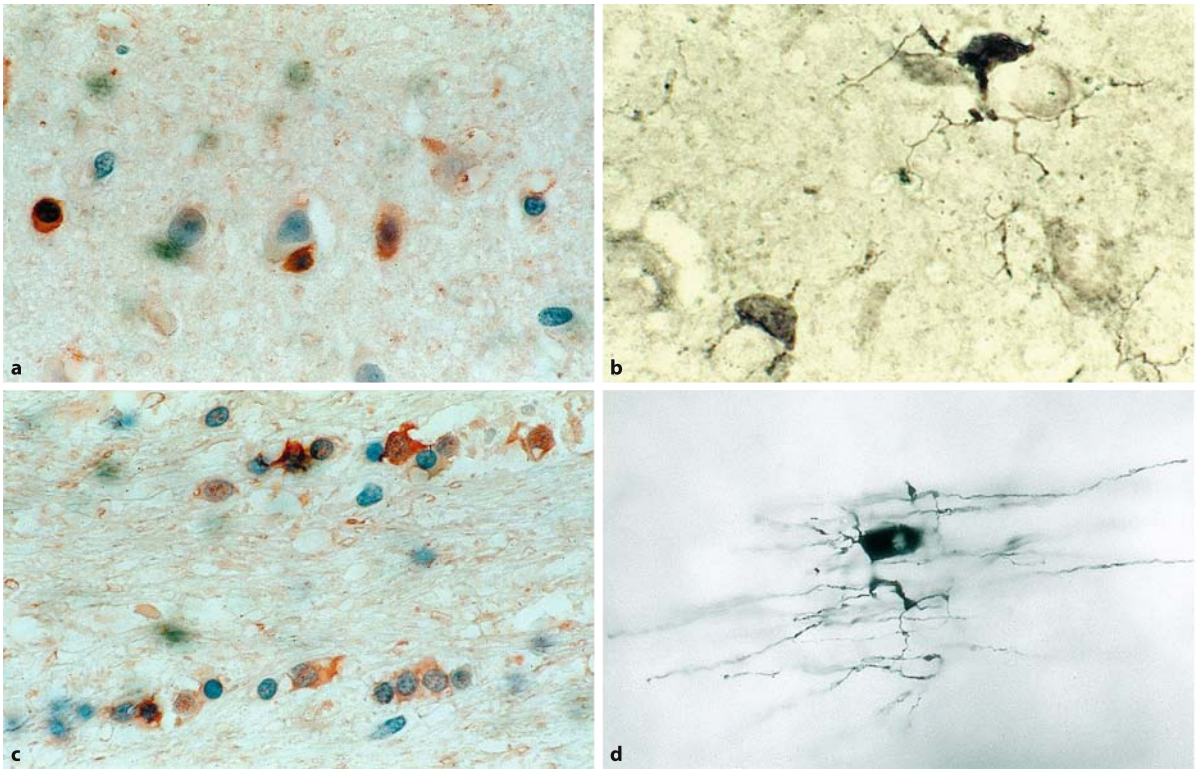

Fig. 3.5a–d. Oligodendrocytes. **a, b** Perineuronal oligodendrocytes = gray matter oligodendrocytes (**a** carbonic anhydrase II = CA II; magnification ×500; **b** silver stain; magnification ×1,000); **c, d** interfascicular oligodendrocytes = white matter oligodendrocytes (**c** CA II; **d** silver stain; magnification **c** ×500, **d** ×1,000)

stages during maturation (Grinspan 2002). The result is the identification of numerous signaling molecules inducing oligodendrocyte development.

Oligodendrocytes can be demonstrated by the silver technique and by antibodies to myelin basic protein (MBP), myelin oligodendrocyte glycoprotein, platelet-derived growth factor, galactocerebroside, or to proteolipid protein (Levine et al. 2001; for review, see Friedman et al. 1989). Also specific for oligodendrocytes are the monoclonal antibodies Rip (Friedman et al. 1989), Otex 1 (Mori de Moro et al. 1990), and CC-1 (Bath et al. 1996). In addition, oligodendrocytes have been found to selectively express carbonic anhydrase II (CA II) (Cammer et al. 1977; Ghandour et al. 1980), gluthathione-*S*-transferase, isoenzyme pi (Tansey and Crammer 1991), and cell-surface sphingolipids, such as galactocerebroside (Raff et al. 1978).

3.3.2 Function

The function of oligodendrocytes is still largely unknown. Different functions have been attributed to the various types of oligodendrocyte.

1. Peters et al. (1991) propose that perineuronal oligodendrocytes may contribute to *neuronal nutrition*. It has also been suggested that under certain conditions, such as in remyelination, these satellites are able to produce myelin (Ludwin 1978; Polak et al. 1982). The total amount of myelin oligodendrocytes are able to synthesize is thought to remain relatively constant (Blakemore 1981). It is on the basis of these findings that neurons are considered to be the regulators of myelination.
2. Interfascicular oligodendrocytes are known to be involved in the *myelination and remyelinating processes* (Harrison and McDonald 1977). In the early stages of myelin formation the cytoplasmic processes sequentially ensheathe the axons. Following demyelination, the myelin sheath regenerates chiefly by forming near internodes. Before remyelinated fibers may be recognized (within 3 weeks) demyelinated axons are surrounded by processes from one or more cell types, such as

astrocytes and debris-laden mononuclear phagocytes. None of these cell types, however, is able to produce a membrane that spirals around the axons or which is compacted in a myelin-like fashion. The regenerated myelin sheaths are formed by oligodendrocytes, which possess microtubules but no filaments (Harrison and McDonald 1977).

3. Little is known about the function of *perivascular oligodendrocytes*.
4. Oligodendrocyte precursor cells have processes that are in contact with synapses and the nodes of Ranvier, an indication, as mentioned above, that these structures fulfill a *regulatory function* in transmitting information via bioelectric signals (Levine et al. 2001). Although they divide slowly, these cells constitute about 70% of cells labeled by a pulse injection of bromodeoxyuridine (labeling index: 0.2–0.3%; cf. Horner et al. 2000).
5. Oligodendrocytes as a cell group also play an active role as an antigen-presenting cell type and are thus involved in *immunological processes*. Though oligodendrocytes are negative for MHC class I and II expression in normal human CNS (Sedgwick and Hickey 1997), under pathological conditions oligodendrocytes may show an increase in class I MHC expression (Benveniste 1997). This is because INF-ɣ, normally produced by activated T-cells and absent from the intact CNS, becomes a potent modulator of MHC antigen expression under pathological conditions, such as T-cell infiltration or disrupted blood–brain barrier.
6. No systematic studies have yet clarified *the influence of neurons or astrocytes* on oligodendrocytes. Fulcrand and Privat (1977) thought oligodendrocytes need neuronal input, but they did not examine whether there must be physical contact between the two cell types or whether neurons influence oligodendrocytes via secreted factors. Astrocytes and oligodendrocytes are coupled in situ by gap junctions (Massa and Mugnaini 1982). Oligodendrocytes can perform their myelination repertoire without gap junctions, which suggests that these junctions fulfill a function not necessarily directly related to the formation of myelin.
7. Little is known either about the *interactions between oligodendrocytes*. Oligodendrocytes are aligned in closely apposed rows, the cells being joined by tight junctions (Massa and Mugnaini 1982). This may indicate intense interaction among these cells, the details of which remain unknown.

3.3.3 Pathology

Oligodendrocytes are compromised in many neurological diseases, including demyelinating diseases (e.g., multiple sclerosis), metabolic diseases (e.g., Pelizaeus-Merzbacher's disease), infectious diseases (e.g., progressive multifocal leukoencephalopathy), neurodegenerative diseases (e.g., Alzheimer's disease), and tumors (e.g., oligodendrogliomas). Under pathological conditions oligodendrocytes assume the various functions described above, the nature of the function partly dependent on the particular cell type. However, this cell type is mainly activated under conditions of myelin degeneration, and their main function is remyelination. Destruction of oligodendrocytes induces unchecked demyelination, with disastrous consequences for brain function.

Myelin formation was recently examined by Campagnoni and Skoff (2001) to aid our understanding of oligodendrocyte function. They found that myelin basic protein (MBP) and myelin proteo-lipid protein (PLP/DM20) genes encode classic MBP and PLP isoforms. The products of non-classic MBP isoforms appear to be components of transcriptional complexes in the nucleus of oligodendrocytes. The products of non-classic PLP/DM20 isoforms appear to make up part of the intracellular transport particles within oligodendrocytes. The same authors reported evidence that PLP/DM20 proteins play a role in neuronal death mechanisms, paracrine and autocrine regulation of oligodendrocytes and neurons, oligodendrocyte migration, and intracellular transport.

Matsushima and Morell (2001) developed an experimental animal model designed to induce myelin degeneration and remyelination by dietary introduction of the copper chelator *bis*-cyclohexanone oxaldihydrazone (Cuprizone). After ingestion of the toxin in this model, oligodendrocytes suffer a specific primary insult and undergo apoptosis. Soon thereafter, recruitment of microglia begins and myelin phagocytosis ensues. Next, oligodendrocyte progenitor cells proliferate and invade the demyelinated area. Once the Cuprizone challenge is ended, remyelination commences and is almost completed in a matter of weeks. It can be inferred from their findings that different cell types communicate by soluble factors.

Remyelination is to a certain extent accomplished either by surviving oligodendrocytes, or by cells newly differentiated from the adult progenitor pool. The *oligodendrocyte precursor cells* in injured CNS constitute a reactive glial population that goes through hypertrophy and mitosis under stimulation from an array of cytokines and growth factors. If there is demyelination, these cells divide and differentiate into new oligodendrocytes that replace the ones that were lost. Activation and proliferation of

these cells also occur in response to other types of CNS damage, including excitotoxicity, mechanical injury, and viral infection.

Ischemic oligodendroglial injury was recently described in a neonatal rodent stroke model (Liu et al. 2002). The authors showed that myelin proteins are restored in the brain after moderate, but not after severe, cerebral hypoxia-ischemia. Dewar et al. (2003) gave an excellent review on this topic and demonstrated that oligodendrocytes may be targets of injury in acute ischemia. Alterations of their distinct cytologic features and specific immunocytochemical reaction gave evidence of oligodendrocyte damage in animal models. For example, oligodendrocytes became immunoreactive for the cytoskeletal protein tau (Dewar and Dawson 1995; Irving et al. 1996, 2001; Uchihara et al. 2000).

Oligodendrocytes have also been shown to *inhibit the regenerative response to axonal injury* (Schwab 1993 – see also p. 66).

3.4 Microglia and/or Mononuclear Phagocytes of the CNS

Microglia make 5–12% of the CNS glia (Lawson et al. 1990). If microglia constitute 10% of the total glial cell pool, and if glial cells are at least 10 times as numerous as neurons in the CNS, then microglia are as numerous as neurons (Streit 1995). The proliferative activity, i.e., the microglial turnover rate, is very low (0.05% – Lawson et al. 1992), which means this cell type has a long life span within the brain tissue.

Rio Hortega (1932) ascribed to microglia a mesenchymal origin. Especially during embryonic development, hematopoietic monocytes invade the CNS as well as the CSF and the perivascular spaces, and mature within the brain parenchyma into typical process-bearing resident microglia (Ling and Wong 1993). Only a few authors still question this process (Fedoroff 1995).

Research on bone marrow transplantation (BMT) has provided information on the turnover rate of mononuclear CSF cells. When bone marrow cells from male donors are transplanted into female hosts, in situ hybridization with Y-chromosome-specific probes showed that by the time complete donor type hematopoiesis had become established (19–97 days after BMT), all cells within the CSF were donor derived (Hibi et al. 1997). In another study, perivascular cells within the brain contained the donor marker, while parenchymal microglia did not (Unger et al. 1993).

These recent findings as former observations (for review see Oehmichen 1978) indicate that mesenchymal cells derived from the bone marrow patrol the CNS continuously and that the perivascular and meningeal macrophage population is slowly replaced by hematogenous macrophages. The population of parenchymal microglia, in contrast, seems to be quite stable in the mature normal brain and may not be replaced by new bone marrow-derived macrophages (Bauer et al. 2001).

Additionally we have to point to another cell population within the CNS with similar functional properties as microglia: *dendritic cells*. Dendritic cells are a subclass of antigen-presenting cells critical in the initiation and regulation of adaptive immunity against pathogens and tumors as well as in the triggering of autoimmunity (for review see Pashenkov et al. 2003). Dendritic cells are present in normal meninges, choroid plexus, and CSF, but absent from the normal brain parenchyma. Inflammation is accompanied by recruitment and/or development of dendritic cells in the affected brain tissue.

3.4.1 Morphology, Classification, and Immunoreactivity

Microglia can be differentiated by localization or functional stage. The term "mononuclear phagocyte" (Oehmichen 1978) is well chosen and designates all monocyte-derived cells within the CNS. The following cell types are distinguished (Oehmichen 1978; Hickey et al. 1992; Gehrmann and Kreutzberg 1995; Perry and Gordon 1997):

1. *Leptomeningeal and choroidal macrophages* (Fig. 3.6a, b). These cells are phenotypically macrophages, express macrophage antigens, and are localized within the subarachnoid space and ventricular system. They have a relatively high replacement rate (60% – Hickey et al. 1992).
2. *Perivascular macrophages* (Fig. 3.6c). These are important immunoregulatory cells to be distinguished from so-called pericytes. They are enclosed by a basal lamina, express macrophage markers, and may act as sensors of CNS perturbations. They are activated by CNS inflammation and are primary targets of human immunodeficiency virus (HIV) infection in the CNS (Williams et al. 2001). Their turnover rate is about 30% (Hickey et al. 1992).
   Leptomeningeal, choroidal, and perivascular macrophages can all be induced to phagocytosis. Unlike other glial cells, even compared to resting microglia, they are efficient and active antigen-presenting cells (Hickey and Kimura 1988; Ford et al. 1995).
3. *Perivascular microglia* (Fig. 3.6d). These cells form a subtype of resting parenchymal microglia. Perivascular microglia come in direct contact with the adjacent basal lamina and thus, like pe-

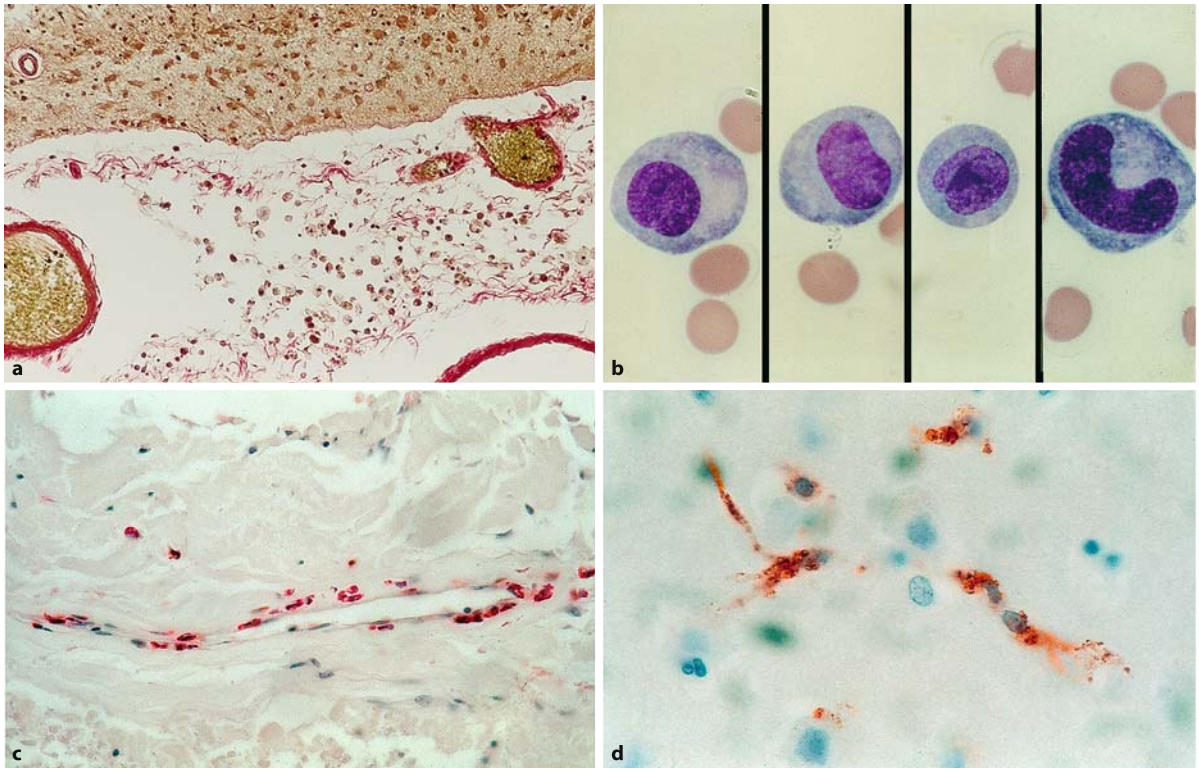

Fig. 3.6a–d. Mononuclear phagocytes. **a** Subarachnoid macrophages as seen on microscopic sections (v. Gieson stain); **b** subarachnoid macrophages as seen in CSF specimens (see Oehmichen 1976; Giemsa stain); **c** perivascular macrophages within Virchow-Robin space (CD68 reactivity); **d** perivascular microglia in the next vicinity of capillaries (CD68 reactivity; magnification **a, c** ×300, **b, d** ×1,000)

rivascular astrocytic endfeet, form part of the perivascular glia limitans (Lassmann et al. 1991).

4. *Ramified resting microglia in the normal CNS* (Fig. 3.7). This cell type has a small heterochromatic nucleus and fine, ramified processes which exhibit a stellate morphology in the gray matter and a bipolar, longitudinal morphology in the white matter. Under pathological conditions they may transform into "activated microglia" (see below).

Leptomeningeal, choroidal, and perivascular macrophages exhibit the same immunoreactive pattern as macrophages and activated microglia and may be termed "mononuclear phagocytes." Ramified resting microglia are demonstrated by the silver carbonate method (Rio Hortega 1919), by immunohistochemical procedures (for review see Gehrmann and Kreutzberg 1991; Streit 1995), and by histochemical techniques (Oehmichen 1980).

As late as the 1990s it was thought that the blood–brain barrier prevented macrophages from invading the CNS. It was observed that a disrupted blood–brain barrier did not invariably result in invasion of the CNS parenchyma by monocytes. In addition it was noted that circulatory monocytes cross the intact blood–brain barrier in response to the degeneration of other cell types or to inflammatory substances within the parenchyma. Like activated T-lymphocytes, monocytes are also known to cross the intact blood–brain barrier under non-pathological conditions (Hickey 1999).

For a long time, the demonstration of resting and activated microglia only succeeded due to silver techniques. Selective immunohistochemical staining is only possible because of the expression of specific surface proteins in microglia. Visualization in vivo is possible (Banati 2002) using ^{11}C-labeled ligands for the peripheral benzodiazepine binding site (PBBS), which binds to activated but not resting microglia with relatively cellular selectivity.

3.4.2 Pathology

Under pathological conditions a cell type appears which stains like resting microglia, the so-called activated microglia. Activated resting microglia in animal experiments (mice) express OX-42 and CR3-complement receptors (Graeber et al. 1988a) plus F4/80 and Mac-1 antigen (Perry et al. 1985). In pa-

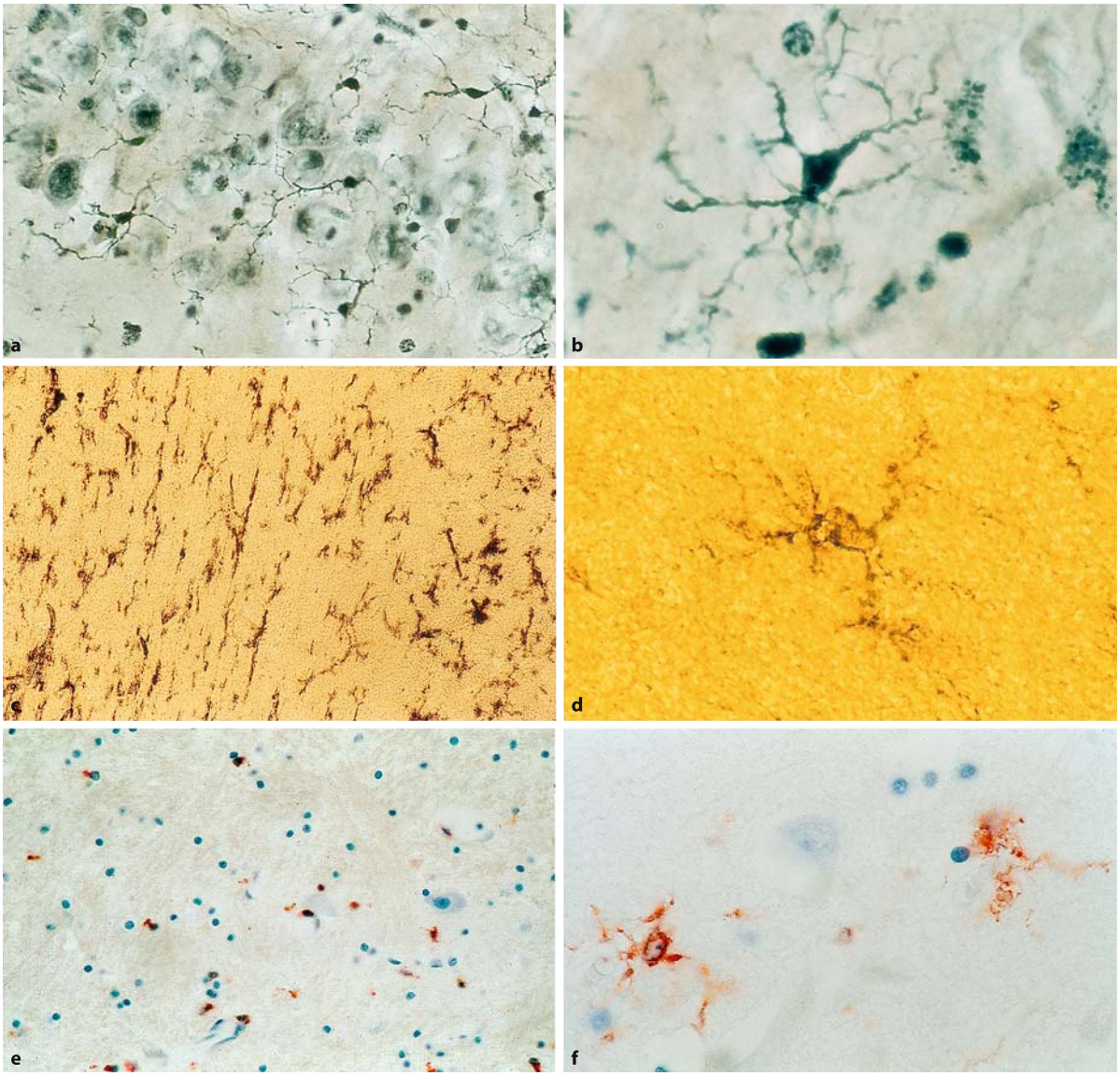

Fig. 3.7a–f. Ramified resting microglia in normal CNS. **a, b** Silver stain; **c, d** UDPase; **e, f** CD68 reactivity (magnification **a, c, e** ×500; **b, d, f** ×1,000)

thological human brain tissue, activated microglia can be detected in routine paraffin material using the monoclonal antibody LN-3 (Sasaki et al. 1991). Activated microglia also express MHC class I and II antigens (Streit et al. 1989) in addition to almost all other macrophage-specific antigens.

Activated microglia possess an ability to proliferate locally, to emigrate to the site of injury, to change morphologically, immunophenotypically, as well as functionally (Gehrmann and Kreutzberg 1995). Two types of activated microglia are recognized:

- *Activated, non-phagocytic microglia* (Fig. 3.8a). These cells are hypertrophic and have processes which are more numerous than those of resting microglia. They express vimentin, several macrophage markers, including CR3 complement receptor, MHC class I and II, and CD4 antigen (Streit and Kreutzberg 1987). They are characterized by intense upregulation of CD68 and CD14 (Beschorner et al. 2002).
- *Activated phagocytic microglia* (Fig. 3.8b-d). Morphologically these cells are characterized by an ameboid cell structure lacking processes as seen after traumatic (Fig. 9.8) or ischemic events (Fig. 14.12–14.15); functionally they resemble non-phagocytic microglia, but are additionally capable of phagocytosis of neurons (Fig. 3.8e), of fat (Fig. 3.8f), of myelin (Fig. 3.3d), etc. and are capable of releasing immunomodulatory compounds. Microglia may respond to sterile CNS in-

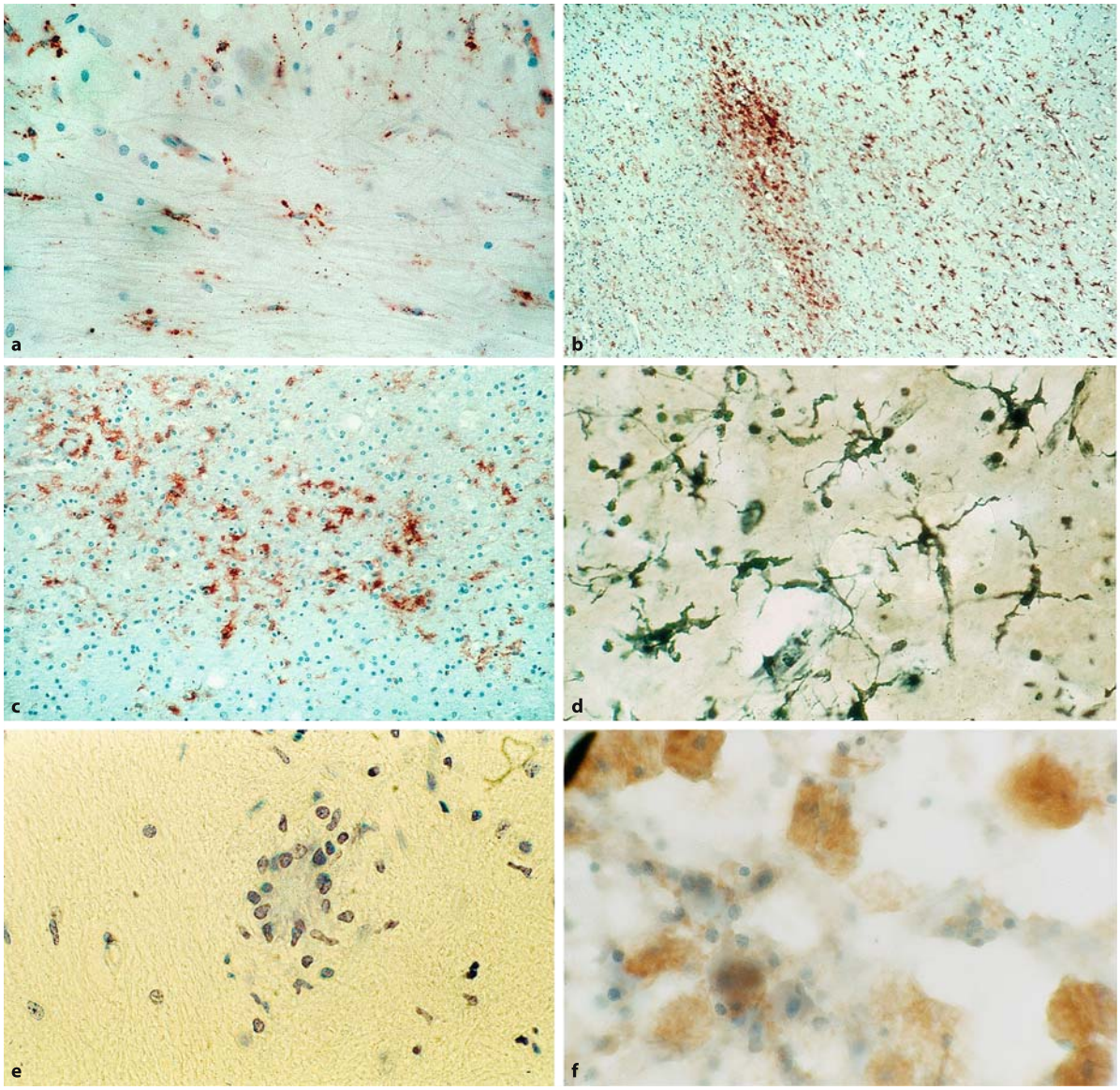

Fig. 3.8a–f. Activated microglia. A moderate (**a**) and a distinct cluster-like increase (**b, c**) of activated microglia demonstrated by CD68-immunohistochemistry as well as by silver stain (**d**) (magnification **a** ×500; **b** ×100; **c** ×500; **d** ×1,000); **e** perineuronal aggregation of microglia (satellitosis or microglial nodule) as an indication of neuronal phagocytosis (Nissl stain; magnification ×1,000); **f** lipid-containing phagocytes (Fettkörnchen-Zellen) as an indication of the scavenger function of microglia (oil-red 0; magnification ×1,000)

jury as a consequence of their scavenger function, such injury also stimulating a release of growth factors that participate in the scarring process of gliosis.

Graeber et al. (1997) suggested that microglia are a "sensor" of the pathological status of the human CNS. Under certain physiological and especially pathological conditions of the CNS microglia react very quickly. Microglia are slightly more numerous in elderly brains and they show more phagocytotic activity (Peters et al. 1991). Under conditions of dehydration, microglial cells proliferate in the posterior pituitary and the supraoptic nucleus (Lawson et al. 1993).

It has recently been shown that monocytes aggravate neuronal degeneration, for example in cases of HIV-infected macrophages which produce a neurotoxic substance (Giulian et al. 1990). In other conditions involving rapid recruitment of macrophages, they secrete neurotoxic compounds (Piani et al. 1991) and can damage myelin (Coffey et al. 1990 – for review see Giulian 1995).

Two observations have potential practical (forensic) applications: Lassmann (1997) used the detection of myelin degradation products within brain macrophages to estimate the age of trauma-induced demyelination (1–14 days), and thus to stage lesions of CNS white matter (cf. Oehmichen et al. 1986). Meyermann et al. (1997) applied various immunoreactive macrophage markers to show that although MBI may induce upregulation of various antigens, it does not induce macrophage proliferation at the margins of mechanically induced hemorrhages – in contrast to the processes resulting from an ischemic lesion.

A sophisticated questioning of the functional potential of microglia was given by Streit (2002). He examined the possible consequences of microglial dysfunction as a result of aging, genetics, or epigenetics. He supposed that microglial senescence was a potential factor in the pathogenesis of Alzheimer's disease. His hypothesis is based on observations of microglial abnormalities, especially microglial deramification, spheroid formation, gnarling and fragmentation of processes in Alzheimer's disease (Streit et al. 2004),

A further question must be answered: the fate of activated microglia. Obviously, a part of activated microglia will leave the CNS by migrating along lymphatic pathways (Oehmichen et al. 1979b). Another portion may disappear by focal cell death induced by interleukin-13 (IL-13) in association with IL-4 in a time-dependent manner (Yang et al. 2002).

3.4.3 Function

A cell type's immunophenotypical properties are an indication of its phagocytic and immunological functions (Oehmichen 1983; Gehrmann and Kreutzberg 1995).

1. Resting microglia as well as the group of mononuclear phagocytes upregulate Fc and complement receptors (Oehmichen 1978), which could also be demonstrated in resting microglia using a monoclonal F4/80 antibody (Perry et al. 1985).
2. Resting microglia normally lack MHC class I and only a few microglial cells express MHC class II (Perry and Gordon 1997). The immunological situation created by inflammatory processes (neuritis, brain abscess, glioma, viral infection, neurotoxin lesion) leads to the activation of resting microglia and infiltration of the CNS by blood monocytes, which express MHC classes I and II.
3. Recent investigations give evidence of the expression of "scavenger" receptors (class A, Bi and CD36) by microglia, astrocytes, cerebral microvascular endothelial cells, etc. (Husemann et al. 2002). These receptors are cell surface proteins that mediate cell adhesion to, and endocytosis of, various native and pathologically modified substances, and participate in intracellular signaling, lipid metabolism, and host defense against bacterial pathogens. Neonatal microglia express scavenger receptors, while these receptors are not expressed in normal mouse or human adult brain microglia.
4. Activated microglia synthesize tumor necrosis factor (TNF) in the very early phase (minutes to a few hours) after induction of ischemia (Lambertsen et al. 2002). TNF is a potential neurotoxic cytokine.
5. Activated microglia upregulate vimentin (Graeber et al. 1988b) and both MHC classes I and II, ED-1, etc. (see above).
6. Activated microglia perform all of the immunological functions attributed to macrophages in sterile and non-sterile inflammation: they release immunomodulatory compounds and interact with other immunocompetent cells.

Moreover, the functional potential of microglia is not limited to their surface protein expression but it is additionally characterized by their interaction with cytokines (for review see Hanisch 2002). Cytokines constitute a significant portion of the immuno- and neuromodulatory messengers that can be released by activated microglia. By virtue of potent effects of resident and invading cells, microglial cytokines and chemokines regulate innate defense mechanisms, help the initiation and influence the type of immune response, participate in the recruitment of leukocytes to the CNS, and support attempts at tissue repair and recovery. Moreover, microglia can also receive cytokine and chemokine signals as part of their communication with astrocytes, neurons, endothelium, and leukocyte infiltrates.

The inflammatory response, therefore, is marked by the appearance of phagocytes, which arise from activated resting microglia as well as from invading monocytes, which bear scavenger receptors within 5–8 h after wounding (Giulian et al. 1993). In the rat brain their numbers were found to peak 2 days after the traumatic event.

Meanwhile there is additional evidence of the reciprocal interactions between microglia and neurons and complex signaling systems (Polazzi and Contestabile 2002). The signal relates to the suppression of immunological properties of microglia by neurons in the healthy brain and between damaged neurons and microglia. The authors propose that microglial activation, consequent to neuronal injury, is primarily aimed at neuroprotection (Polazzi and Contestabile 2003). The loss of specific communication between damaged neurons and microglia is viewed as being responsible for the transformation of microglia to a hyperactive state, allowing them to escape neuronal

control and giving rise to persistent inflammation, resulting in exacerbation of neuropathology.

3.4.3.1 Resting Microglia

It is still not known exactly what function resting microglia perform within normal brain parenchyma. They may participate in tissue homeostasis and in the early defense against injury and infection (Gordon et al. 1988; Perry and Gordon 1997). Because resting microglia and mononuclear phagocytes cross react, using different antibodies, resting microglia seem to take up the same functions in the CNS as resting macrophages in the tissue of other parenchymal organs, i.e., both a scavenger function and an immunological function. The most important function appears to be their transformation under pathological conditions into intrinsic phagocytes. Their ability to be activated is expressed above all in their capacity to proliferate, to phagocytose, and to release immunomodulatory compounds. Microglia form a network of antigen-presenting cells whose main function is immune surveillance (Oehmichen 1983; Perry and Gordon 1997). Under pathological conditions resting microglia change into mobile, phagocytic cells that are capable of neuronophagia (Banati et al. 1993) and which release proteases, proinflammatory cytokines (IL-1, TNF-α, IL-6, etc.), anti-inflammatory cytokines (IL-10, TGF-β), cytotoxic molecules (nitric and oxygen radicals), prostanoids (PGD_2, PGE_2, thromboxane B_2), and chemokines (IL-8, etc.) (Aloisi 2001).

3.4.3.2 Perivascular Microglia

Perivascular microglia apparently participate in functions of the blood–brain barrier system. Together with *leptomeningeal phagocytes*, they fulfill a scavenger function within the CSF, especially under pathological conditions such as hemorrhage, stroke or infection (for review of literature up to 1982 see Oehmichen 1982b; 1982–1995: see Gehrmann and Kreutzberg 1995). They are involved in the immunoreactive response as they are antigen-presenting cells. Some data appear to indicate that perivascular microglia return to the spleen and lymph nodes bearing the material they have gathered in the CNS (Oehmichen et al. 1982a, b; Broadwell et al. 1994). Direct labeling of a particulate antigen in the CNS, however, could not show that these cells triggered an immune response to the antigen (Matyszak and Perry 1998, cf. Graeber et al. 1992).

3.4.3.3 Activated Microglia (Macrophages)

Activated non-phagocytic microglia is involved in immunological processes as a regulatory cell in the defense against pathogens and tumor. Activated phagocytic microglia phagocytose necrotic cells – especially necrotic neurons (Fig. 3.8e), cell particles, and other debris resulting from, e.g., edema, myelin degradation (Figs. 3.3d, 9.15), necrosis, i.e., lipids (Figs. 3.8f, 9.16), or red blood cells in hemorrhages (Figs. 9.17, 9.18). Activated microglia may ingest extravascular erythrocytes, which can be demonstrated as erythrocyte- or siderin-bearing macrophages (Figs. 9.17, 9.18). They may also contain ingested nuclear material, myelin, and lipids, which are changed by intracellular digestion (Oehmichen et al. 1986; Lassmann 1997). In special cases the ingested substances may enable retrospective diagnosis and timing.

3.5 Additional Cell Types and Tissue Components

The cell types and different tissues described in the following protect the CNS parenchyma from extracerebral influences, such as blood constituents and microorganisms, and thus maintain intracerebral homeostasis (for a survey of these cell types see Bargmann et al. 1982).

3.5.1 Leptomeningeal and Perivascular Cells

The leptomeninges are composed of the two more delicate components of the meninges, the *pia mater* and the *arachnoid mater*, considered together. The pia mater contains the blood vessels that penetrate the brain, while the arachnoid mater is composed of the arachnoid membrane and trabeculae, the latter stretching from the membrane to the pia. Since this situation arises from a progressive enlargement embryologically of the extracellular space of the originally solid leptomeninges, the arachnoid trabeculae are surrounded by the subarachnoid space containing CSF.

The term *pia mater* is applied to the entire brain and spinal cord surface. Moreover, funnel-shaped pia mater accompanies vessels that extend into the brain. The undersurface of the pia mater possesses a well-defined glial basement membrane. The portion of the glial membrane that courses along the penetrating vessels is called the *membrana gliae perivascularis*.

The *arachnoid membrane* constitutes the outer limit of the arachnoid. The membrane spans the sulci of the cerebrum and cerebellum and lies near the brain stem. The *arachnoid trabeculae* composed of collagen fibrils, fibrocytes, and fibroblasts span the subarachnoid space and attach the arachnoid membrane to the pia mater.

The vessels entering the cortex are thin-walled, comprised merely of a basement membrane, endothelium, and a single layer of smooth muscle cells. The *Virchow-Robin space* (perivascular space) lies between the vessel basement membrane and the glial basement membrane.

Both the *subarachnoid space* (Fig. 3.6a, b) and the Virchow-Robin space (Fig. 3.6c) are filled with CSF, which contains single macrophages and isolated lymphocytes (Oehmichen 1976). Two-thirds of the CSF is produced by the choroid plexus. To reach the subarachnoid space, CSF courses from the lateral to the third ventricles through the interventricular foramina (of Monro), the third ventricle, the cerebral aqueduct of the midbrain, the fourth ventricle, the two lateral foramina of Luschka and the midline foramen of Magendie. It exits the intracranial spaces via arachnoid villi or via lymph channels at the level of the nerve roots (for review: Oehmichen et al. 1982a, b).

3.5.2 Parenchymal Vessels

Parenchymal vessel walls of the brain are very similar in construction to those of other organs (for details, see Chap. 28, pp. 542 ff). *Normal arteries* possess an intimal layer composed of *endothelial cells* with longitudinally oriented nuclei and perikarya. A basement membrane covers the endothelial cells. The internal elastic lamina separates the intimal layer from the lamina media, which consists of smooth muscle cells. The lamina adventitia is formed of loose connective tissue containing collagenous fibers, pericytes, fibroblasts, and perivascular macrophages, which are typical of the Virchow-Robin space. The *normal veins* of the brain are characterized by a wide lumina and relatively thin vessel walls. They have no internal elastic lamina.

Brain capillaries differ from those of other organs by their complete or almost complete impermeability (blood–brain barrier) and lack of fenestrations. The neighboring endothelial cells are bound together by tight junctions or *zonulae occludentes*, which prevent the passage of tracer substances. This barrier function is absent in vessels of the choroid plexus, pineal body, pituitary gland, area postrema, tuber cinereum, and median eminence.

Under *pathological conditions*, shrinkage of endothelium can occur and thus leads to the formation of fenestrations. The tight junctions can also fail, or pinocytotic vesicles may arise within the endothelial cells, all of which are associated with a breakdown in the blood–brain barrier (cf. Chap. 4, pp. 42f). Endothelial cells may proliferate, as seen in glioblastoma, or as a consequence of ischemic and/or toxic damage to the CNS.

3.5.3 Choroid Plexus and Ependyma

The cells of the surface of the choroid plexus (choroidal cells) as well as of the ventricular system (ependymal cells) originate from neuroectodermal ependymoblasts of the neural tube. The *choroid plexus* possesses fronds produced by elaborate infolding of the plexus surface. The fronds exhibit ramified villous processes, each supported by connective tissue. The choroid plexus has clearly defined projections into the third, fourth, and lateral ventricles of the brain. Its surface is covered by a thin epithelium composed of low columnar, cuboidal, or squamous cells mounted on a basement membrane. Choroidal cells secrete two-thirds of the CSF (roughly 500 ml/day in an adult), the remaining one-third (roughly 250 ml/day in an adult) arising from the interstitial fluid of the brain. The choroidal CSF can be thought of as fresh fluid diluting and rinsing the more stagnant and metabolite-laden extrachoroidal, tissue-derived CSF.

The ventricular surfaces are lined by cuboidal to columnar cells with cilia and microvilli, the *ependymal cells*. Adjacent cells are bound to each other by desmosomes. The hypothalamic wall of the third ventricle contains a specialized ependymal cell type called the tanycyte. The functions of ependymal cells are secretion, absorption, transport, receptor tasks, and provision of a barrier between the CSF and brain (Del Bigio 1995).

3.5.4 Pathology of the CSF and Cells Within the CNS

Disturbance of CSF turnover can lead to a pathological reaction in the form of *hydrocephalus* (cf. pp. 54 ff). The turnover can be disturbed by disruption of CSF reabsorption, particularly by diseases of the arachnoid villi. Subarachnoid hemorrhage due to an efflux of red blood cells can cause blockage of the arachnoid villi, and thus a backup of CSF, while the ventricle to CSF pathways for CSF flow remains open (communicating hydrocephalus). Disturbance of the pathways communicating between the ventricular system and subarachnoid space may cause internal hydrocephalus (non-communicating hydrocephalus). The pathways can also be congenitally blocked

or impeded by an atresia (congenital non-communicating hydrocephalus) or the blockage can result from infection (postmeningitic hydrocephalus) or tumor, giving rise in each instance to an obstructive, i.e., high pressure, hydrocephalus. Disease processes, e.g., following mechanical violence or stroke, can lead to a reduction in the brain parenchyma, producing a so-called hydrocephalus ex vacuo.

All of the above mentioned cell types discussed here line the surfaces of the brain and protect it against extracerebral influences (Adams et al. 1982). The vessels of the brain are especially well suited by their barrier function to guarantee homoeostasis within the brain parenchyma.

The CNS was once thought to be an immunologically privileged organ, exempted from immune reactivity and *immune surveillance*. This is attested to by the absence of MHC molecules basic to antigen presentation from resident cells of the nervous system, but not from perivascular cells and CSF macrophages. Under normal circumstances the aforementioned resting microglia are present in the CNS and subject to activation. Normal CSF contains a few lymphocytes (Oehmichen 1976), and activated (but not resting) T-lymphocytes can cross the blood–brain barrier to carry out immune surveillance of the normal brain parenchyma (Wekerle et al. 1986). A constant surveillance of the intact healthy CNS is performed by activated T-cells. Recent investigations show that B-lymphocytes enter all parts of the normal brain in very low numbers and that the B-lymphocytes within the brain parenchyma display an activated (CD23 positive) phenotype (Anthony et al. 2003).

Under pathological conditions, the situation changes considerably, the alterations involving both the endothelial cells and leukocytes (cf. Chap. 29, pp. 582 ff). The CNS is subjected to massive infiltration by immune cells (Flügel and Bradl 2001; Hickey 2001) dependent on antigens (Hickey et al. 1997) and release of various cytokines (Benveniste 1997). When attachment and transendothelial migration of blood-derived immunocompetent cells occur, cell surface glycoproteins called adhesion molecules, expressed on both lymphocytes and endothelial cells, exert extensive control over the leukocytes. When emigration from the vascular compartment into the extravascular compartment is to occur, leukocytes first establish loose contact with endothelial cells via C-type lectins, or selectin molecules, especially the P-selectin (CD62), which appears within minutes after a mechanical or ischemic insult on the surface of endothelial cells. Attachment of the leukocyte to the endothelial cell is mediated by adhesion molecules such as the intercellular adhesion molecules (ICAMs) and the vascular cell adhesion molecule-1 (VCAM-1). Integrins such as the lymphocyte function-associated antigen-1 (LFA-1) may contribute to a cell's ability to migrate out of a vessel.

The endothelium of the CNS normally expresses no or only low levels of adhesion molecules. If there is inflammation of the CNS, adhesion molecules are widely expressed. TNF-α, a cytokine released by macrophages, plays an especially crucial role in the induction of adhesion molecules. Once leukocytes have entered, T-cells (and possibly B-cells) recognize their antigen, thus initiating the next step in the induction of inflammation. Antigen-presenting cells other than astrocytes, oligodendrocytes, and endothelial cells include perivascular cells, microglia, and leptomeningeal macrophages. In macrophages, proinflammatory cytokines upregulate the antigen-presenting function. The chief cytokine in this regard is IFN-γ, which is released by activated T-cells (Sedgwick and Hickey 1997).

The role of complement in the emigration of leukocytes in inflammation and injury is still not entirely known (Morgan 1999). Administration of the complement inhibitor sCR1 just before brain injury has been shown to greatly inhibit infiltration of neutrophils into the injured area, an indication that local activation of complement contributes to inflammation (Kaczorowski et al. 1995). In aneurysm rupture causing cerebral hemorrhage, complement activation is combined with potentially life-threatening cerebral vasospasm (Ostergard et al. 1987). Complement activation and reperfusion injury may follow transient cerebral ischemia in stroke and transient ischemic attacks, with fatal consequences (Czurko and Nishino 1994).

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Cell and Tissue Reactions 4

Similar types of tissue reaction result as a final common pathway from a wide array of different internal brain pathophysiological states and external insults. Since these cellular and tissue reactions are largely independent of the specific type of insults, they are, therefore, non-specific. The tissue reactions are to be differentiated according to their specific pathogenetic mechanisms, though these mechanisms as well as the phenomena are overlapping as demonstrated in Fig. 4.1; brain ischemia as a type of metabolic disturbance, edema, intracranial pressure, necrosis, herniation and inflammation are influencing themselves and are dependent on each other. Some will be mentioned again in later chapters as viewed from different forensic aspects; therefore, a certain redundancy is unavoidable. Immediately following, we offer a survey of the individual types of reaction and their fundamental pathophysiological principles and morphology.

4.1 Increased Brain Volume – Edema

4.1.1 Definition

If brain volume increases, both blood and CSF are displaced until the intracranial pressure (ICP) increases. The consequent pression of the brain against the inelastic dura mater (Fig. 4.2) and the skull can lead to a lethal series of complications in clinical neurology. The following remarks are based largely on Ironside and Pickard (2002).

Brain volume depends on the following factors:

1. Water content (cerebral hydration). The brain has a normal water content of about 75%. A disturbance of the blood–brain barrier (BBB) can lead to an increase in the fluid content, with a consequent increase in brain volume.
2. Intracranial blood volume (Hirai et al. 1986). This can be driven upward by a number of factors: arterial hypertension (Marshall et al. 1969); enhanced cerebral blood flow secondary to elevated cerebral perfusion pressure (Artru et al. 1976); a decline in the cerebrovascular resistance of arterioles, capillaries, and postcapillary vessels (Langfitt et al. 1965) due to hypercapnia, hypoxemia associated with severe elevation of arterial pressure (Marmarou et al. 1997), or due to obstruction of the venous outflow of the brain. Elevated cerebral blood volume, also known as "brain swelling," is a congestive process.
3. Cerebrospinal fluid (CSF) pressure. The central nervous system (CNS) of the average adult contains a CSF volume of approximately 120–140 ml. Among the causes of a rise in CSF pressure is acute obstructive high pressure hydrocephalus (see pp. 54 f).

A number of additional factors may also influence brain volume. The congested brain expands particularly rapidly under high arterial pressure (Leech and Miller 1974). Nawashiro et al. (1995) used experimental closed brain injury in rats to demonstrate a rapid and widespread increase in regional cerebral blood flow and impaired cerebral autoregulation. In humans a variety of factors act in concert after the incidence of severe brain injury. Cerebral computed tomography (CCT) and magnetic resonance imaging (MRI) studies have shown that brain edema is the major fluid component of brain swelling (Marmarou et al. 1997, 2000). A reactive hyperemia is an additional factor and may be the mechanism underlying mechanical/ischemic brain injury (Seida et al. 1989). Moreover, regional cerebral ischemia additionally is attributed to a compromised, leaky microvasculature rather than to vasospasm of larger vessels (Schröder et al. 1998).

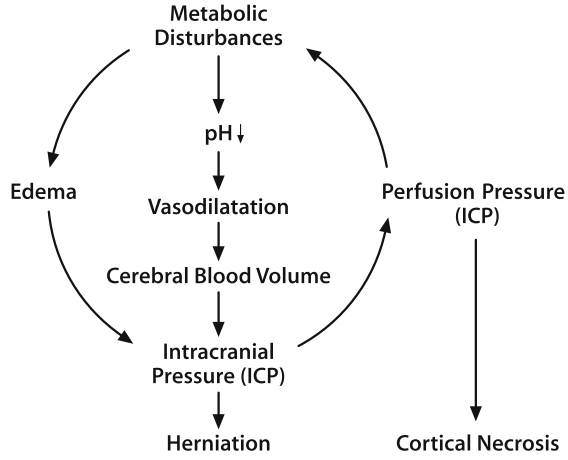

Fig. 4.1. Schematic demonstration of overlapping pathogenetic mechanisms that are associated with different types of tissue reactions by a causal link: metabolic disturbance, i.e., edema, increasing cerebral blood volume, perfusion pressure and herniation, i.e., brain swelling and cortical necrosis

The conclusion that brain swelling is due primarily to edema and not congestion of blood appears to be valid also for children (see Chap. 20, pp. 415 f). Cerebral blood flow in children with severe head injuries is not substantially increased over that in uninjured children (Zwienenberg and Muizelaar 1999). This has also been demonstrated following experimental generation of brain trauma in newborn and juvenile pigs (Armstead and Kurth 1994). The experimental findings of Biagas and coworkers (1996), in contrast, demonstrated a delayed rise in cerebral blood flow following experimental contusion in young and adult, but not in elderly, rats.

4.1.2 Clinical Features

Normal adult ICP is less than 2 kPa (1 kPa=7.5 mm Hg=7.5 torr), mild elevations in pressure range from 2 kPa to 3 kPa, moderate elevations attain 4 kPa, while major intracranial hypertension exceeds 5 kPa (Miller and Ironside 1997). Normal CSF pressure in adults is 0–1.3 kPa, with an upper limit of 2 kPa. While a short-term rise in ICP pressure of up to 10 kPa may be tolerated so long as it does not cause distortion of the brain (Johnston and Paterson 1974), a MBI-induced rise of more than 8 kPa with distortion of the brain can result in herniation and brain death syndrome.

The classic symptoms associated with elevated ICP are vomiting, headache, papilledema, and coma.

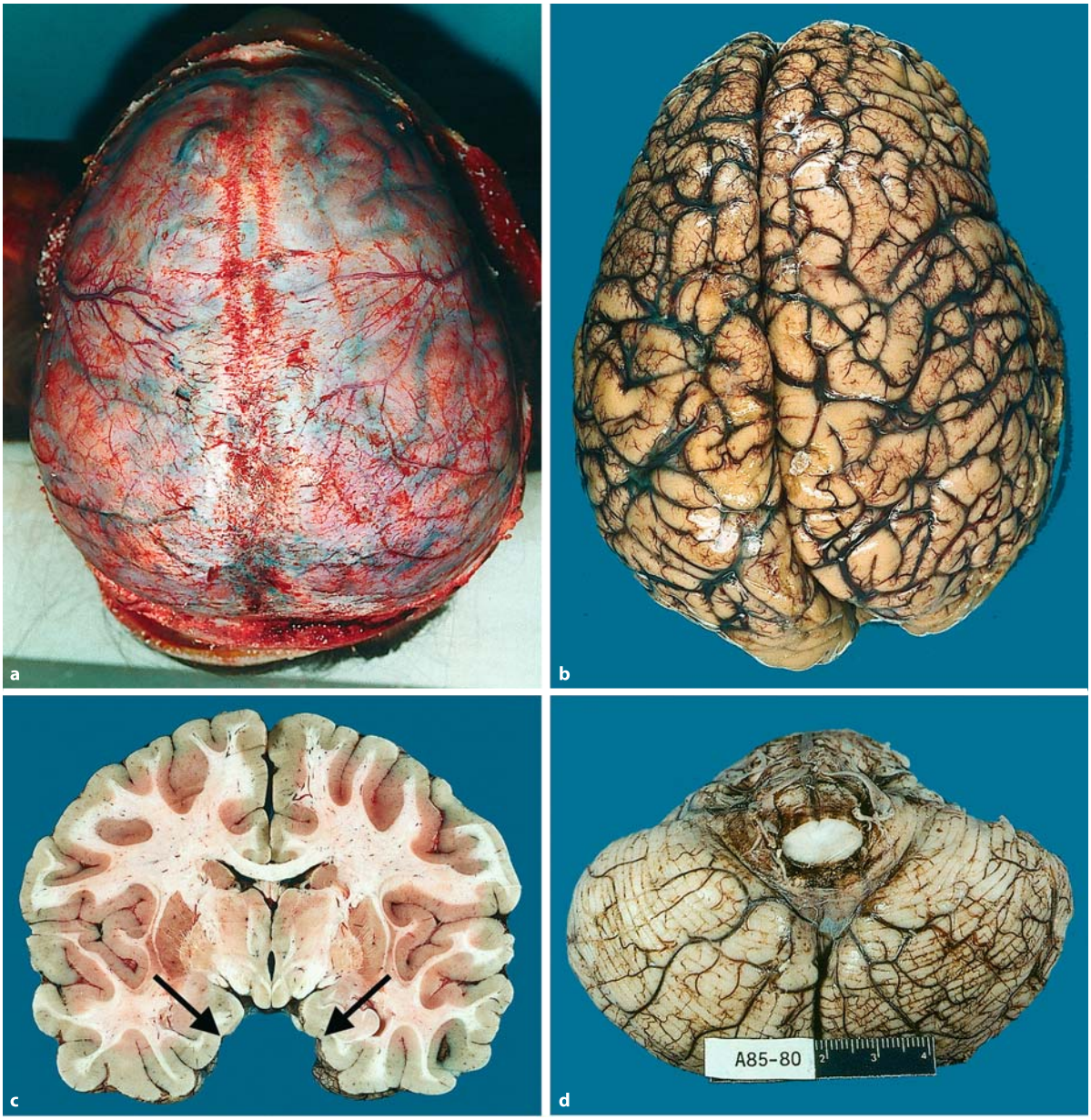

Fig. 4.2a–d. Macroscopic findings in brain swelling. **a** Tightened dura; **b** flattened gyri; **c** compressed ventricles and notches (arrows) which give evidence of a slight herniation; **d** compressed cerebellar tonsils

Distortion or pressure on the floor of the fourth ventricle are most likely responsible for the *vomiting*, while stretching and distortion of the dura mater and major intracranial blood vessels, all sensitive to pain, probably account for the *headache*. The *papilledema* is not a direct result of the rise in water content, but the consequence of an accumulation of axoplasm in the optic papilla secondary to the blockade of axoplasmic flow from ganglion cells along the optic nerve. Papilledema is a common symptom of chronic intracranial hypertension. It is not, however, a common feature of MBI (Selhorst et al. 1985), and its absence does not necessarily mean that ICP is normal. A further increase of ICP leads to a *loss of consciousness* and *coma*.

Elevated ICP affects other organ systems as well. It often induces *arterial hypertension* and systolic blood pressure may climb to 40 kPa or more. The arterial hypertension is caused by an increase in sympathetic activity. Cases of raised ICP with *myocardial involvement* often exhibit pathological alterations consisting of subendocardial hemorrhage and widespread focal myocardial necrosis as well as electrocardiographic changes such as T-wave inver-

sion and elevation of the ST–segment, which point to myocardial ischemia (Connor 1968). *Respiratory disturbances* associated with elevated ICP often precede apnea. Central neurogenic hyperventilation is observed in connection with the midbrain lesion. In patients with raised ICP, neurogenic pulmonary edema can complicate the clinical course. The *mucosa* of the *digestive* and *urogenital tracts* can become hemorrhagic, eroded, and ulcerated, gastric erosions being particularly common in comatose patients with elevated ICP.

4.1.3 Pathogenesis

A fundamental distinction must be made between global and focal cerebral edema. The former follows acute systemic hypoxic events, e.g., transitory cardiac arrest or chronic hypoxia in respiratory diseases. Global cerebral edema may also be associated with metabolic diseases, intoxications, and inflammation. Focal cerebral edema results from focal tissue destruction or alteration of brain tissue that has undergone membrane failure in cells and vessels due to infarction or traumatic hemorrhage or tumor. The tissue surrounding the central lesion has passed only the upper threshold of electrical silence and thus retains the capacity to recover if perfusion is restored in time (Harding and Copp 1997). This zone resembles the *penumbra* surrounding the moon in full eclipse (Astrup et al. 1981). Because these tissue changes are partly reversible, they are of considerable therapeutic interest (see pp. 63 f).

Information on the incidence of intracranial hypertension has been gained mainly from survivors of MBI. Miller and his associates (1977) reported that ICP levels exceeded 2.7 kPa for 5 min or longer in 44% of 160 patients in one series and in 53% of another series of 215 patients (Miller et al. 1981). Raised ICP was found in more than 70% of cases in a more detailed prospective study of elevated ICP in victims with severe head injury by Marmarou and colleagues (1991). Jones and colleagues (1994) found elevated ICP in more than 80% of 74 brain injury patients (54 severe, 17 moderate and 3 minor) undergoing artificial ventilation with ICP monitoring. These findings indicate that intracranial hypertension is a common event, especially in comatose patients. Certain features detected by CCT are consistently associated with elevated ICP. Loss of the images of the third ventricle and perimesencephalic CSF cisterns, and dilatation of the lateral ventricle contralateral to a mass lesion, as well as the absence of these features are no guarantee that ICP will remain normal (Teasdale et al. 1984; O'Sullivan et al. 1994).

Elevated ICP is also common in patients who are *comatose from causes other than brain injury* (Chandler and Kindt 1976). Among the possible causes are liver failure (hepatic coma), intracranial hemorrhage (subarachnoid and intracerebral), post-hypoxemic states (cardiorespiratory arrest, near drowning), infection (meningitis, abscess, and encephalitis), as well as various other types of inflammation and intoxication.

Adams and Graham (1976) published neuropathological criteria for determining at autopsy whether ICP in victims of *brain injury* was elevated during life. The same team (Graham et al. 1987) compared the nature of the brain damage in patients with and without elevated ICP after suffering a non-missile brain injury who had survived long enough to receive treatment in a neurosurgical unit. Pressure necrosis of the parahippocampal gyrus, an indicator of high supratentorial ICP and tentorial herniation, was present in two-thirds of the 434 patients in their most recent study. It was closely associated with skull fracture, brain swelling, diffuse axonal injury, hypoxic brain damage, and extensive supratentorial hematoma. The brain stem was damaged in 68% of victims with pressure necrosis, the anterior lobe of pituitary was necrotic in 45%, and there was hemorrhagic infarction in the distribution of the posterior cerebral artery in 36%.

4.1.4 Types of Brain Edema

Klatzo (1967) distinguishes two types of edema: vasogenic edema and cytotoxic edema (Table 4.1). This distinction continues to be of both theoretical and practical value (cf. Kimelberg 1995a, b; Mendelow et al. 2000).

4.1.4.1 Vasogenic Edema

Blood vessels in the CNS are uniquely restricted in their permeability. Many substances are exchanged between the blood and brain parenchyma at slower rates and the concentrations in CNS at steady state are lower than in other organs (Lee 1982). Dyes as well as proteins, drugs, and microorganisms introduced into the CSF enter the brain freely, while those introduced into the blood stream do not. This limited permeability is attributed to the BBB, a specialized feature of the CNS that restricts the entry of viruses and bacteria, emigration of immune cells, and diffusion in the CNS of drugs and soluble molecules from the systemic compartment.

Intravenously applied Evans blue will bind to serum albumin and permeate the BBB only under pathological conditions. This phenomenon is demonstrated after experimentally induced ischemia of one hemisphere by means of macroscopic observation (Fig. 4.3a) and by means of fluorescence micros-

Table 4.1. Classification of the two types of edema: vasogenic edema and cytotoxic edema

Vascogenic edema	Cytotoxic edema
Intercellular accumulation of fluid associated with volumetric enlargement of the brain	Intracellular accumulation of fluid and (possibly) secondary increase of the brain volume
Perifocal edema (penumbra) surrounding hemorrhages, tumors, abscesses, etc.	Ischemia (generalized or focal), intoxications, especially by triethyltin and cyanide, metabolic diseases, etc.
Injury of endothelial cells (tight junction)	Injury of brain cell membranes in neurons by metabolic or electrophysiologic mechanisms
Increased vascular permeability with leakage of plasma including plasma proteins	Impairment of the cellular Na-K membrane pump
Involvement of the white matter	Involvement of the gray (and white) matter
Enlargement of the extracellular spaces	Hydropic swelling of astrocytes and (mostly irreversibly injured) neurons
Swelling of the perivascular astrocyte foot processes	
Light-microscopic demonstration of plasma proteins in the perivascular neuropil and astrocytes	Light-microscopic demonstration of potassium loss in astrocytes and neurons

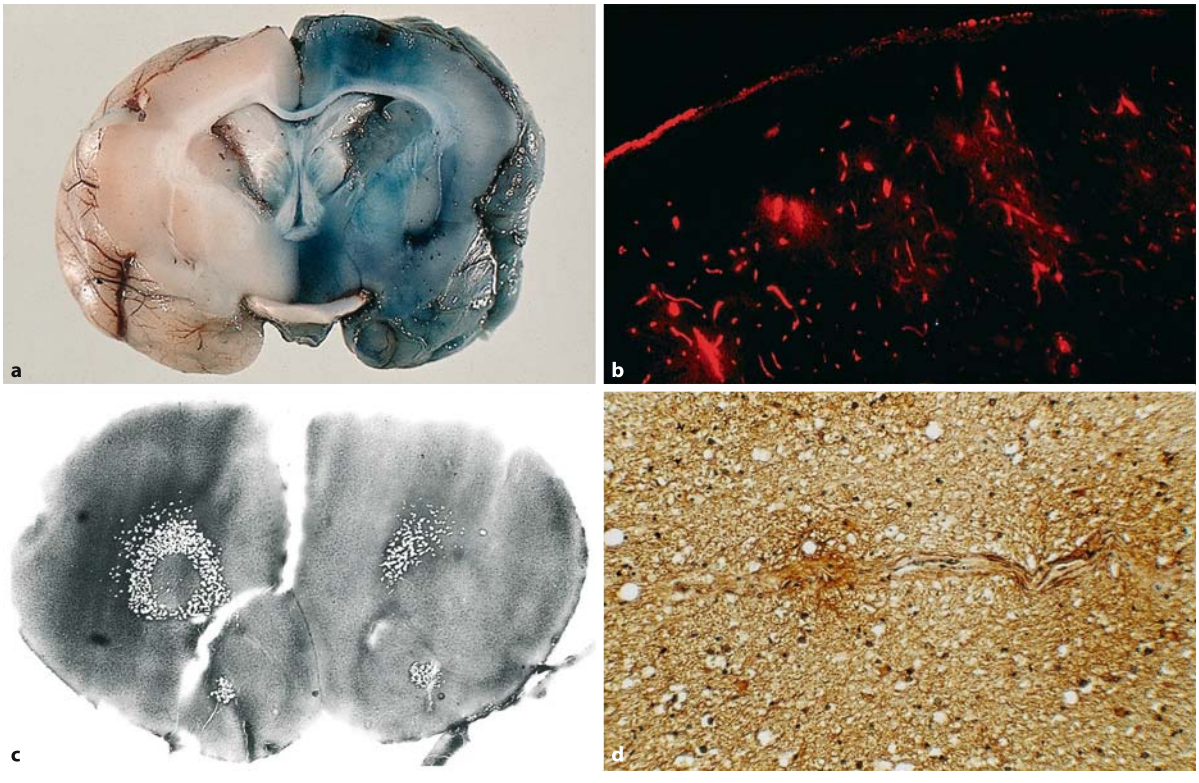

Fig. 4.3a–d. Vasogenic and cytotoxic edema. Experimentally induced ischemia of the right hemisphere in gerbils results in a disruption of the blood–brain barrier (vasogenic edema: **a, b**) and a potassium loss (cytotoxic edema – see. Oehmichen et al. 2000: **c**); **d** human brain expresses extravasated albumin (brown color) exclusively during the very early postmortem interval (see Oehmichen and Gencic 1980a) (**a, b** Evans blue fluorescence; magnification **b** ×100; **c** histochemical demonstration of potassium; **d** albumin reactivity, magnification ×300)

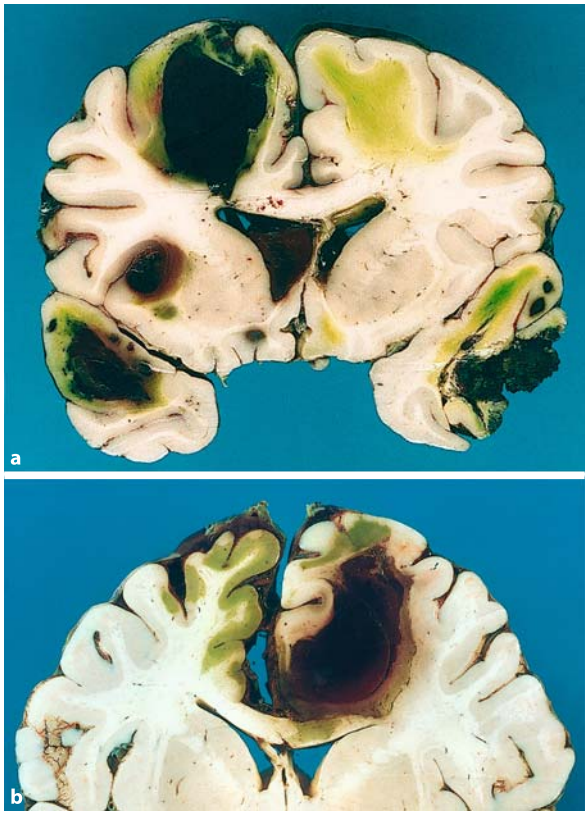

Fig. 4.4a, b. Vasogenic perifocal edema in a case of a traffic accident associated with liver failure and elevated bilirubin level. **a** Massive intracerebral hemorrhages and green-colored edema; **b** focal hemorrhage; perifocal as well as contralateral green-colored edema

copy (Fig. 4.3b). The demonstration of albumin in human brain using immunohistochemistry will only succeed during the very early postmortem interval (Fig. 4.3d) – before a general diffusion of blood serum occurs within the brain parenchyma – as a morphological marker of the diffuse postmortem BBB disturbance. Under experimental conditions an accumulation of plasma proteins in Purkinje cells (Oehmichen and Gencic 1980a, Ikegaya et al. 2004) takes place.

Anatomically the BBB consists of a capillary endothelium containing intercellular tight junctions and specialized enzymes, such as transpeptidases, dehydrogenases, decarboxylases, and monoamine oxidases (Reese and Karnowsky 1967; Brightman and Reese 1969; Lee 1982). The intercellular junctions are most conspicuous near the luminal surface where the cell membranes fuse. A basement membrane in contact with astrocytic foot processes surrounds the endothelial cells. Pericytes are enclosed by an envelope of the perivascular basement membrane, which splits to enclose the pericyte. Brain capillaries are almost totally invested by astrocytic processes. Astrocytes exert inductive actions during development and are thereby largely responsible for the special attributes exhibited by endothelial cells, such as the presence of tight junctions between the cells (Abbott et al. 1992). Astrocytes and microglia both contribute to the formation of the BBB (Prat et al. 2001).

There is an inverse *hemodynamic* relation between ICP and cerebral blood flow (CBF): the higher the ICP, the lower the CBF. If cerebral circulation and circulatory autoregulation are normal, a drop in ICP will induce only a slight increase in CBF until a threshold level of about 8 kPa is attained. CBF is regulated by mechanisms such as compensatory dilatation of small arteries and arterioles.

Patients suffering from acute MBI, intracranial hemorrhage, or hypoxic brain injury need a mean arterial blood pressure above 8 kPa to maintain perfusion. The brain damage in such circumstances is associated with a rise in cerebrovascular resistance due to the vessels‘ spastic reactivity. Baseline ICP levels may even need to be higher in order to drive sufficient blood through the brain tissue (Chan et al. 1992). Should CBF drop below 10 (ml/min)/100 g, potassium levels in the intercellular spaces rise, while intracellular sodium and calcium increase. Cellular edema causes the cells to swell and a calcium influx triggers a series of autodestructive processes.

The BBB can be compromised by the following three mechanisms (see Miller and Ironside 1997):

1. Enhanced vesicular transport and creation of transendothelial channels by perturbation of endothelial plasmalemma, increased pinocytic activity, the activity of free oxygen radicals, or an increase in superoxides. Subarachnoid application of hemoglobin and hemoglobin degradation are known to cause brain edema (Huang et al. 2002).
2. Disconnection of the interendothelial tight junctions, e.g., by substances of very high osmolarity.
3. Structural or biochemical modification of the endothelial membrane that intensifies its permeability.

It has also been known for a long time that the ability of certain substances to pass through the BBB depends on their specific properties:

- Their nature regarding the capacity of the BBB for active transport (Broman and Steinwall 1967)
- Their affinity for carrier molecules (Lajtha 1968).
- Their molecular radius (Thompson 1970).
- Their lipid solubility (Oldendorf 1977).

As shown in detail later, the permeability of the BBB also depends on age. A good example of this is *bilirubin encephalopathy*, which is caused by bilirubin crossing the BBB of certain nuclei during the perinatal period – a feat it is incapable of in later life – and inflicting damage on nerve cells and, to a lesser

degree, on astrocytes (for further information see pp. 452 ff). Thus for bilirubin at least the BBB appears to be less efficient at birth than in children or adults (Haymaker et al. 1961). In MBI with intracerebral hemorrhages and associated elevation of the bilirubin level the perifocal edema can be marked by a green color demonstrating extravascular bilirubin as demonstrated in Fig. 4.4. In senile and mentally disturbed patients, the BBB has been found to have a lower rate of transport, a reduced uptake of glucose and other nutrients, plus a diminished outflow of metabolic wastes (Quadbeck 1967, 1968).

4.1.4.2 Cytotoxic Edema

The movement of water from the vascular compartment to intracellular or interstitial spaces is not regulated *biochemically* by the BBB since hydrostatic and more powerful osmotic gradients enable free water to diffuse passively across capillary membranes. The passage of ions and molecules of various sizes is controlled by lipid-soluble substances in the endothelial wall and by ionic channels and active pumps. The white matter of the brain is 68% water, the gray matter 80% (Adachi and Feigin 1966). A rise in brain water content entails an increase in brain volume, i.e., brain edema.

As a result of energy failure (deprivation of oxygen and glucose), which disables the sodium-potassium membrane ATPase pump system, water accumulation within the cells follows an osmotically obliged response to an increase in intracellular sodium and loss of potassium (Fig. 4.3c). The influx of osmotically drawn water causes swelling of the cell. The energy failure is accompanied by an influx of sodium and chloride and an efflux of hydrogen ions, potassium, and bicarbonate. There is a parallel disturbance of the voltage- and ligand-gated mechanisms that regulate the entry of calcium into the cell that initiates a calcium-mediated destructive sequence. Cytotoxic edema is the result of the action of various cytotoxic agents, e.g., of cyanide or triethyl tin (also see Chaps. 16, 17).

Brain cells can also swell without a concomitant increase in brain volume if fluid shifts from an extracellular to an intracellular space. Although this does not produce an immediate rise in ICP, cellular edema ultimately draws water from the vasculature into the brain, increasing brain volume and precipitating a rise in ICP.

Ischemic edema is a cytotoxic edema whose clinical effects depend on how much and for how long cerebral blood flow is reduced (Bell et al. 1985). Klatzo (1967) showed that the initial cytotoxic edema following permanent occlusion of a major blood vessel causes irreversible ischemic cell damage, resulting in a secondary vasogenic edema when endothelial cells are damaged. Even temporary ischemia with subsequent reperfusion will induce reactive hyperemia and secondary endothelial damage that produces a secondary vasogenic edema (Greenwood 1991).

As a whole, the brain is resistant to pure *hypoxia* (diminished oxygen supply) (pp. 276 ff, see also Miyamoto and Auer 2000), which causes no or only partial breakdown of the BBB and which may be reversible after recovery (Bakay and Lee 1968; Auer 2000). *Anoxia* (complete lack of oxygen), by contrast, results in a rapid rise in BBB permeability that becomes irreversible after just a few minutes (pp. 280 ff). If anoxia acts in combination with complete *ischemia* secondary to ligation of both common carotid and subclavian arteries, the BBB can retain its impermeability for as long as 3 h (Broman 1949; Blank and Kirshner 1977). *Incomplete ischemia*, however, will rapidly and completely break down the BBB (Bakay and Lee 1965).

Kimelberg and colleagues (1997) could demonstrate the potential toxic mechanisms of this type of edema on neurons. They describe a primary cytotoxic effect on astrocytes that induces astrocytic swelling. This swelling in turn leads to the release of excitatory amino acids such as glutamate, whose levels increase in extracellular spaces following the incidence of MBI (Kanthan and Shuaib 1995). A rise in extracellular glutamate levels causes cell death due to an influx of Ca^{2+} via the neurons' activated ionotropic glutamate receptors (Choi and Rothman 1990).

Other authors have offered a somewhat different explanation for the irreversible injury: it may be induced by simultaneously generated free radicals or extravasated plasma components that stimulate the activation of nitric oxide synthase (NOS) in reactive cells. Nitric oxide thus generated may contribute to diffuse degeneration of the white matter (Gotoh et al. 1998). The accumulation of plasma proteins within neurons and microglia in combination with cytochrome-C release by astrocytes can lead to DNA fragmentation and cell death (Matz et al. 2001).

4.1.4.3 Conclusion

Klatzo's (1967) classification of brain edema has proved to be a useful aid in distinguishing between various pathogenetic mechanisms and their sequelae. In experimental and clinical practice however it must be assumed that brain swelling is caused by a combination and/or a temporal overlapping of a number of processes, as described by Kimelberg et al. (1997).

Non-invasive diffusion-weighted (DW) MRI is able of calculating changes in the apparent diffusion coefficient (ADC) of water protons in the brain (Garcia et al. 1995; Chu et al. 2001). A decline in ADC has

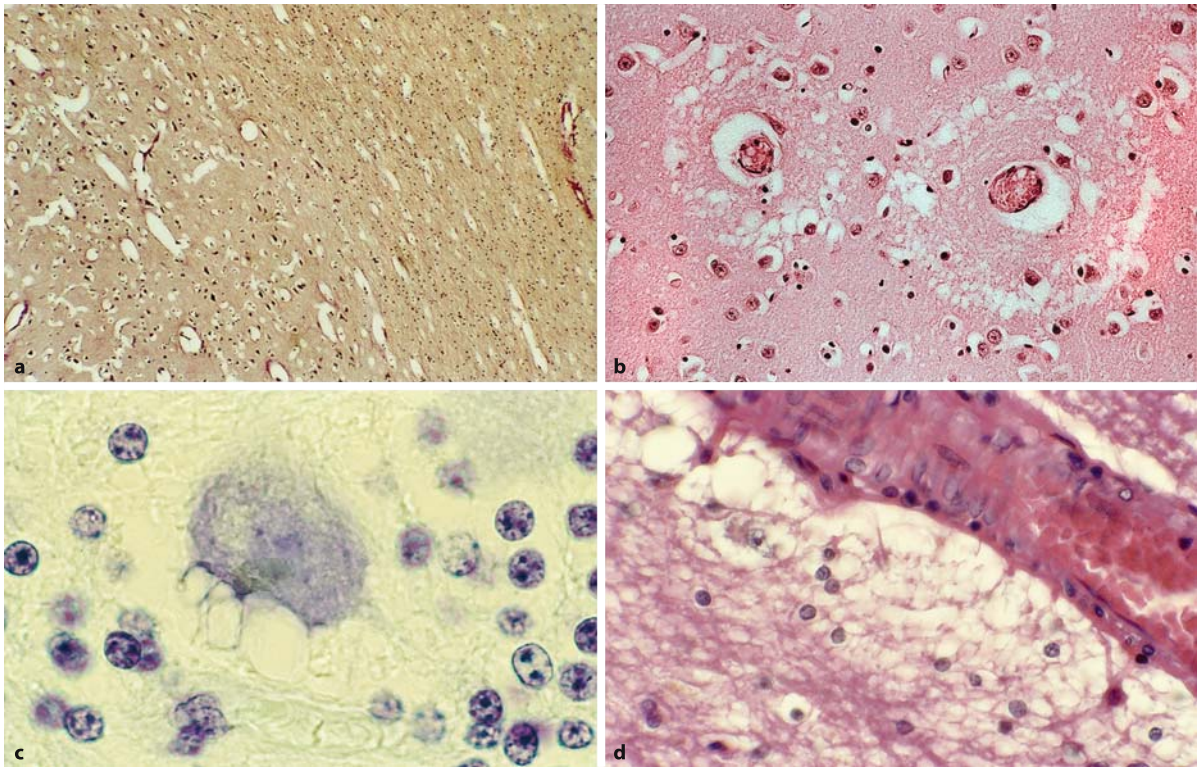

Fig. 4.5a–d. Microscopic features indicative of a preponderate cytotoxic edema. **a, b** Cortical spongious alteration as a result of perineuronal (**c**) and perivascular (**d**) swelling of astrocytic processes (**a** van Gieson stain; **b, d** H&E; **c** Nissl stain; magnification **a** ×100; **b** ×500; **c, d** ×1,000)

been attributed mainly to a reduction of the extracellular space and a rise in intracellular volume, although other contributing factors are possible (Pierpaoli et al. 1996). In this manner cellular (cytotoxic) edema can be differentiated from extracellular (vasogenic) edema and a correlation made with the severity of injury and consequent deficit. Because DW-MRI (see also Mendelow et al. 2000) enables edema types to be determined intra vitam under clinical conditions, current classifications of edema types could be revised in light of new findings. However, we should remember that all edema ultimately arises from the blood. It is the size of the leak in the brain vasculature that gives rise to the artificial distinction between cytotoxic and vasogenic edema, cytotoxic edema being mainly water and vasogenic edema including proteins also derived from the blood.

4.1.5 Neuropathology

Brain swelling caused by edema, congestion or a rise in CSF pressure can obliterate the subarachnoid space, flatten the gyri, reduce ventricular size (Squier 1993, Fig. 4.2), and cause herniation (see pp. 51 ff). At autopsy the white matter seems softer in consistency and paler than normal. The normal, sharp demarcation between gray and white matter is lost, often with thinning of the cortex overlying the zone of white matter edema. The arcuate fibers are spared.

In rare cases of vasogenic edema associated with liver insufficiency combined with elevated bilirubin levels in serum the spread of edema may be characterized by a greenish-yellow color (Fig. 4.4). Under normal conditions bilirubin is not able to permeate the BBB, with one exception: the newborn (see pp. 452 ff).

Cytotoxic edema, which predominates in gray matter, is characterized by astrocytic swelling and the enlargement of perineuronal and perivascular spaces indicative of the swelling of astrocytic foot processes around neurons, capillaries, and arterioles (Fig. 4.5). The hallmarks of *vasogenic edema* include swelling of pericapillary astrocytic processes and of oligodendrocyte cytoplasm, plus the spread of exudate in the extracellular space of white matter (Fig. 4.6). Macroscopically vasogenic edema induces a slight green discoloration of the white matter.

Histologically, edema, vasogenic edema in particular, features extensive cytoplasmic vacuolation in the white matter with status spongiosus where a clear space surrounds small vessels and nuclei (Fig. 4.6). Ultrastructurally, few visible changes are evident in

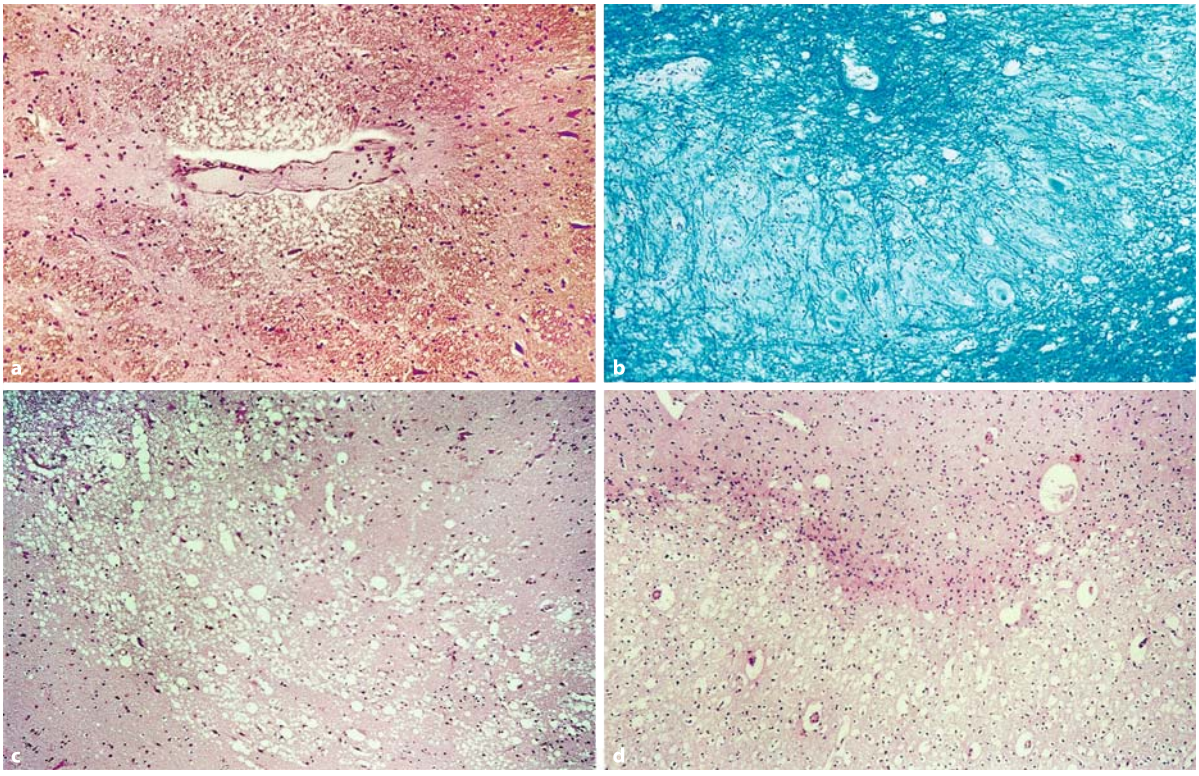

Fig. 4.6a–d. Microscopic features of a predominantly vasogenic edema. **a** The beginning of extravasation is marked by a perivascular spongious structure which (**b, c**) will lead to a widespread diffuse or (**d**) a focal, sharp demarcated edema and beginning necrosis (**a, c, d** H&E, **b** Luxol fast blue; magnification **a, c, d** ×200; **b** ×100)

the cerebral capillaries. The brain parenchyma, in contrast, exhibits swelling of glial processes or dendrites, splits in the myelin laminae and, less often, enlargement of the extracellular space. Vacuolation may be especially prominent in myelinated fiber bundles and constitute the earliest and most consistent elementary edema-induced change. Following immersion fixation, however, these phenomena can often be difficult to distinguish from (postmortem) artifacts.

These phenomena may be associated in the beginning with a leukocyte emigration (Fig. 4.7a) and in the last stage with astrocytic hyperplasia and hypertrophy (Fig. 4.7c, d). Astrocytes and macrophages also ingest extravasated plasma proteins. Myelin sheaths undergo increasing fragmentation and macrophages phagocytose lipid breakdown (Figs. 3.8f, 9.15b, 9.16). *Oligodendrocytes* are much less likely to partake in the alterations of edematous brain tissue.

Most cases of brain edema exhibit a combination of cytotoxic and vasogenic edema. Inhibition of ion pumping or secondary retrograde reaction can cause swelling of neurons. The usual reaction is neuronal shrinkage, commonly combined with swelling of neighboring glial cells, especially of astrocytic processes. Irreversible changes in the myelin sheath are unequivocally manifested by the apposition of macrophage reaction in the form of compound granular cells. Involvement of the white matter by edema of this severe degree coincides with a so-called edematous necrosis (Jacob 1947). The final phase of terminal edema can be marked by cystic alteration or glial scaring.

4.1.6 Space-Occupying Effects

Brain swelling is one of a wide variety of neurological conditions, among them tumors, hemorrhages, and ischemia/hypoxia, that can induce an increase in ICP. A rise in ICP leads not only to compression of the brain, but to diminished CSF volume, shifting, and herniation, as well as to secondary complications such as ischemia and hemorrhage. If not treated, ICP can rapidly progress to death due to brain stem compression secondary to cerebellar or uncal herniation (Meyer 1920). Focal expanding mass lesions must be distinguished from diffuse space-occupying processes.

- *Diffuse brain lesions* such as inflammation, bilateral intracranial hemorrhage, total brain ischemia (cardiac arrest) or intoxication are macroscopically characterized (Fig. 4.2) by a tension of

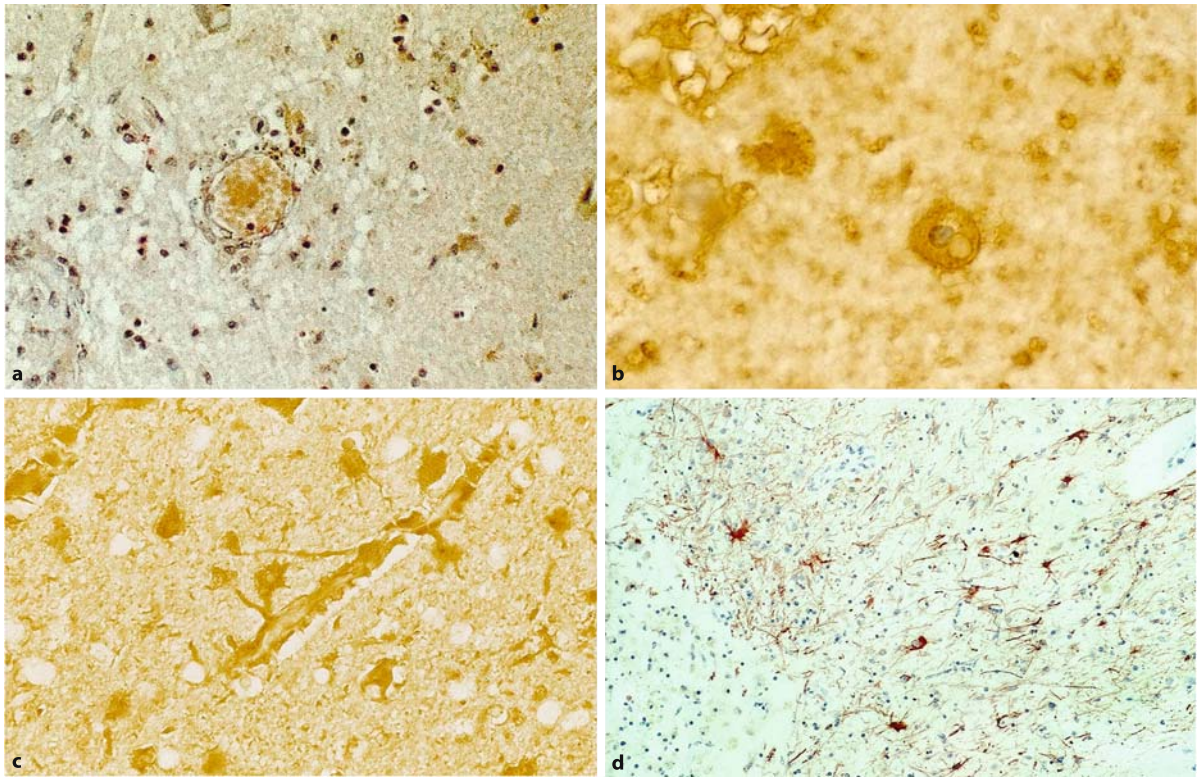

Fig. 4.7a–d. Cell response to edema and beginning edematous necrosis. **a** The first stage is characterized by a leukocyte infiltration, the second stage (**b**) by an increase of macrophages ingesting albumin and red cells in the case of a simultaneous hemorrhage; **c, d** the last stage is marked by an astrocytic reaction whereby the sessile astrocytes contain albumin (**c**), and the astrocytes increased in number upregulate GFAP and vimentin (**d**) (**a** N-AS-DCIAE, **b, c** albumin reactivity, **d** GFAP reactivity; magnification **a, d** ×300, **b** ×1,000, **c** ×500)

the dura, gyral flattening, and by narrow ventricles that are symmetrically compressed. No lateral shift of midline structures is seen, but rather central herniation of the diencephalon (centrencephalic herniation) and by cerebellar tonsillar herniation and compression of the medulla oblongata. Bilateral herniation may occur and various types of herniation result from caudal displacement of the brain parenchyma (for types of herniation, see below).

- *Focal intracranial processes* such as abscess, tumor, infarction or subdural hemorrhage (Fig. 4.8a, b) are also capable of inducing a life-threatening homolateral rise in ICP. Because they allow time for intrinsic compensatory mechanisms to operate, particularly reduced CSF volume, slowly expanding focal lesions are less likely to cause an early increase in ICP and brain shift. However, the distortion and herniation of the brain in such cases can be considerable. Rapidly expanding focal lesions, by contrast, are more likely to produce an immediately elevated ICP. Brain death often supervenes in such cases before much distortion or herniation can occur.

Distortion of the brain results from compressive forces exerted by adjacent structures, which leads to overall expansion of the hemispheres. The dura mater may become so tense as to compress the terminal branches of the cerebral arteries, with consequent *ischemic or hemorrhagic necrosis* of cortical structures (Lindenberg 1955) or impairment of perfusion (Janzer and Friede 1979) accompanied by *perisulcal infarcts*.

Continued expansion of the mass may provoke *contralateral displacement of the midline structures* (see Chap. 7 and Fig. 4.8a). If the contralateral foramen of Monro is obliterated, the contralateral lateral ventricle may become enlarged, triggering a further rise in ICP. A lesion that expands in the frontal lobe may displace the free margin of the anterior part of the falx cerebri (Fig. 4.8a, d). If a lesion expands in the temporal lobe, a disproportionately pronounced shift of the third ventricle will occur (Fig. 4.8a), with upward displacement of the Sylvian fissure and neighboring branches of the middle cerebral artery.

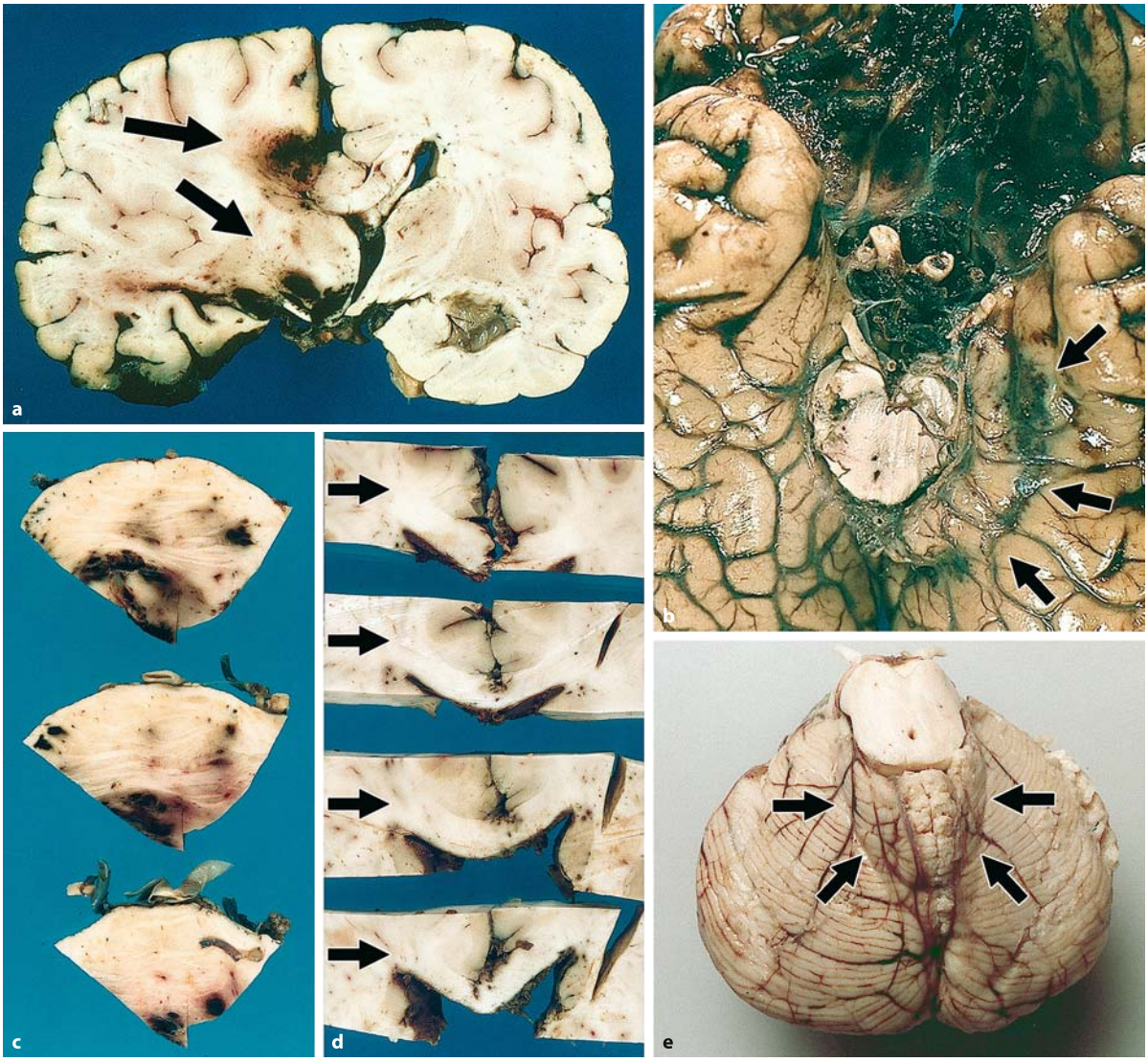

Fig. 4.8a–e. Unilateral intracranial pressures. **a** Subdural hemorrhage on the left parietal lobe leads to a distinct shift (upper arrow) of the midline structures from left to right, which may be associated with a hemorrhage in the left cingulate gyrus and a left midbrain hemorrhage (lower arrow), **b** a hippocampal hemorrhage (arrows), as well as (**c**) a pontine hemorrhage; **d** a hemorrhage in the upper frontal lobe may lead to a notch, a hemorrhage or a softening of the corpus callosum; **e** a rare tentorial displacement caused by an infratentorial space-occupying process is demonstrated by notches on the upper cerebellar surface (arrows)

4.1.7 Herniation

The ultimate result of the space-occupying process is development of lateral and then downward herniation, visible at several loci:

1. Falx cerebri (cingulate, or subfalcine herniation).
2. Tentorium cerebelli (lateral, or uncal herniation).
3. Thalamus/hypothalamus (central, or diencephalic herniation) which may result in downward displacement and hemorrhage in the midbrain and pontine tegmentum.
4. Foramen magnum (tonsillar herniation).

4.1.7.1 Uncal Herniation

A bilateral expanding supratentorial mass can cause herniation-induced notches as well as hemorrhages of the uncal area. This in turn exerts downward pressure on the medial part of the parahippocampal gyrus toward and through the tentorial incisura (Figs. 4.8b, 4.9). The clinical and morphological se-

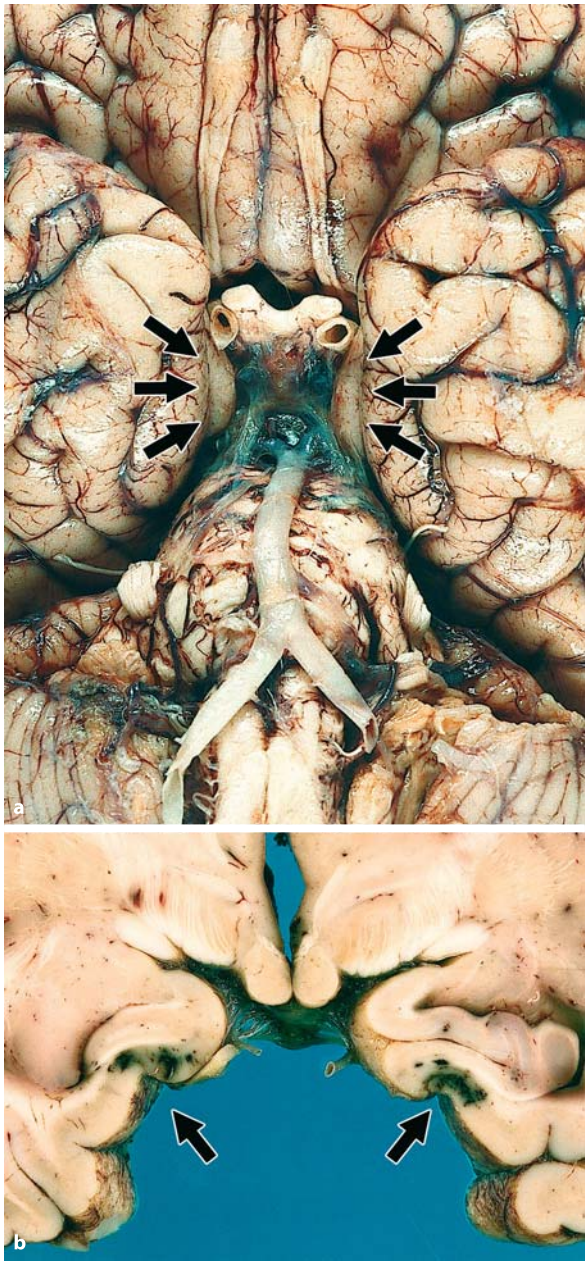

Fig. 4.9a, b. Symmetrical (bilateral) supratentorial pressure causes bilateral uncal herniation as demonstrated by notches (**a** arrows); these notches may be marked by a hemorrhage and tissue necrosis (**b** arrows)

quelae of uncal herniation depend on the magnitude of the supratentorial pressure and on anatomical variations in the size of the tentorial notch, position of the brain stem within the notch, position of the oculomotor or third nerve, and the inter-oculomotor nerve angle. They also depend on the structure and course of the posterior cerebral artery, known to play a role in herniation syndromes (Adler and Milhorat 2002).

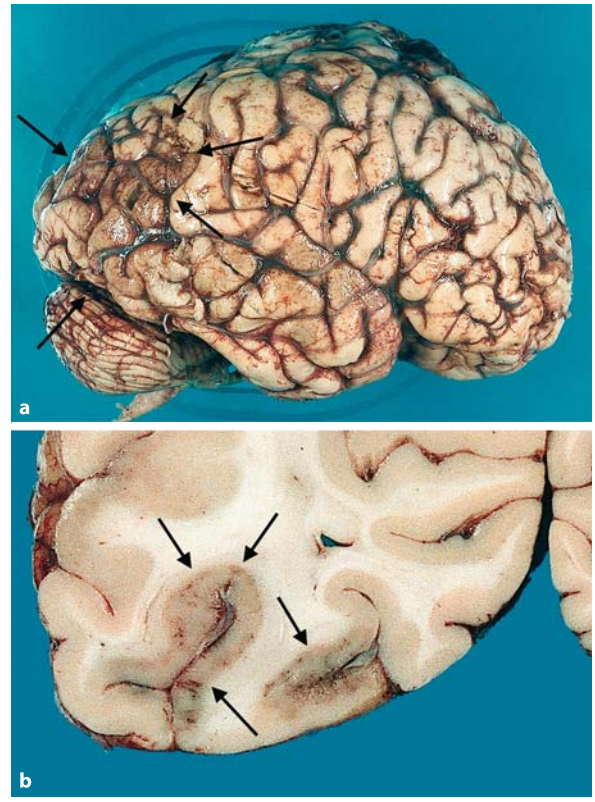

Fig. 4.10a, b. Supratentorial pressure induced compression of the basal arteries, especially of the posterior cerebral artery, which leads to a hemorrhagic infarct of the occipital lobe (arrows)

Herniation of the parahippocampal gyrus (Fig. 4.9) creates narrowing of the midbrain along its transverse axis and compression of the aqueduct. This pushes – in the case of a unilateral expanding mass – the contralateral cerebral peduncle against the opposite free tentorial edge (Fig. 4.8b), pinning the ipsilateral oculomotor nerve between the petroclinoid ligament or free edge of the tentorium and the posterior cerebral artery. The lesion of the ipsilateral oculomotor nerve is associated clinically with ptosis and dilatation of the ipsilateral pupil, which becomes unresponsive to light.

The elevated ICP produces a wedge of hemorrhagic necrosis along the parahippocampal gyrus groove (so-called pressure necrosis, to be differentiated from "herniation contusion" – see Figs. 4.8b, 4.9b). Pressure necrosis can result from an ICP exceeding 5.4 kPa (see Adams and Graham 1976). It is analogous to necrosis due to brain retractor pressure in neurosurgery. Clinically, uncal herniation is accompanied by an abrupt worsening of the patient's neurological status, with loss of consciousness and onset of decerebrate rigidity, both due to midbrain impairment caused by pressure coming from above.

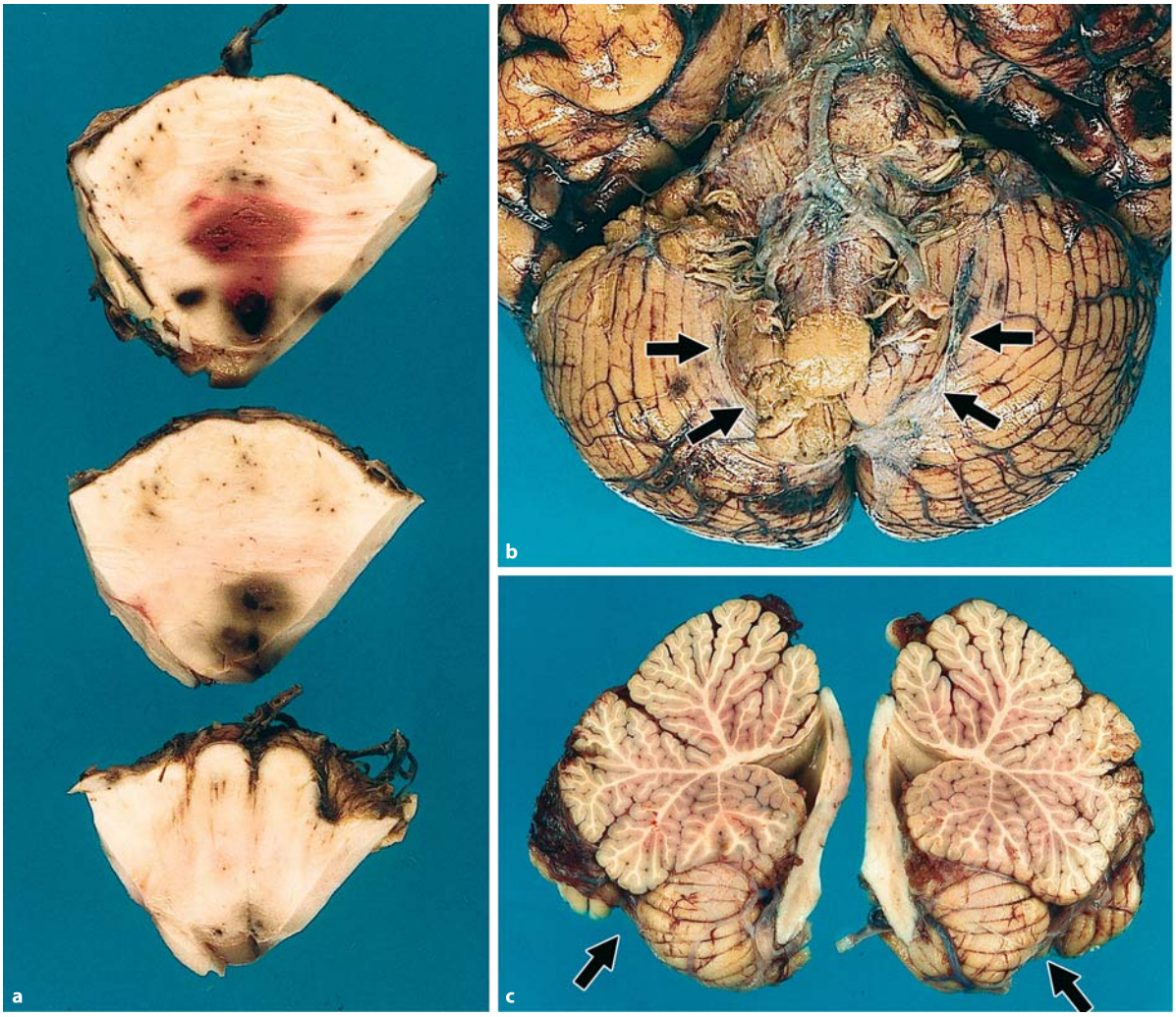

Fig. 4.11a–c. Herniation-associated pontine hemorrhage as caused by downward axial displacement (**a**) of the dorsal brain stem; displacement of the cerebellar tonsils (**b, c**) through the foramen magnum which is caused by supratentorial and infratentorial displacement (pressure marks – see arrows)

Compression of arteries can also cause secondary necrosis: if the anterior choroidal artery is occluded, the result can be infarction of the medial part of the globus pallidus; posterior cerebral artery occlusion can cause hemorrhagic infarction of the thalamus, of the medial and inferior surfaces of the cortex of the occipital lobe (Figs. 4.10, 9.24), and of the temporal lobe including the hippocampus.

4.1.7.2 Cingulate Herniation

Herniation of the ipsilateral cingulate gyrus under the free edge of the falx results from the unilateral growth of a mass in the frontal or parietal lobe and causes selective displacement of the pericallosal arteries away from the midline (Fig. 4.8a, d). Should this compromise circulation through the pericallosal arteries, the parietal parasagittal cortex can become infarcted, which is expressed clinically as weakness or sensory loss in one or both legs.

4.1.7.3 Central Transtentorial Herniation

A frontal or parietal mass lesion can induce downward axial displacement of the diencephalon (Fig. 4.8a) and rostral brain stem (Figs. 4.8c, 4.11a). The consequent symmetrical herniation of both parahippocampal gyri (Fig. 4.9a, b) may be manifested clinically by bilateral ptosis and failure of upward gaze. The final clinical result is loss of consciousness, decerebrate rigidity, and bilateral dilatation of the pupils with loss of the pupillary light reflex. The blood pressure rises due to increased sympathetic activity.

Hemorrhage or *necrosis* of the *midbrain and/or pons* are the possible sequelae of supratentorial space-occupying processes located adjacent to the midline (Figs. 4.8a, 4.11a, 9.23). These lesions are caused by caudal displacement and anterior-posterior elongation of the rostral brain stem and by side-to-side compression by the tentorial hernia, coupled with relative immobility of the basilar artery. Progressive displacement stretches and narrows the central perforating branches of the basilar artery which supply the rostral brain stem, causing spasm, infarction or hemorrhage.

An early complication of expanding masses in the posterior cranial fossa is *displacement of the cerebellar tonsils* through the foramen magnum (Figs. 4.2d, 4.11b, c). This may also be caused, however, by lesions occupying the supratentorial space. Morphologically, the tips of the tonsils display hemorrhagic necrosis and grooving of the ventral surface of the medulla where it impinges on the anterior border of the foramen magnum. Clinically these changes give rise to apnea, which can occur while the victim is still conscious. Among the other common neurological deficits are decerebrate rigidity and impairment of brain stem reflexes.

4.1.7.4 Upward Tentorial Displacement

Upward tentorial displacement (Fig. 4.8e) is produced by enlargement of an infratentorial mass in the posterior cranial fossa. Both the fourth ventricle and aqueduct become compressed and displaced contralaterally. There is upward herniation of the superior surface of the cerebellum, which is distinguished clinically by the abrupt manifestation of bilateral extensor rigidity and loss of pupillary light response.

4.1.8 Forensic Implications

A number of clinical complications associated with brain swelling, brain edema, and BBB can arise during diagnostic and therapeutic interventions in the CNS carried out by physicians or nursing personnel. Since the sequelae are foreseeable – and in most cases avoidable – these complications will be dealt with briefly in the following.

- In patients with elevated ICP, a lumbar puncture of the CSF can give rise to herniation. Papilledema, though not always associated with ICP, must be excluded before every CSF puncture. Should other clinical signs of high ICP be present, a CT examination must be carried out prior to puncture.
- Pharmacotherapy must not be performed without knowing whether the agent can permeate the BBB and affect the CNS. This is especially true of substances such as antibiotics or cytostatics that are intended to reach and act upon the CNS. Other substances are not intended to reach the CNS because they are toxic there; thus, the contraindication for intrathecal application of vincristine (see p. 359).
- If CNS edema already exists, the BBB may be (pathologically) permeable to substances not intended to reach the CNS, some of which can then have a toxic effect. A MBI-induced perifocal edema, for example that arises in the context of polytrauma-induced shock, can produce greenish discoloration of the perifocal edema as a consequence of an accompanying hepatic insufficiency, which can have an additional neurotoxicologic effect on the neurons.
- The status of the BBB may well be age dependent, its postnatal status differing from that of adults. Blood group incompatibility between mother and child during pregnancy or after birth can cause bilirubin encephalopathy (see pp. 452 ff). The BBB appears to be less permeable in the elderly.
- A cytotoxic effect can be mediated by alcohol in MBIs with consequent loss of neurons. Alcohol lowers cerebral perfusion pressure (CBF) and depresses ventilation. It diminishes respiratory drive in response to elevated $PaCO_2$ levels. Ethanol-induced respiratory depression and hypotension can increase the morbidity and mortality associated with brain injury. The theoretical considerations of Kimelberg et al. (1997) appear to contradict these empirical findings, arguing rather that alcohol inhibits both the excitotoxin receptor function of neurons (Simson et al. 1991) and the influx of Ca^{2+} via NMDA receptor ion channels.

4.2 Hydrocephalus

4.2.1 Classification and Pathogenesis

Hydrocephalus is characterized by abnormal accumulation of fluid within CSF spaces, i.e., within the cerebral ventricles and subarachnoid space. By this time, there is atrophy of the brain parenchyma and additional ventricular enlargement. CSF is formed by the choroid plexus at a rate that remains unchanged within a wide range of ICP values: 15–25 ml/h will avert a long-lasting imbalance between its formation and absorption. Elevated CSF pressure is associated

Table 4.2. Causes of obstructive hydrocephalus. Source: Garton and Piatt 2004

Prematurity (posthemorrhagic hydrocephalus)
Myelomeningocele
Other congenital or developmental conditions affecting the brain
Dandy–Walker malformation
Arachnoid cysts
Interhemispheric cysts
Aqueductal stenosis
Encephalocele
Brain tumor
Subarachnoid hemorrhage
Mechanical brain injury
Aneurysmal subarachnoid hemorrhage
Congenital or developmental conditions affecting the skull
Crouzon's and Pfeiffer's syndromes
Achondroplasia
Meningitis

only with acute or obstructive hydrocephalus (see below).

The subarachnoid space and ventricular system are connected via the foramina of Luschka and Magendie in the basal cisterns. CSF is absorbed by the arachnoid villi, which do not fully develop until adolescence or young adulthood (Grassman and Potts 1974). In fetuses and infants, CSF is absorbed mainly through nerve roots and periventricular and arachnoid veins.

External hydrocephalus ex vacuo involves diffuse loss of gray matter that gives rise to external atrophy, with dilatation of the subarachnoid space (Fig. 31.6a, b). Diffuse loss of white matter can cause expansion of the ventricular system, the so-called *internal hydrocephalus ex vacuo* (Fig. 31.6c). The causes of the gray and white tissue damage may vary, but CSF kinetics and anatomic pathways are important considerations (see also pp. 482 f).

A distinction is made between *normal pressure hydrocephalus* of still unknown etiology (Adams et al. 1965; Hurley et al. 1999), *low pressure hydrocephalus*, and *high pressure hydrocephalus*. The latter is caused by accumulation of fluid secondary to elevated CSF production (*hypersecretory hydrocephalus*) or insufficient resorption (*malabsorptive hydrocephalus* or *communicating hydrocephalus*). Distension of the ventricles results from pressure-induced fluid build up in the cerebral ventricles (reversible) or from pressure-induced (irreversible) atrophy as a result of parenchymal loss. Fluid may also enter the periventricular tissue (trans-ependymal resorption of CSF seen on neuroimaging). Normal pressure hydrocephalus can feature repeated brief episodes of elevated ICP, possibly in the form of an *intermittent pressure* or *occult hydrocephalus*.

Normal pressure hydrocephalus can also result from a *hydrocephalus ex vacuo*, which is associated with primary ventricular system enlargement and white matter destruction. It is often found in victims of severe brain injury, in alcoholics, and vascular disease patients with multi-infarct dementia or other types of progressive degenerative brain disorders, especially age-dependent dementia (Miller and Ironside 1997). *Hydrocephalus ex vacuo* can also be caused by long-lasting generalized brain edema with high ICP.

The *causes of obstructive hydrocephalus* are MBI, subarachnoid hemorrhage, meningitis and arachnoid fibrosis, Arnold-Chiari malformation, aqueductal stenosis (for complete list see Table 4.2, for review see Garton and Piatt 2004). The latter can be either congenital due to atresia or acquired due to inflammation, compression or reactive gliosis, hemorrhages or tumor. The responsible congenital abnormalities consist in most cases of replacement of the aqueduct lumen by numerous random, narrow channels or ependymal nests.

4.2.2 Neuropathology

External hydrocephalus, whatever the causes are, exhibits dilation of the subarachnoid space, with no increase in collagenous fibers or cellular elements, but an increase in CSF. The causative encephaloclastic disease may be diagnosed on the basis of other phenomena, such as liver cirrhosis in alcoholics, or loss of neurons in the presence of plaques and tangles in senile dementia or Alzheimer's disease.

Typical macroscopic features of *internal hydrocephalus* include an enlarged ventricular system (Fig. 4.12a, b) (Weller and Shulman 1972), interstitial edema, disruption of the ependymal cells lining the ventricle, and axonal and myelin destruction in the periventricular white matter (Del Bigio 2004). Secondary changes in neurons reflect compensation to the stress or ultimately the disconnection. Proliferating astrocytes and/or gliosis (Fig. 4.12c) replace in part the interrupted ependymal cell line. These glial nodules appear granular or like small tumors (Fig. 4.12c) upon macroscopic inspection of the inner surface of the ventricles (Fig. 4.12b). There is also a partial reestablishment of flattened ependymal

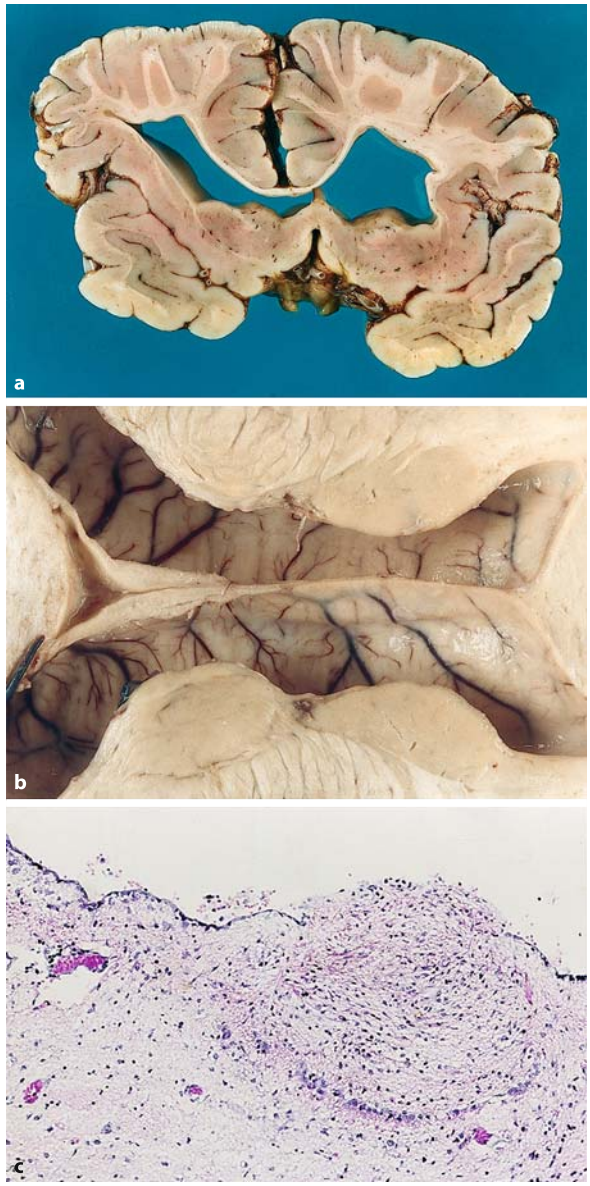

Fig. 4.12a–c. Internal hydrocephalus. **a** Expanding ventricular system associated with an atrophy of white matter; **b** the ventricular surface is commonly marked by a granular surface structure, which (**c**) microscopically is characterized by multiple glial nodules which replace lost segments of the ependymal layer (H&E, magnification ×200)

cells, and a decline in the number of axons with parallel proliferation of glial fibers in the periventricular white matter. In chronic hydrocephalus with high pressure hydrocephalus, a flattening of the gyral crests is seen (Fig. 4.13a); in addition a small reactive glial zone around the ventricular system (Fig. 4.13b) may develop which can be separated from the intact white matter at autopsy (Fig. 4.13c).

4.2.3 Clinical Features

In adults, the clinical symptoms of hydrocephalus are non-specific; in infants and children they may be specific (see Chap. 21 – pp. 482 f) and depend on the causes and the time course of the hydrocephalus. The salient symptoms comprise psychopathological alterations such as dementia, memory disturbances, and loss of orientation, culminating in the most severe cases in loss of consciousness.

The first step in diagnosing hydrocephalus involves the use of imaging techniques, MRI and CCT, to establish its presence. The second step seeks to determine the underlying cause, and again employs as its methods of choice MRI and CCT, in combination with clinico-chemical (Fishman 1980) and cytological analysis of the CSF itself (Oehmichen 1976a).

4.3 Cell and Tissue Decay

"Necrosis" (for review see Lindenberg 1982) is commonly used to designate the death of tissue components, including that of cells and their processes in a defined area of blood and oxygen supply. After a severe episode of ischemia, MBI or epilepsy, it is typical to find necrotic cell death within the injury core. In addition, a substantial number of neurons in regions surrounding the injury core have been observed to die via the programmed cell death pathways due to secondary effects derived from the various types of insults (Liou et al. 2003). "Apoptosis" (for review see Vermes et al. 1998) is applied to the selective (programmed) death of one or more individual cells. Apoptosis is the more active and physiological form of cell death. In necrotic cell death, a stimulus such as ischemia, hemorrhage, mechanical or chemical damage alters cell homeostasis thus causing cell death, whereas in apoptosis an internal death stimulus triggers the innate cellular suicide program, the latter (not the stimulus itself) mediating the cellular demise (Beal 1995). In the following, the various pathogeneses and mechanisms of these types of cell death will be described, along with their different morphologies and underlying molecular factors.

4.3.1 Injury-Induced Cell Death: Necrosis

The most common *cause of necrosis* is ischemia. Other causes include mechanical injury (contusion

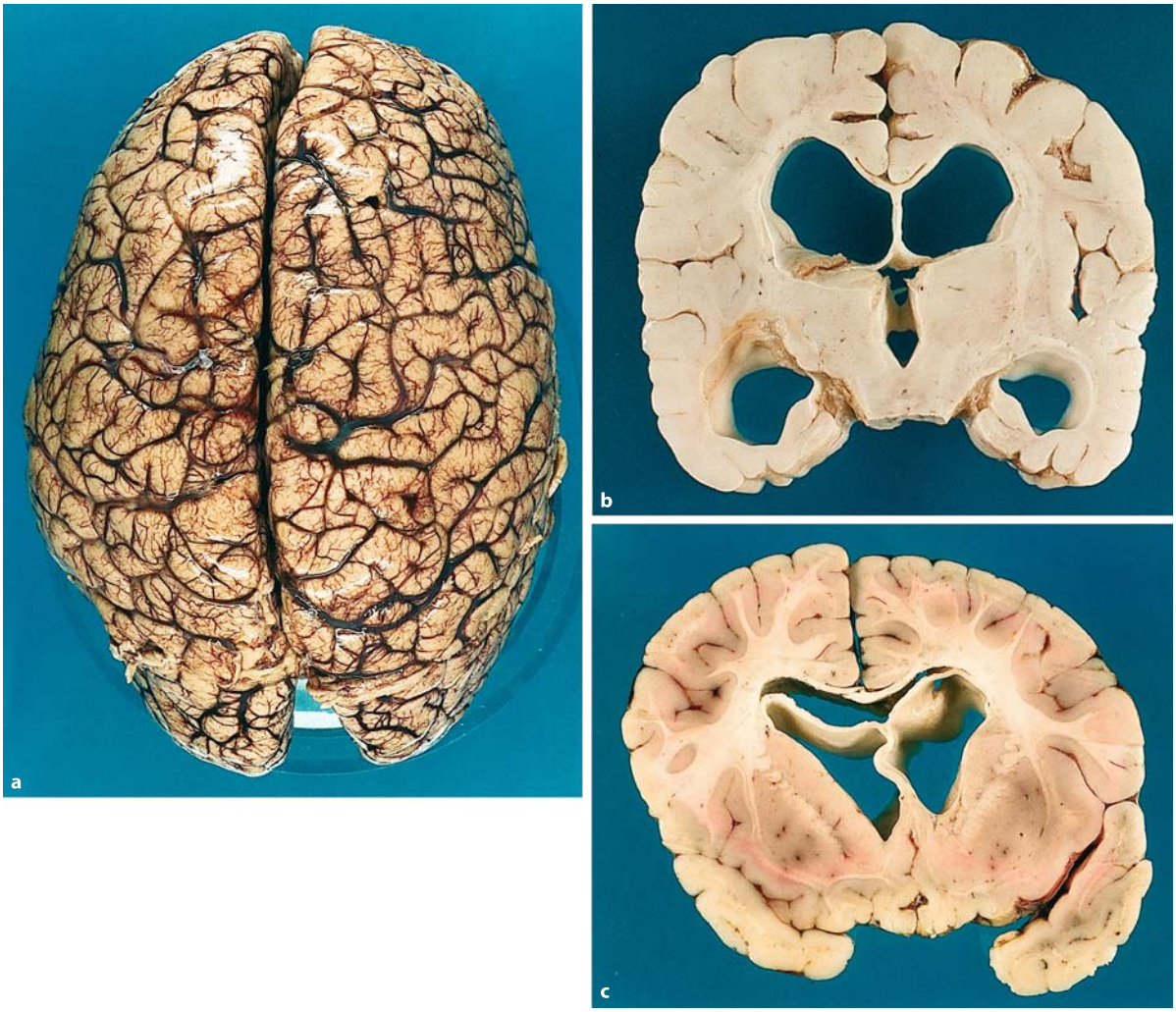

Fig. 4.13a–c. High pressure hydrocephalus. **a** Increased brain volume and flattened gyral crests; **b** extreme periventricular gliosis with atrophy of the caudate nuclei; **c** dissociation of the glial surface membrane of the ventricular system

necrosis), toxic agents (formic acid in methyl alcohol), heat (thermocoagulation), freezing (cryosurgery), infections (poliovirus), and overexposure to ultrasound. Each case, however, involves the action of additional factors independent of the type of primary traumatic event. Chief among these factors are free radicals and nitric oxide (NO). Reaction products of NO and O_2, including potent oxidizing molecules such as peroxynitrite and nitrogen dioxide, can be more toxic than NO itself.

The type of brain necrosis depends in large part on the duration of local circulatory arrest:

1. Transient ischemia only destroys neurons and oligodendrocytes, inducing *incomplete necrosis* or selective neuronal necrosis (Scholz 1953).
2. Prolonged ischemia, termed "infarction," gives rise to complete necrosis of all tissue components.

4.3.1.1 Incomplete Necrosis

Morphologically cell necrosis, especially neuronal necrosis, features irreversible changes of the cytoplasm (condensation, hydropic swelling, intense eosinophilia, loss of structure, homogenization) (Fig. 4.14) and of the nucleus (pyknosis, karyolysis, karyorrhexis) (Majno and Joris 1995).

Time Course. The data vary on how soon after the onset of ischemia the first microscopic neuronal changes become evident. Some authors report an interval of 30 min (Jacob and Pyrkosch 1951), others 14/15 h (Müller 1930). The data may differ in part due to prolongation of the necrotic process for as long after death as brain temperature remains favorable (Lindenberg 1982).

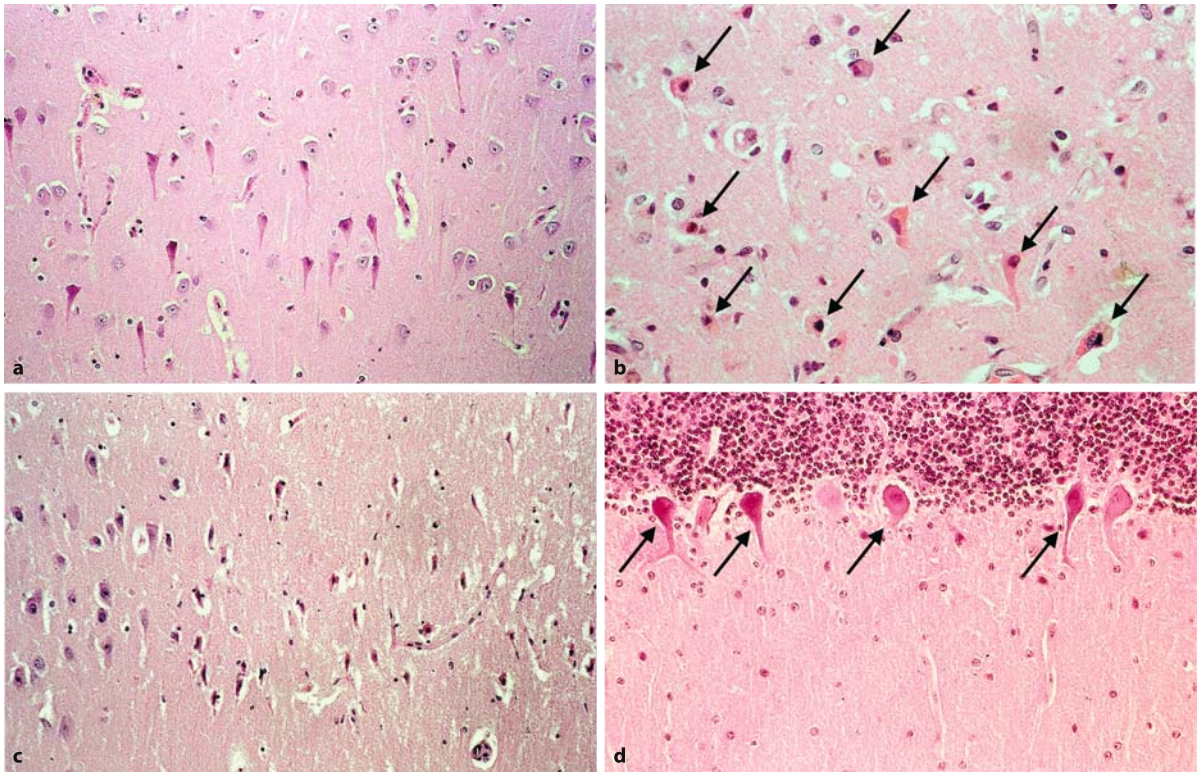

Fig. 4.14a–d. Neuronal necrosis caused by ischemia. **a, b** Eosinophilic cortical nerve cells characterized by (**b**) a pyknotic nucleus and an intense eosinophilia of the cytoplasm (arrows); **c** time-dependent reduction of the nerve cells as seen in the CA1-segment of the hippocampus; **d** ischemic neuronal necrosis in the Purkinje cell layer of the cerebellum (ischemic neurons, see arrows) (**a–d** H&E; magnification **a, c** ×200, **b, d** ×300)

Inflammation. Necrotic tissue and cells always attract neutrophils, macrophages, and sometimes lymphocytes. The tissue can activate the scavenger function of resting microglia for elimination of myelin as well as cell debris. Hsu et al. (1995) have published an overview of the association between cell-mediated injury and cellular reactions. *Lipid inflammatory mediators* are crucial for cellular interactions in sterile inflammation. Among the mediators involved in inflammatory processes as a reaction to cell necrosis are thromboxane A_2, leukotrienes, and prostaglandins, collectively termed eicosanoids (Hsu et al. 1995).

4.3.1.2 Tissue Necrosis: Infarction

Prolonged ischemia-induced tissue necrosis is termed "infarction" or liquefactive necrosis. The infarcted area displays macroscopically evident pallor on H&E, Nissl, and myelin preparations within 3–5 h as an indication of acidosis. A narrow halo of even greater pallor surrounds the necrotic area (Fig. 4.20a). Around the necrotic area, vessels are distended and release fluid into the infarcted tissue and surrounding tissue by way of a vascular network (perifocal edema).

Neurons become thorny and severely shrunken within 12–36 h, with darkly staining incrustation of their pericellular structures. A survival time of 12 h leads to homogenization of the cytoplasm and nuclear and cytoplasmic pallor. Between 36 h and 48 h, the neurons disappear except for the nuclei (see Fig. 4.14c).

Within 1–2 h the necrotic tissue is characterized by an emigration of neutrophil leukocytes (Fig. 4.15a, b). Within 18 h the necrotic area exhibits proliferation and extensive activation of microglial cells (Fig. 4.15c–f). Along the infarct margin, macrophage numbers increase. Hypertrophic astrocytes appear along the border zone within the brain parenchyma after 4–6 days (Fig. 4.16). The infarct liquefies at its center and macrophages phagocytose the debris. The final stage of cortical liquefactive necrosis is termed "laminar necrosis" (Fig. 4.17a–c) associated with intense gliosis during the final phase (Fig. 4.17d). The final stage of ischemic involvement of the basal ganglia and the thalamic nuclei is a cystic necrosis (Fig. 4.18). Ischemic damage of the hippocampal area is characterized by a segmental loss of neurons in the hippocampal cortex (Fig. 4.19a, b) associated

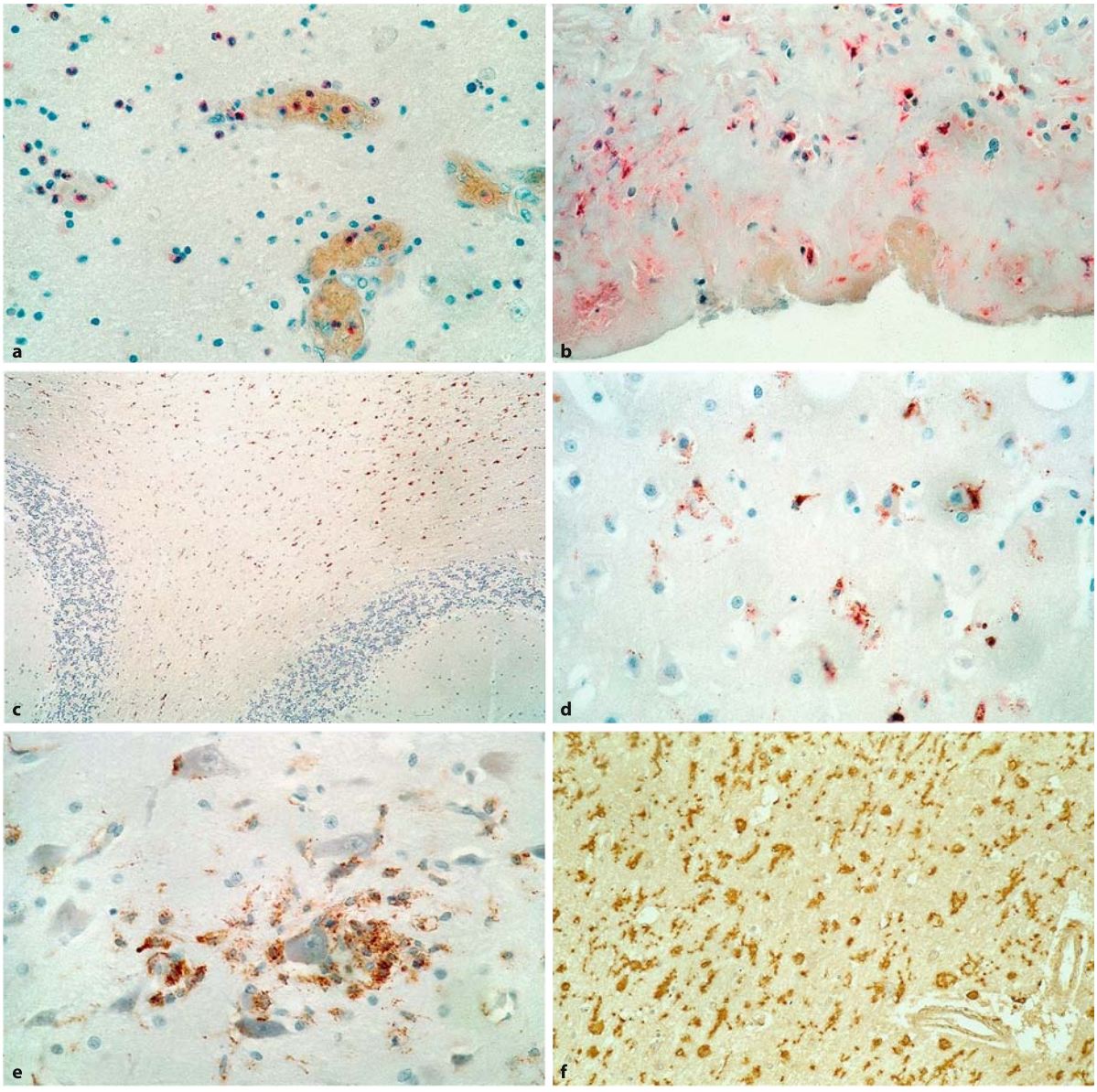

Fig. 4.15a–f. Cytologic sequelae of regional necrosis. **a, b** An early leukocyte reaction is demonstrated by means of N-AS-DCIAE; **c–e** CD68 reactive macrophages in the cortex as well as (**f**) in the white matter increase (magnification **c** ×100; **a, b, d, f** ×500, **e** ×1,000)

with compensatory (early) microglial activation (Fig. 4.19c) and secondary gliosis (Fig. 4.19d).

Another type of brain tissue necrosis is the rare phenomenon "*persistent coagulative necrosis*" first described by Spielmeyer (1922) (Fig. 4.20), which affects cell tissue elements. Within gray matter the outlines of dead neurons are recognizable, their cytoplasm is intensely eosinophilic and usually contains numerous, often large, vacuoles, and the nucleus stains poorly with hematoxylin. This picture, which is recognizable within the first 4–6 h, is followed by decreasing stainability of nucleus and cytoplasm until a barely recognizable ghost cell is all that remains. Acute and enduring deprivation of blood supply causes necrosis of cells and tissue components, the lesion remaining in a state of "coagulation" for a prolonged period. The cells appear only as shadows and the necrotic tissue persists within the brain as a foreign body and sometimes becomes encapsulated in mesenchymal tissue. The pathogenesis of this rare type of necrosis is still unknown (Escolá and Hager 1963; Cervos-Navarro and Ferszt 1977).

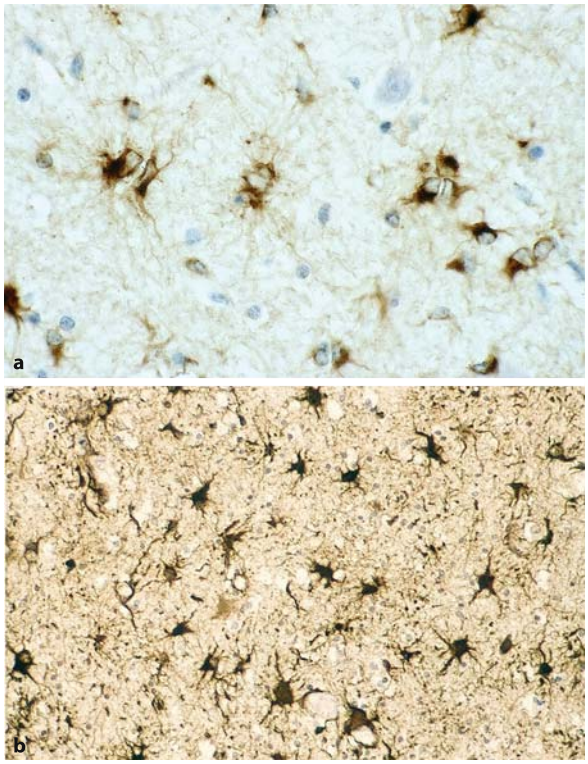

Fig. 4.16a, b. Activated astrocytes along the border zone of necrosis. **a** Astrocytic reaction in the cortex and (**b**) in the white matter (GFAP reactivity; magnification **a** ×1,000, **b** ×500)

4.3.2 Gene-Regulated Cell Death: Apoptosis

Apoptosis can be differentiated from necrosis based on differences in their pathogenesis, cell reactions, and morphologic features. Apoptosis is the programmed death of a cell as regulated by specific death genes (for review see Clarke 1998). It initiates a delayed secondary death of neurons in response to environmental changes, deficient metabolic and trophic supply, and changed gene transcription. During apoptosis, the integrity of mitochondria is compromised and various pro-apoptotic proteins are released into the cytoplasm. This results in activation of caspases, proteases that orchestrate the death of the cell (Waterhouse 2003). Apoptosis requires active protein synthesis (McIntosh et al. 1998; Raghupathi et al. 2000). A single cell can undergo a switch between the two types of cell death based on several pathways (McConkey 1998; Fiskum et al. 1999; see also Leist et al. 1990) (for further informations, see p. 620).

The characteristic *morphology* of apoptosis exhibits cleavage of the internucleosomal chromatin that can be identified in situ using the terminal

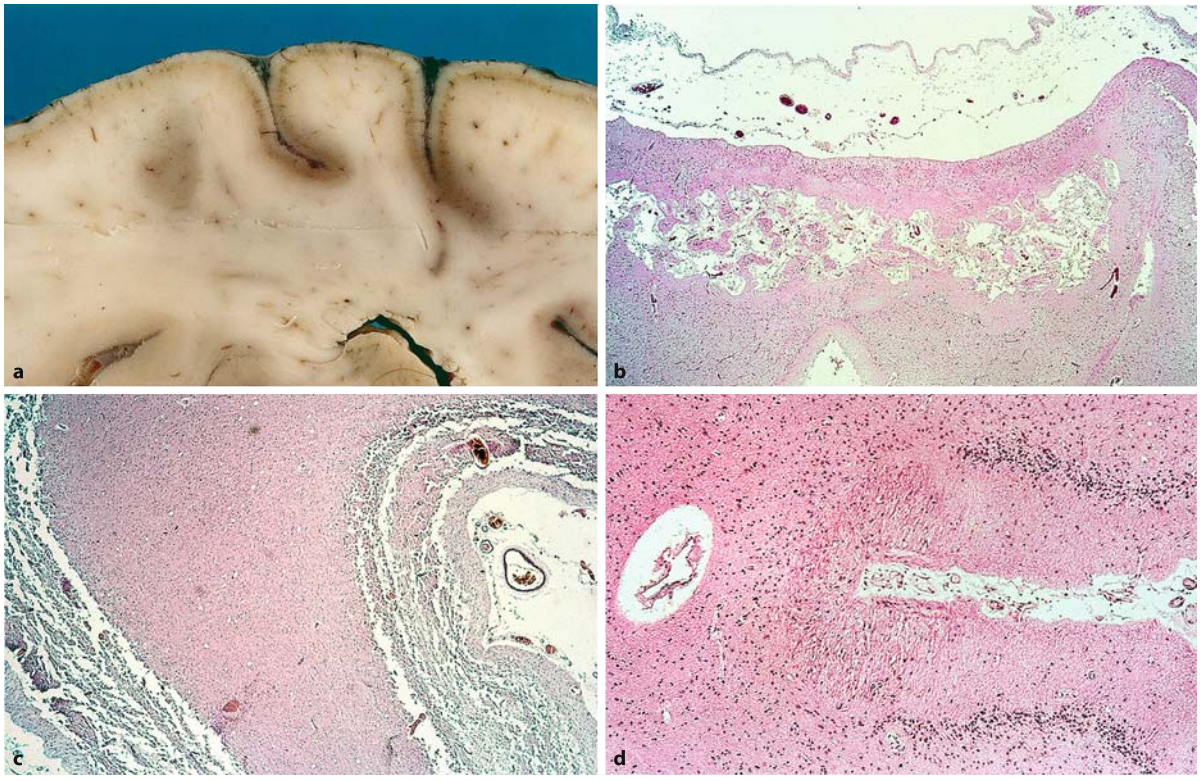

Fig. 4.17a–d. Cortical necrosis, i.e., laminated necrosis. **a** Macroscopy of long-time survival of cortical necrosis which is associated with a complete cortical (cystic) necrosis (**b**) while in the cerebellum the necrosis (**c**) is totally replaced (**d**) by a distinct gliosis (**b–d** H&E; magnification **b, c** ×100; **d** ×200)

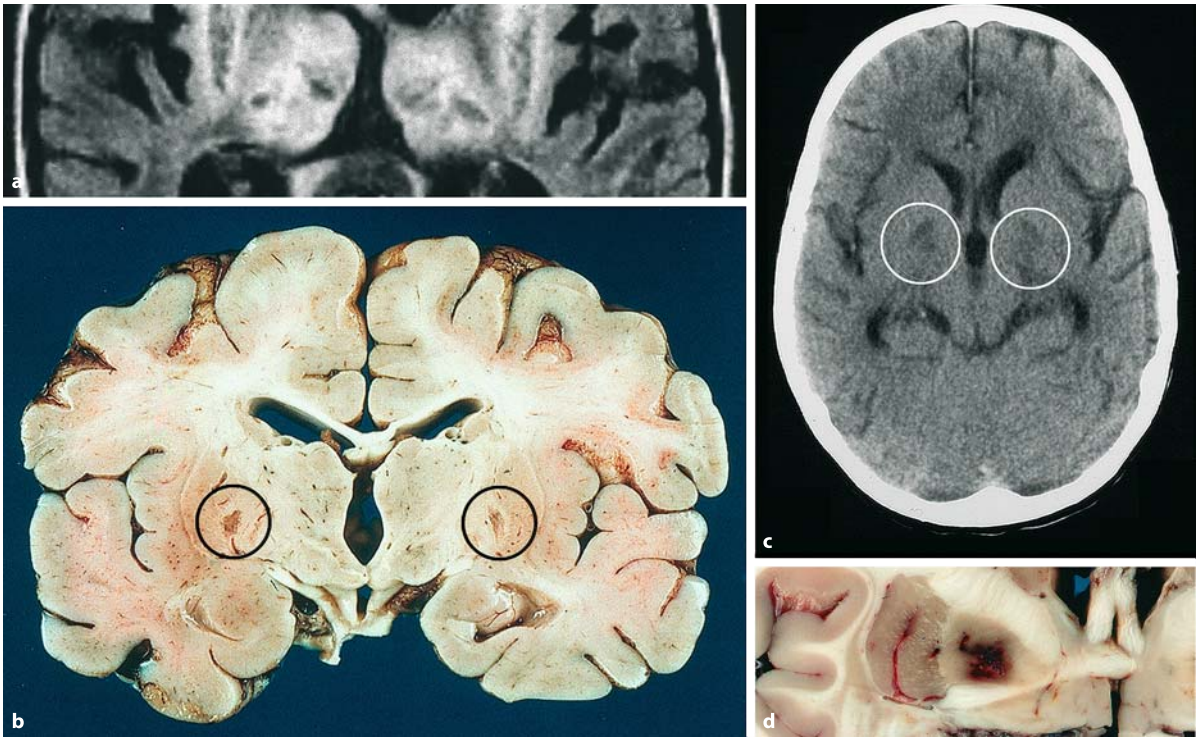

Fig. 4.18a–d. Global ischemia leads to cystic necrosis of the basal ganglia. Two cases are demonstrated: (**a, c**) and (**b, d**) with a long survival time after cardiac arrest demonstrating necrosis of the pallidum (**a, b:** MRI)

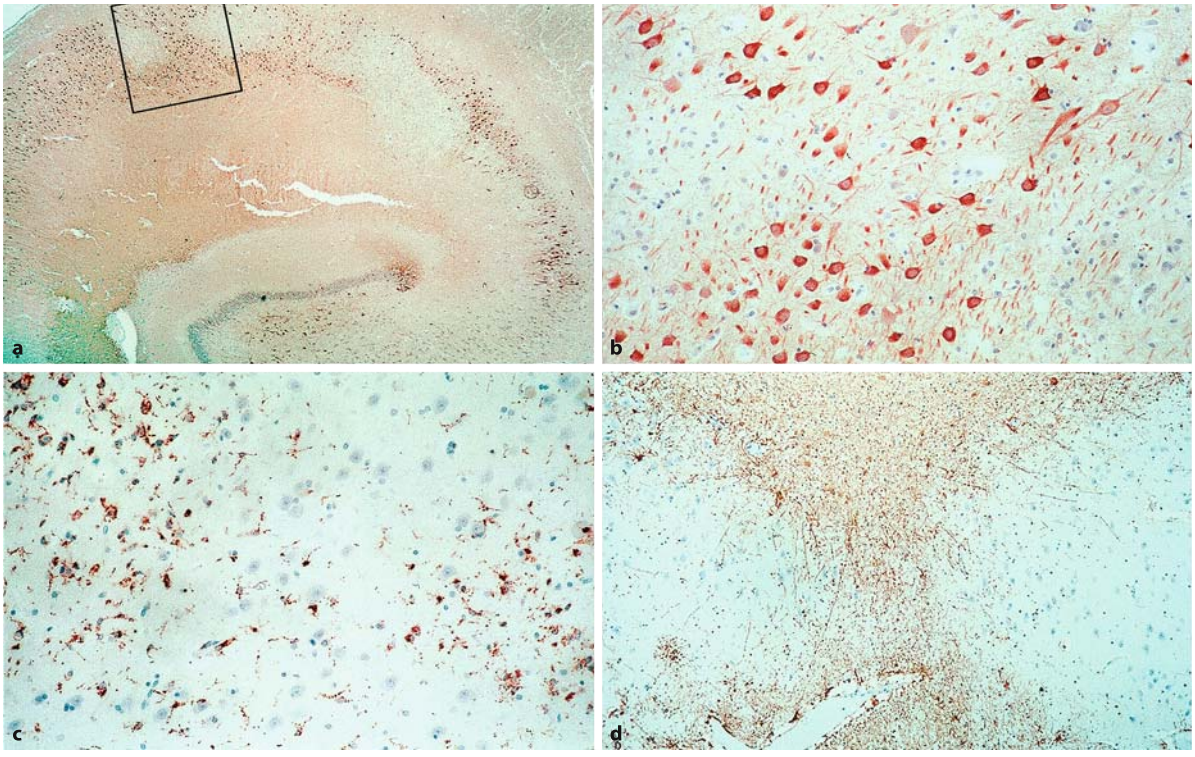

Fig. 4.19a–d. Neuronal loss in the hippocampal area (CA1 sector) and glial reaction (see also Fig. 14.14, p. 309). **a** The Ammon's horn CA1 sector is characterized by a distinct loss of nerve cells; **b** by high magnification of the marked sector (see **a**) intact neurons are seen in the center as well as a bilateral loss of neurons; **c** the lost neurons are replaced by CD68 reactive microglia and **d** in cases of longer survival time, by astrocytes (**a, b** MAP2 reactivity; **c** CD68 reactivity; **d** GFAP reactivity; magnification **a** ×50; **b, c, d** ×500)

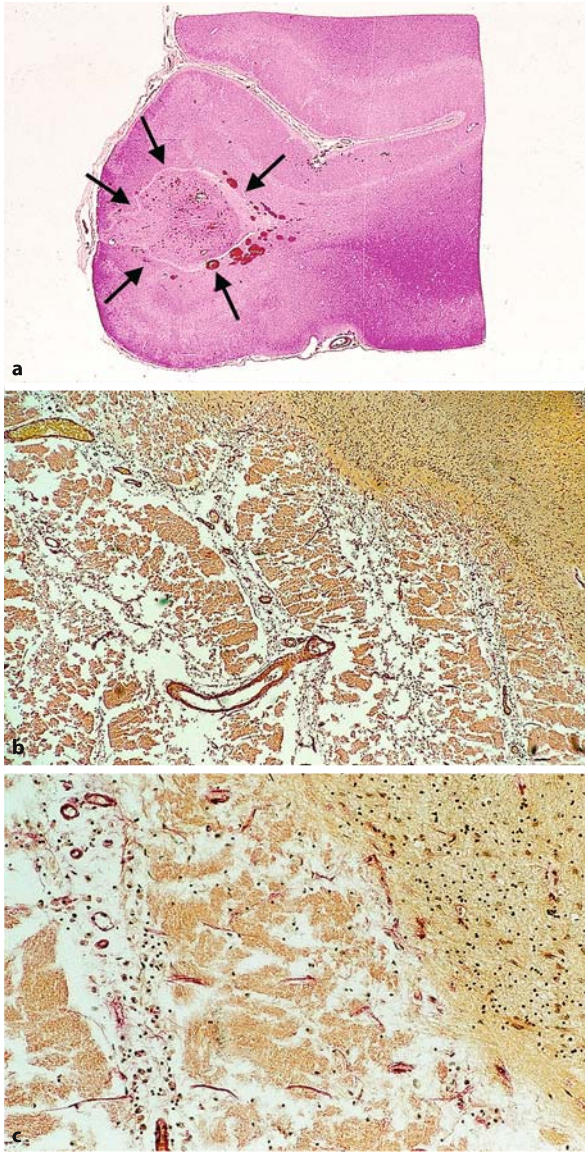

Fig. 4.20a–c. Coagulation necrosis. **a** Necrotic area is limited by a spongious border zone (arrows); **b, c** fragments of intact tissue components are visible and not phagocytosed (**a** H&E; **b, c** van Gieson stain; magnification **a** ×5; **b** ×100; **c** ×200)

deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) method (Gavrieli et al. 1992). Apoptosis causes pyknosis of the nucleus and condensation and shrinkage of the cell body. As it progresses, budding and karyorrhexis occur, and ultimately a breakup into clusters of apoptotic bodies (Majno and Joris 1995).

The *time course* of apoptosis following a traumatic event is as follows: about 4 h after a traumatic event, apoptosis begins, and remains demonstrable for about 3 days (Yakovlev and Faden 1997).

Three *major factors* are known to *participate* in the apoptotic cascade of "delayed" neuronal death (for review Kermer et al. 1999; see also Huppertz et al. 1999):

1. Immediate early gene transcription factors (*c-jun*, *jun-B*, *jun-D*, *c-fos*, AP-1, ATF, NF-κB)
2. Proteases (calpains, caspases)
3. Glutamate-mediated toxicity (free radicals, protein-kinases, Ca^{2+} homeostasis, second messenger systems)

The death-inducing activity of the Bax, Bad, Bid, Bcl-x_s family members is thought by Raghupathi et al. (2000) to be in dynamic equilibrium with their survival-promoting cognates Bcl-2, Bcl-x_L. Shifts in the protective intracellular Bcl-2-family-protein levels can tilt the balance toward cell death by activating the death-inducing cysteine proteases, caspases (Thornberry and Lazebnik 1998).

The death of single cells releases insufficient quantities of chemoattractants to allow effective concentrations of molecular species to reach the vascular endothelium. For this reason a genuine cell reaction does not occur. Neighboring cells that are not professional phagocytes cannibalize the cell debris in a process specific to apoptosis (Majno and Joris 1995). In inflammatory diseases, an essential factor in the resolution of the inflammatory attack is the clearance of apoptotic leukocytes by tissue-specific phagocytes (Platt et al. 1998). This process has been termed the "safe, phagocytic clearance of dying, yet intact leukocytes undergoing apoptosis" involving rapid recognition, uptake, and degradation.

Microglial cells were recently shown to be capable of *protecting neurons*, cerebellar granule neurons in particular, from apoptosis (Polazzi et al. 2001): molecules are released by apoptotic neurons that enable the anti-apoptotic activity of microglia. In vitro, normal microglia release molecules capable of rescuing neurons from apoptotic death.

4.3.3 Necrosis Versus Apoptosis

Microglia, astrocytes, and oligodendroglia may participate in apoptotic or necrotic processes. The reaction of neurons highly sensitive to injuries such as ischemia, hypoglycemia, infection, and mechanical trauma are described above and classified systematically in Table 4.3. A review by Rosenblum (1997) includes a comparison of various hypotheses regarding the underlying causes of "delayed" neuronal death, among them excitotoxicity, calcium, and apoptosis. Rubin (1997) and Abe (1999) review the phenomenon of neuronal apoptosis as it appears in various neurological diseases.

Table 4.3. Different pathophysiological and phenomenological features of necrosis and apoptosis. Sources: Granville et al. 1998; Abe 1999; König and Rosenberg 2000; Jellinger and Stadelmann 2000

Features	Necrosis	Apoptosis
Causes	Toxic influences Massive ischemia Radiation (high dose)	Developmental/programmed degenerative changes Growth factor deprivation Mild ischemia, radiation, etc.
Cellular processes	Non-coordinated events Cell membrane rupture Mitochondrial swelling Energy independence No protein synthesis No RNA synthesis	Programmed cascade Membrane phospholipid asymmetry Organelles preserved/shrunk Energy (ATP) dependence Requires protein synthesis Requires new RNA transcription
Molecular events	ATP depletion Enzymatic digestion Protein denaturation Diffuse DNA digestion	Mitochondrial permeability transition Mitochondrial cytochrome c release Caspase activations Internucleosomal endonucleases Transglutaminase activation Poly(ADP-ribose) polymerase cleavage
Tissue distribution	Group of cells	Single cells
Tissue reaction	Lysis and release of cellular contents resulting in inflammation of surrounding tissues	Phagocytosis of membrane-enclosed vesicles by macrophages or neighboring cells; little or no inflammation
Morphology		
Cell	Swelling	Cell shrinkage, loss of membrane contact with neighboring cells
Plasma membrane	Loss of integrity, enhanced permeability	Blebbing formation of apoptic bodies
Organelles	Damaged	Intact
Nucleus	Disintegrated	Condensed and fragmented
Lysosomes	Ruptured	Intact
Mitochondria	Defective, ATP-depleted, swollen, ruptured	Swelling, permeability transition, may rupture
Biochemistry		
DNA	Non-specific degradation	Internucleosomal DNA cleavage
Protein	Non-specific degradation	Activation of caspases, calpains
Substrates	Non-specific hydrolysis	Specific substrates
Anti-death molecules	Bcl-2 (in some cases) (Kane et al. 1995)	Bcl-2 family, IAPs, FLIPs, crmA, caspase inhibitors
Adenosine triphosphate requirement	No	Yes

4.3.4 Penumbra

Astrup et al. (1981) first defined the ischemic penumbra as brain tissue perfused at a level within the thresholds of functional impairment and morphologic integrity, which has the capacity to recover if perfusion is improved. Because tolerance of tissue to ischemic damage is dependent on residual flow and duration of flow disturbance (Heiss and Rosner 1983), the ischemic penumbra is a dynamic process;

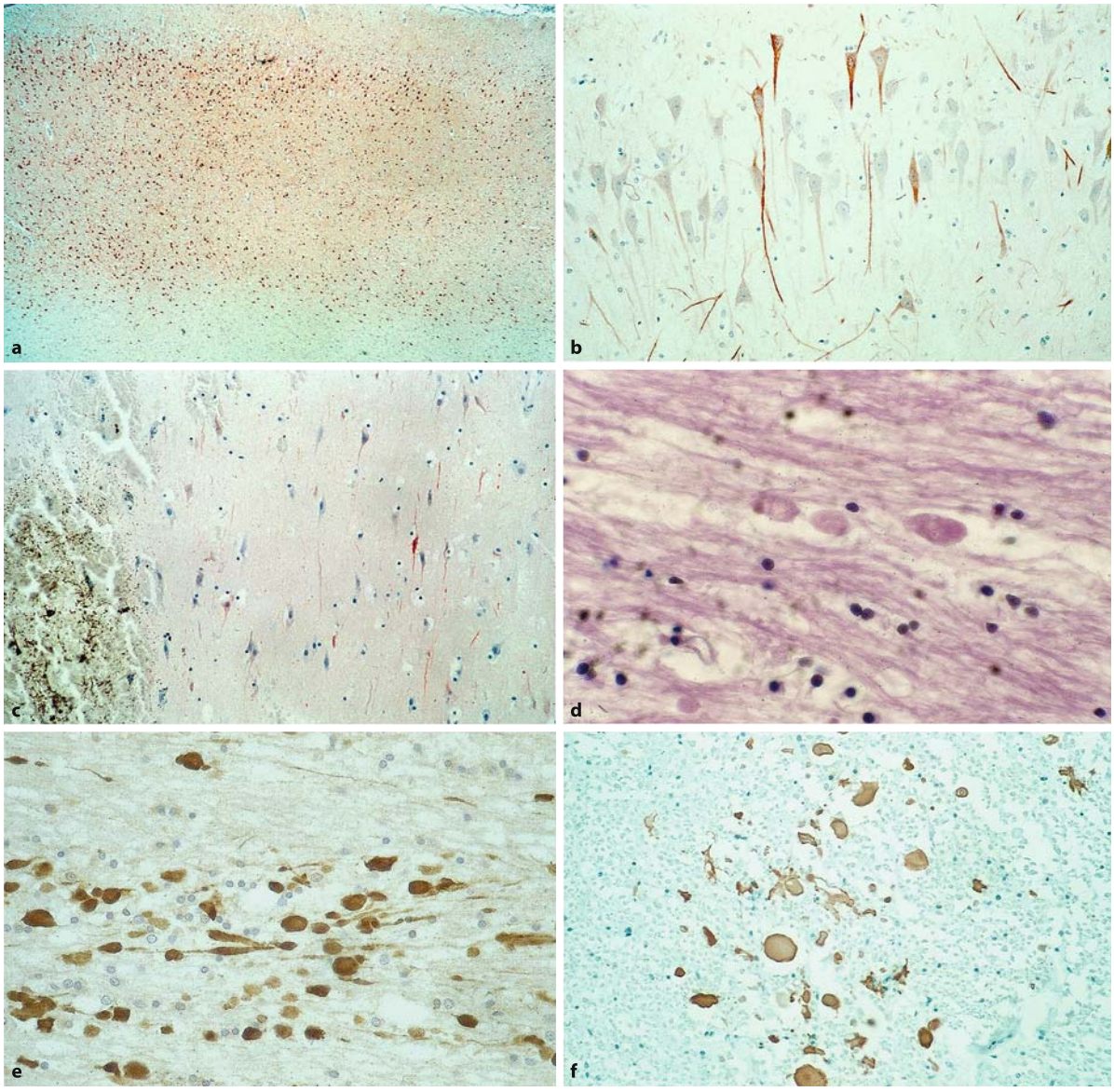

Fig. 4.21a–f. Dendritic and axonal injury. **a** Dendritic processes and neuronal perikarya are reactive with a MAP2 antibody which (**b**) lose their reactivity within a short time after an ischemic period as well as in cases of (**c**) MBI-induced hemorrhage; **d** axonal injury is demonstrable by axonal bulbs or balls using H&E stain as well as (**e, f**) by their reactivity to β-APP antibody (magnification **a** ×50; **b** ×500, **c** ×100; **d–f** ×1,000)

it exists for a short period even in the center of ischemia, from which the conversion into irreversible necrosis propagates over time to the neighboring tissue.

Focal ischemia results in necrosis at the infarct core and activation of complex signal pathways for cell death and cell survival in the penumbra. Increased expression of caspase-1, -3, -8, and -9, and of cleaved caspase-8 has been observed in the penumbra (for details, see Ferrer and Planas 2003). But for a limited time interval, penumbral tissue has the potential for recovery and, therefore, is the target for interventional therapy in acute ischemic stroke (time window, Heiss 2000).

4.3.5 Dendritic Injury

Relatively little is known about the effects of injury of the dendritic processes of neurons. Axotomy of a motor neuron induces loss of some presynaptic terminals and the retraction of processes (Blinzinger and Kreutzberg 1968; Summer and Watson 1971). Abnormalities in dendritic spines have been report-

ed during the perinatal period in cases of developmental retardation (Purpura 1975, 1976).

Li et al. (1997) showed that expression of microtubule-associated protein 2 (MAP2) in perikaryons and dendrites is a sensitive marker of dendritic lesions in spinal cord trauma (Fig. 3.2b; see also Chap. 10 – pp. 226 f). As early as 4 h after moderate or severe compression of the spinal cord, loss of MAP2 immunoreactivity in dendrites and nerve cell bodies became evident in the injured segment. This phenomenon continued for the duration of the 9-day experimental period. How much MAP2 immunoreactivity is lost depends on how hard the cord is impacted (Li et al. 1995). The loss of immunoreactivity may result from an (impact-induced) influx of calcium, activating calcium-dependent proteolytic enzymes capable of degrading MAP2 (Inuzuka et al. 1990). The same phenomena may be observed as a result of hypoxic lesions in the hippocampal area (Fig. 4.21a, b).

4.3.6 Axonal Injury

Axonal injury is characterized by an interruption of axonal fibers (Fig. 3.2b) as demonstrable – for example – as a result of a gunshot: the axons will be fragmented (Figs. 8.13b, 9.19). Moreover, axonal injury induces an anterograde (Wallerian) and retrograde degeneration of the injured axons. The terms "anterograde" and "retrograde" refer to the directions of conduction of the nerve impulse along the axon, i.e., the degeneration following focal damage proceeds in a centrifugal or centripetal direction (for review see Brodal 1982).

An interrupted anterograde flow of proteins along the axon can cause the phenomenon of *axonal injury*. This phenomenon was once demonstrated by H&E stain and by silver staining techniques within 16–24 h after a traumatic event (Strich 1956; Adams et al. 1982). But since the injured axon is selectively characterized by expression of β-amyloid precursor protein (β-APP) (Fig. 4.21d–f; cf. Gentleman et al. 1993; Sherriff et al. 1994), it is now routinely confirmed in 105–180 min (Blumbergs et al. 1995; Oehmichen et al. 1999), in adult brains as well as in infant brains (Reichard et al. 2003). β-APP expression is seen even if the axonal injury is moderate or the axotomy delayed or incomplete (Povlishock 1992). Although axonal injury was long thought to be a morphological correlate of MBI, it is now known to be a non-specific phenomenon also associated with acute intoxication (Nies et al. 2002) or hypoxia/ischemia (Oehmichen et al. 1999).

In a recent study Graham et al. (2004) evaluated the pattern of β-APP immunoreactivity. The authors identified three different types:

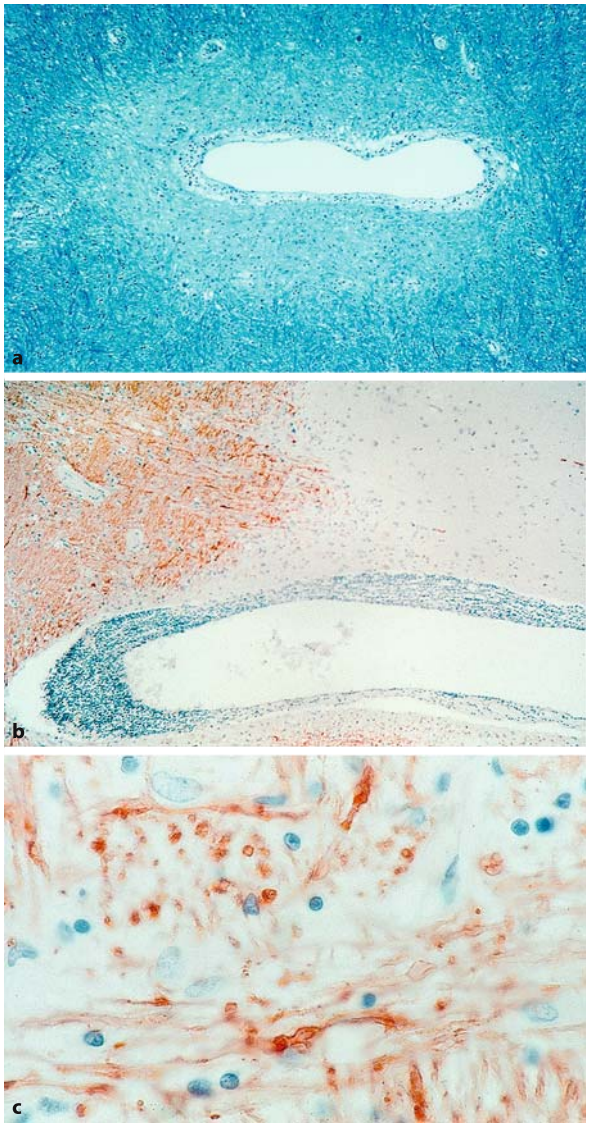

Fig. 4.22a–c. Demyelination as represented in a case of multiple sclerosis with perivenous lymphocytes. **a** Structural disintegration of the perivascular white matter using Luxol fast blue stain or (**b, c**) demonstrating myelin basic protein (= MBP) reactivity (magnification **a** ×50; **b** ×300; **c** ×1,000)

1. A diffuse – multifocal type – in MBI, CO poisoning and hypoglycemia;
2. A type corresponding to the outlines of an infarct or hematoma with evidence of raised intracranical pressure;
3. A mixture of (1) and (2) which was seen in serve MBI.

It is still unclear which events trigger axonal degeneration within the CNS and PNS. Kapoor et al. (2003) suggest a link between nitric oxide (NO) and subsequent molecular events that previously have been indicated as contributors to reversible and irrevers-

ible axonal injury. Waxman (2003) demonstrates the axonal death cascade induced by hypoxia, ischemia, mechanical trauma, inflammation or NO. The molecular events involving sodium channels and the Na^+/Ca^{2+} exchanger lead to an increase in intracellular calcium, which can provoke axonal degeneration.

Axonal injury of myelinated axons is always accompanied by a demyelinating process, i.e., a loss of myelin, which will be eliminated by mononuclear phagocytes (see: Fig. 9.15b). The sequelae will be a glial scar lacking myelin as demonstrable by Luxol fast blue stain (Fig. 4.22a) or by immunohistochemistry using an antibody against myelin basic protein (Fig. 4.22b, c).

4.3.6.1 Anterograde (Wallerian) Degeneration

Interrupted axons or injured neurons exhibit disintegration of the distal stump. Breakdown of the distal axonal stump is known as "Wallerian degeneration" and begins several days after a traumatic event. Its salient morphological features are lysis of axons and myelin, Schwann cell proliferation, and phagocytosis by invading macrophages. Axonal and myelin degeneration follow a time course described in detail by Brodal (1982) (see also p. 242).

4.3.6.2 Retrograde Degeneration

Axotomy induces a characteristic centripetally directed morphological change of the neuron termed *retrograde axonal degeneration*. This retrograde alteration is characterized by rounding of the neuronal contours, swelling of the neuronal cytoplasm, and a decline in the number of Nissl bodies at the center of the cytoplasm (central chromatolysis – see Fig. 3.1c). The nucleus becomes slightly deformed and is displaced to the periphery of the perikaryon. These changes correspond to the changed or increased neuronal gene expression after axotomy (Graeber et al. 2002). Axotomy is followed in hours by rapid upregulation of the immediate early genes, such as *c-fos*, *c-jun*, *jun-B* (Haas et al. 1993), in association with the upregulation of heat shock proteins (Kalmar et al. 2002). The one constant change associated with acute retrograde changes may be chromatolysis. These changes are sometimes accompanied by local proliferation of satellite glial cells whose time course has also been described by Brodal (1982) (see also pp. 242 and 304 f).

4.3.7 Regenerative Capacity

It is accepted as common knowledge that plasticity-associated molecular and structural events occur in the injured brain. These are at least partly responsible for functional recovery. Increases in dendritic arborization, spine density, and synaptogenesis in both peri-injury and intact cortical areas are the potential morphological strategies that enable the brain to reorganize its neuronal circuits (Keyvani and Schallert 2002).

On the other hand we have to consider that the scarring process is an ineffective regenerative process which is associated with cell proliferation. The cell proliferation will be – especially within the first 48 h after the traumatic event – non cell-specific, as immunostaining with markers for immature and mature astrocytes, activated microglia, neural precursors, and mature neurons will be negative (Chirumamilla et al. 2002). Nevertheless, it is also accepted that both retrograde degeneration and the axonal injury-induced bulbs and swelling of the proximal axonal stump are markers of a regeneration process. Although the CNS has little innate capacity for repair, this capacity does exist for the peripheral nervous system. It is not known why axons in the adult CNS are not capable of better regeneration; it is known that they do in fact regenerate, as was recently reconfirmed by von Euler et al. (2002).

The observations of Schwab and Caroni (1988; Schwab 1993) are of major importance. They show that proteins released by oligodendrocytes inhibit axonal elongation. This inhibitory protein has since been identified and cloned (Chen et al. 2000; GrandPré et al. 2000; Prinjha et al. 2000). These authors also identified the protein (Nogo) of a previously unknown gene that encodes the inhibitory myelin protein in rats and humans. The myelin-derived axon outgrowth inhibitor Nogo protein binds to an axonal Nogo-66 receptor and at least accounts for the lack of CNS repair (Li and Strittmatter 2003; McGee and Strittmatter 2003). It remains unclear, however, what effect other factors may have, whether negative (e.g., the release by neurons of large quantities of glutamate following the incidence of spinal cord injury), or positive [e.g., release of tissue growth factors (Ramer et al. 2000) and cytokines, or induction of the macrophage scavenger function (see also Schwab 2000)].

It is now thought that neurons are renewed throughout life from endogenous stem cells and added to the dentate gyrus. Adult neurogenesis could be demonstrated in the subgranular and subventricular zones of the hippocampus (Kempermann et al. 1998; Cameron and McKay 1999) and the olfactory bulb (Craig et al. 1999). These are the only zones where differentiation of neural stem cells into neurons is

known to take place in the intact adult CNS (Reilly 2002). Because this process does not occur in the adult spinal cord, Svendsen (2002) postulates that the growth of neurites can only be stimulated by newly regenerated astrocytes. Additional findings suggest that adult neurogenesis is actively regulated in large part by astrocytes (Reilly 2002; Song et al. 2002).

Gage (1998) and colleagues (Kempermann et al. 1998) were able to show that exposure to an environmental challenge evokes much greater neurogenesis in old than in young animals. More recent data suggest that the old brain reacts quickly with a neurogenic response to functional challenges, a type of cellular plasticity associated with the continued sensory stimulation and activity of the aging brain (Kempermann et al. 2002; McKhan 2002).

4.4 Inflammation

4.4.1 Principles of Neuroimmunology

The CNS was once described as an "immunologically privileged site" (Medawar 1948). This hypothesis was based mainly on the existence of the BBB (Pachter et al. 2003), which restricts diffusion of soluble molecules and the migration of immune cells out of the systemic circulation into the CNS (Oehmichen 1983). Pericytes, endothelial cells, microglia and astrocytes, by contributing to BBB function (see above), participate in CNS immune regulation (Prat et al. 2001).

Meanwhile a number of basic processes are known (Bauer et al. 2001) that explain how the CNS responds to inflammatory attack by regulating local antigen presentation, by the different cell types, and by its special cytokine environment. It also eliminates inflammation via emigrating macrophages (Oehmichen et al. 1979 – for review Oehmichen 1982; Cserr and Knopf 1997) and destruction of apoptotic T-cells. In vitro and in vivo studies have elucidated the mechanisms underlying immune-mediated (via cytokines, macrophage/microglial toxins, and antibodies) tissue damage, featuring many different potential pathways.

The normal CNS has limited expression of *major histocompatibility complex* (*MHC) class I antigens*, primarily on the endothelium and glial cells, and no expression of *MHC-II* and the various immunoactive adhesion molecules. Fontana et al. (1982) were the first to point out that *cytokines* such as interferon-γ (IFN-γ) are able to stimulate astrocytes to express MHC class II to secrete cytokines (IL-1, IL-3, TNF-α), and to present antigens such as myelin basic protein (MBP) to specific T-cell lines (Fontana et al. 1982, 1984; Massa et al. 1987).

Frei et al. (1987) focused on microglia and found that they too could respond to IFN-γ by upregulating MHC-II. If IFN-γ or IFN-γ and TNF-α are introduced directly into the CNS, there is independent, progressive upregulation of both MHC classes and of adhesion molecules, such as the intercellular adhesion molecule-1 (ICAM-1), which are expressed first by perivascular macrophages (Hickey and Kimura 1988), subsequently by microglia and macrophages throughout the CNS, and finally by astrocytes (Massa et al. 1986). Experimental induction of autoimmune encephalitis (EAE) revealed that perivascular macrophages are the chief presenters of CNS antigens to circulating T-cells (Hickey and Kimura 1988).

The role of the endothelium in antigen presentation within the CNS is ambiguous. Astrocytes too are thought (Waksman 1997) to play an ambiguous role. When presenting antigen to specific T-cells in vitro, they are lysed. It is not known whether T-cells are induced to proliferate or to release inflammatory cytokines, or possibly both, or whether they shut down for lack of suitable co-stimulatory signals (so-called clonal anergy).

The duality of the inflammatory response is crucial to host repair and defense. It may also however cause loss or impairment of function, i.e., although otherwise beneficial, inflammation may impair neuronal function (Perry et al. 1999).

4.4.2 Inflammatory Cells

Instead of the BBB being a limiting factor of the CNS immune response as once believed, today it is thought that the brain itself is an immune system organ (Fabry et al. 1994; Chao et al. 1997). This conclusion is based on the numerous cytological and immunological findings of the past two decades showing that the targets to be protected are neurons, axons, and myelin. In the absence of protection these can become necrotic or succumb to apoptosis, be phagocytosed and disappear. Ultimately all signs of degenerative alteration can be demonstrated. There is no direct correlation however between leukocyte emigration and parenchymal cell death in vivo (Schmid-Schönbein et al. 1999).

Glial cells outnumber neurons in the cortex, where there are eight glial cells for every neuron. Among glial cells in the cortex, astrocytes comprise 80%, microglia 15%, and oligodendroglia 5% (Chao et al. 1997). These cells possess many immunological features marking them as important immunoregulatory cells. Hallmarks of CNS inflammation in particular are activated microglia and astrocytes. Inflammation undoubtedly serves primarily as a host

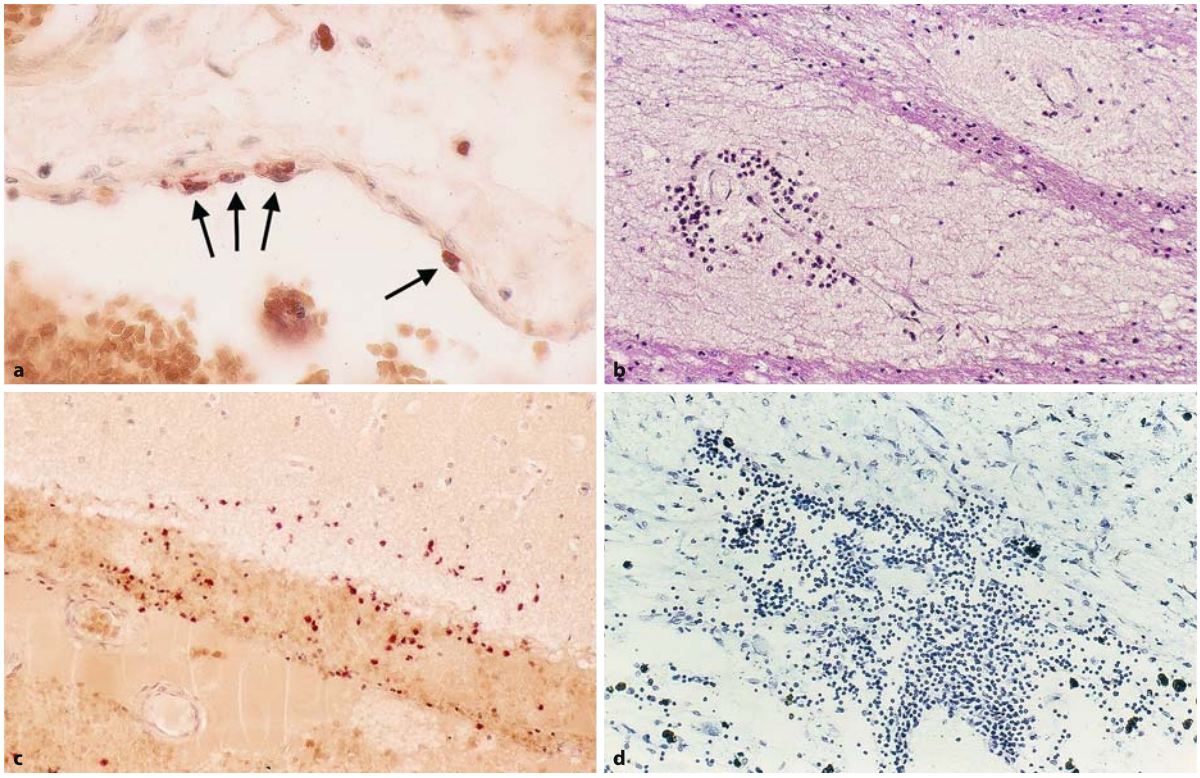

Fig. 4.23a–d. Hematogenous cells as an early inflammatory response. **a** Platelets adherent to endothelial surfaces of a venous vessel (arrows); **b** emigrating leukocytes around a small artery; **c** leukocytic response to an intracranial hemorrhage; **d** lymphocytic aggregation in a scar caused by mechanical brain injury (**a** platelet antibody; **b** H&E, **c** N-AS-DCIAE, **d** Nissl stain; magnification **a** ×1,000; **b–d** ×300)

defense mechanism in peripheral tissue, facilitating essential repair processes by altering local blood flow in the injured tissue, with accumulation of fluid and specialized cells. The brain possesses cellular host defense mechanisms since activated T-cells are capable of crossing the BBB (Hickey et al. 1991).

Cellular mediators of CNS inflammation in the brain have been shown to differ with regard to type and number from those of the periphery (see below). These differences are mainly due to the brain's tight regulatory environment and the balance between inflammation-induced tissue damage and tissue repair (Parsons and Hunter 1999).

The specificity of the immune response appears to be controlled largely by CNS antigen presentation (Sedgwick and Hickey 1997), though the precise nature of the control remains unresolved. CNS antigen presentation according to Hart and Fabry (1995) occurs outside and inside the CNS, with the BBB playing a major role in the regulation of CNS immune function. Parsons and Hunter (1999) showed that the early events leading to T-cell activation by antigen-presenting cells result from MHC binding. Co-stimulatory molecules then bind to the antigen, presenting cell–T-cell complexes for further development of the cascade. MHC is expressed not only on astrocytes and microglia, but under certain conditions also on neurons and oligodendrocytes (Sedgwick and Hickey 1997). MHC II antigens are also expressed under normal conditions in a population of macrophages inhibiting the perivascular space, subarachnoid space, and choroid plexus. This expression may indicate that these cells perform a modulatory function at the blood/CSF interface (Matyszak et al. 1992). Under highly specific circumstances, physiological response mechanisms resembling those at the periphery also appear to take place in the brain.

Under pathological conditions, hematogenous cells that are absent or extremely rare under normal circumstances appear to accumulate in the brain, i.e., platelets (Fig. 4.23a), neutrophilic leukocytes (Fig. 4.23b,c), lymphocytes (Fig. 4.23d), and macrophages. The number and type of inflammatory cells in the CNS vary widely depending on the attracting stimulus or on their inherent ability to attack a CNS antigen.

4.4.2.1 Polymorphonuclear Leukocytes

The intravascular cells, especially the leukocytes, interact with vessel walls as determined by integrins (Hynes 1992), selectins (Bevilaqua 1993), and immunoglobulins of the supergene family (Springer 1990). Among the heterogeneous supergene family are MHC molecules, T-cell receptors, and ICAM-1. During emigration, i.e., extravasation, leukocytes initially come into loose contact with the walls of vessels of the microcirculation via selectin molecules or lectins, producing a rolling motion along the vessel wall (McEver 1994). They are then expressed on the endothelium. The selectin molecules are E-selectin (ELAM-1), L-selectin (LAM-1, LECCAM-1), and P-selectin (CD62). P-selectin plays a role in recruitment of neutrophils to the brain parenchyma (Bernardes-Silva et al. 2001), while E-selectin is thought to participate in both neutrophil and $CD4^+$ T-cell adhesion (Harlan and Liu 1992). Endothelial selectins can be rapidly upregulated following wounding, P-selectin within minutes (<2 h − Zoppo 1997), and E-selectin within a few hours (Granger and Kubes 1994; McEver 1994). Among the stimuli for expression of endothelial cell adhesion receptors are TNF-α and IL-1.

Adhesion of leukocytes to endothelial cells is mediated by adhesion molecules such as Mac-1, the intracellular adhesion molecules (ICAMs), lymphocyte function-associated antigen-1 (LFA-1), and vascular cell adhesion molecule-1 (VCAM-1), all of which, as already mentioned, are upregulated in endothelial cells. In the CNS, ICAM-1 and VCAM-1 (Baron et al. 1993) are constitutively expressed on perivascular cells and some astrocytes. In areas of CNS inflammation they are readily upregulated on endothelial cells and astrocytes (Sobel et al. 1990), which stimulates recruitment of neutrophils to the site of injury. Such neutrophil emigration can be experimentally induced by extravasal injection of cytokines such as IL-1β (Bernardes-Silva et al. 2001) or TNF-α (Schmid-Schönbein et al. 1999).

Neutrophils are the first circulating leukocytes to reach the site of injury. Increase in vascular permeability is caused by the release of free radicals and lysosomal enzymes, giving rise to edema (Weiss 1989). Despite mechanisms evolved to restrict entry of neutrophils into the brain parenchyma, neutrophil recruitment is clearly a feature of acute brain injury, such as that caused by stroke or mechanical trauma. Numerous studies employing a transient or permanent model of focal ischemia in rats and mice have demonstrated that cerebral tissue injury is lessened by neutrophil depletion (Jean et al. 1998). A correlation between the development of cerebral edema and neutrophil recruitment has also been shown in models of MBI (Schoettle et al. 1990). This deleterious effect of neutrophil recruitment contrasts with their beneficial function and phagocytic ability as scavenger cells in cases of bacterial inflammation and of particular importance in cases of sterile inflammation.

4.4.2.2 Lymphocytes

The aforementioned recruitment of T-lymphocytes to the site of injury clearly depends on an accumulation of adhesion molecules, especially of VCAM-1, in the endothelial wall. When activated, T-cells express LFA-1 and can bind ICAM-1 on endothelium (van Kooyk et al. 1993), thus facilitating entry of T-cells into the CNS (Baron et al. 1993).

Few data have been published on the migratory requirements of B-cells. It is thought, however, that B-cells in their fully mature form as plasma cells have no or only limited migratory potential. Immunization of rats with a foreign, non-pathogenic antigen behind the BBB was found to result in the presence of B-cells and plasma cells specific for that antigen in the CNS (Knopf et al. 1994). This finding appears to indicate that, after entering, B-cells remain in the CNS at least in part because they have found their specific antigen (Hickey et al. 1997).

After entering the CNS, the function of T- and B-cells is to recognize their antigen. Among the potential antigen-presenting cells of the CNS are endothelial cells and astrocytes. Under inflammatory conditions, microglial and perivascular cells (members of the mononuclear phagocyte family residing in the CNS) constitute the chief antigen-presenting cells.

4.4.2.3 Microglia and Brain Macrophages

As already mentioned (pp. 27 f), a distinction must be made between activated and resident microglia, and leptomeningeal, perivascular, and choroidal macrophages. All of these cells represent different functional stages of blood monocytes (Oehmichen and Huber 1976; Oehmichen 1976a, b, 1978, 1983; cf. also Perry and Gordon 1997).

Microglia residing in the white matter do not express the MHC I antigen, and only a few express MHC class II (Hart and Fabre 1981). Leptomeningeal, perivascular, and choroidal macrophages, in contrast, do express MHC class II. The resident microglia also feature a downregulation of other antigens, the leukocyte common antigen (LCA), and ED-1 or CD4.

Monocytes emigrate under pathological conditions into the brain parenchyma, where their morphology and antigenic characterization both change. They now participate in the immunological process as macrophages and express MHC class II antigens. They also scavenge cell debris and myelin fragments left over from damaged tissue.

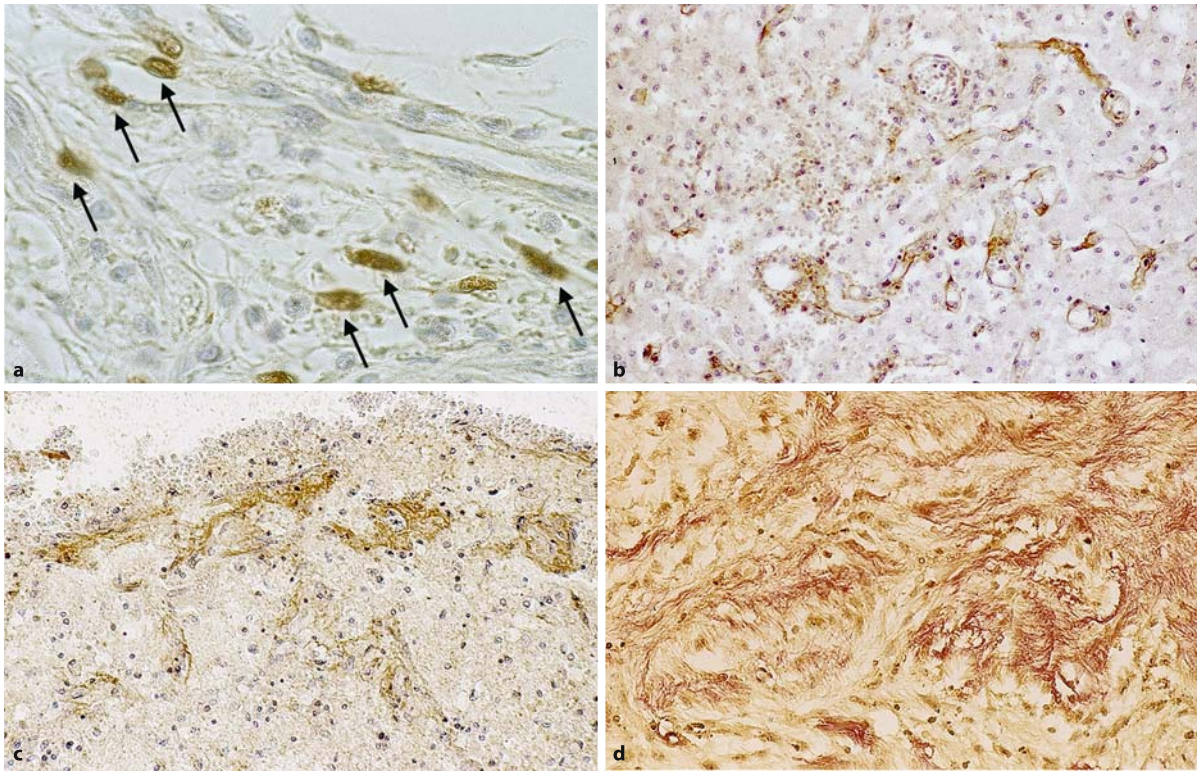

Fig. 4.24a–d. Mesenchymal reaction as a late inflammatory response. **a** Endothelial proliferation as demonstrated by in vivo exposition to bromodeoxyuridine (BrdU); **b, c** increase of the number of capillaries within the injured brain region as demonstrated (**b**) by factor VIII reactivity; **c, d** endothelial reaction associated with an increasing synthesis of collagenous fibers as demonstrated by antibodies to collagen type IV (**c**) and by means of van Gieson stain (**d**) (magnification **a** ×1,000; **b, c** ×300)

4.4.2.4 Astrocytes

Astrocytes are among the first local cells to respond to CNS injury. The main responses are reactive gliosis and swelling of reactive (hypertrophic) astrocytes upregulating GFAP. Reactive astrocytes express acute phase reactive protein (Koo et al. 1991), MHC class Ia (Frank et al. 1986) and MHC class II antigens (Fierz et al. 1985), IL-1 (Griffin et al. 1989), plus multiple other factors (for review see Norenberg 1997).
Astrocytes are known to act in conjunction with cells of the immune system and to be involved in immune/inflammatory processes. They are immunocompetent cells capable of augmenting, amplifying, and sometimes even of regulating an immune response. They produce many immune mediators and can in return be affected by them. By helping to eliminate infectious or foreign agents, astrocytes may contribute to a beneficial response.

4.4.2.5 Endothelial Cells and Collagen Fibers

Given their direct contact with leukocytes in the blood, endothelial cells constitute the ideal site for antigen recognition in the CNS (Sedgwick and Hickey 1997). The scarcity of T-cells in the CNS may be an indication that endothelial cells are the sole site capable of adequate T-cell antigen–MHC interaction. The finding that activated T-cells can enter the CNS through an intact BBB (Hickey et al. 1991), however, is a clear sign that antigen recognition at the endothelial cell surface need not occur.

Endothelial cells are thus regarded as major players in the inflammatory and immune response (Sternberger et al. 1989) and simultaneously guarantee the BBB. They also enable alterations in the form of receptor-mediated events (Dietrich 1999), i.e., an inflammatory response (for details, especially on the expression of adhesion receptors, see above).

Endothelial cells proliferate at the site of brain wounds (Fig. 4.24a). Therefore, the number of capillaries increases and – in a final phase – decreases near hemorrhages or infarcts (Fig. 4.24b, c) in association with an increase in collagen fibers, especially collagen type IV (Fig. 4.24c). This process leads to a network of collagen fibers and glial fibers, which is the last stage in the formation of a brain scar.

4.4.3 Inflammatory Mediators

Among the inflammatory mediators are cytokines and their subgroups, chemokines, in the sense of adhesion molecules. Other mediators of inflammation include effector molecules such as NO, NOS, reactive oxygen species (ROS), and free radicals.

4.4.3.1 Cytokines

Cytokines mediate the initiation, propagation, regulation, and suppression of immune and inflammatory responses (Benveniste 1999). They are proteins with low molecular weight and are synthesized during effector phase immunity. They are secreted by cells and are also expressed on their surfaces. Many different cell types are capable of producing the individual cytokines, which for their part can have a variety of effects on different cell types. Usually acting locally, cytokines begin to act on target cells by binding to specific cell-surface receptors, which generally have a high affinity for their ligands. It takes only minute amounts of a cytokine to evoke a biological response.

In multiple sclerosis or experimental allergic encephalitis, IFN-γ and IL-2 are known to be products of activated T-cells. TNF-α and IL-1 derive from activated astrocytes and macrophages. Astrocytes can be activated by IFN-γ and/or TNF-α, produce IL-1 and IL-3, TNF-α, transforming growth factor β (TGF-β), granulocyte-macrophage colony-stimulating factor (GM-CSF), and other types of molecules such as prostaglandin E_2 (PgE_2) (for review see Waksman 1997).

In human brains, TNF-α, IL-1, and IL-6 in particular can be induced by MBI or cerebral ischemia. Brain ischemia triggers rapid production of TNF-α mRNA, which peaks 6–12 h after ischemia and subsides 1–2 days later. It remains above baseline, however, for up to 5 days (Barone 1999). Neuronal cells in and around the ischemic tissue acutely express TNF-α in a so-called penumbra, but it also turns up several days later in macrophages in the infarcted tissue. TNF-α triggers adhesion molecule expression on activated glial cells and the endothelium, in this manner regulating gliosis, tissue remolding, and scar formation. IL-1 levels rise before and during glial activation and neuronal damage (Rothwell et al. 1999).

4.4.3.2 Chemokines

Chemokines are chemoattractant cytokines. During inflammation they mediate leukocyte entry into the CNS. Among their known functions is the interaction of leukocytes with the endothelial surface, a multistep and sequential process mediated by selectin molecules by which the leukocyte rolls on the endothelium. The end result is firm adhesion. The entire process is mediated by interaction of ICAM-1 and VCAM-1 expressed by endothelial cells and their leukocyte-associated ligands. Moderate levels of ICAM-1 and very low levels of VCAM-1, two molecules responsible for the adhesive properties of granulocytes and of T-cells, are expressed by brain endothelial cells.

Chemokines constitute a subgroup of small cytokines (8–10 kDa) that attract certain inflammatory cell populations, among them lymphocytes, neutrophils and monocytes, to the target tissue (Meeusen et al. 1996; Bonecchi et al. 1998). The number of known chemokines and chemokine receptors continues to expand rapidly (for review see Prat et al. 2001). Three classes of chemokines are known, as defined by the arrangement in the mature protein of conserved cysteine (C) residues, CXC or α-chemokines, CC or β-chemokines, and of CC or γ-chemokines. Astrocytes, endothelial cells (Zach et al. 1997; Weiss et al. 1998), perivascular cells, and macrophages (Simpson et al. 1998) produce and release chemokines.

4.4.3.3 Effector Molecules

ROS and NO are generated in astrocytes and activated macrophages (Hartung et al. 1988). ROS, NO, and other free radicals are effector molecules that contribute to the inflammatory cascade and tissue damage. What role complement plays in CNS damage is not clear (Morgan 1999).

The enzyme NO synthase (NOS) synthesizes NO. Inducible NOS (iNOS) is an isoform of NOS that is induced transcriptionally by immunological stimuli. iNOS, which synthesizes large quantities of NO, participates in inflammation-induced cytotoxicity. In the brain, iNOS message, proteins, and enzymatic activity are induced de novo by cerebral ischemia (Iadecola 1999). iNOS is expressed by neutrophils in permanent ischemia and in vascular cells in transient ischemia. High levels of NO are synthesized by human astrocytes upon stimulation with IFN-γ, TNF-α, IL-1 and potentiate IL-1.

Dalkara et al. (1999) showed that NO plays a detrimental role in experimentally induced cerebral infarction in neuronal NOS knockout mice. The NOS knockout infarcts 24 h after permanent vessel occlusion were 38% smaller than those of wild type. These finding seem to indicate that expression of iNOS is a factor contributing to ischemic brain damage.

An apoptotic pathway mediates NO-induced neuronal cell death and an NMDA receptor antagonist blocks NO-mediated neurotoxicity. Neuronal cell

death was shown by Chao et al. (1997) to be initiated by the release of IL-1 by the microglial cell, this in turn inducing the generation of astrocytes. Neurons are destroyed by NO via NMDA receptor-linked apoptosis.

Cerebral trauma, ischemia, and reperfusion are known to generate hydrogen peroxide and superoxide radicals, which then produce ROS and hydroxyl radicals (Chan 1999). Under normal conditions and following reperfusion injury, mitochondrial respiration creates ROS. Microglia and astrocytes that have been activated by cytokines produce vast quantities of neurotoxic free radicals. An intramitochondrial antioxidant enzyme, manganese superoxide dismutase (MnSOD), scavenges superoxide radicals and thus constitutes the first line of antioxidant defense.

4.4.4 Types of Inflammation

As already pointed out, inflammatory responses are based on an inflammatory cascade, whose details have become increasingly clear in recent years. Three basic types of inflammatory response are known: sterile inflammation, cell-mediated inflammation, and antibody-mediated inflammation. These types of response are mutually exclusive, but characterized by occasional overlapping.

4.4.4.1 Sterile Inflammation

In cases of mechanical violence, spontaneous intracerebral hemorrhage or stroke, sterile inflammation features an initial phase of infiltrating neutrophils and a second phase of infiltrating mononuclear phagocytes (bone marrow-derived monocytes, i.e., activated microglia and macrophages). Macrophages and neutrophils produce cytotoxic cytokines such as TNF-α, proteolytic enzymes (Anthony et al. 1997), reactive oxygen intermediates (Cross et al. 1998), cell death-inducing surface molecules such as Fas-ligands (D'Souza et al. 1996), or even excitotoxins (Lipton 1998). The macrophages in particular take up the scavenger function and eliminate tissue and cellular debris. They also release mediators that promote the scarring process, i.e., induce fibroblasts to produce collagenous fibers and stimulate astrocytes to proliferation and produce fibrils, aiding healing by the production of a fibrillary glial-collagenous scar.

4.4.4.2 Cell-Mediated Inflammation

Multiple sclerosis (MS) is the classic model of T-cell-mediated inflammation whose inflammatory infiltrates are chiefly comprised of T-lymphocytes, fewer B-lymphocytes, as well as activated microglial cells and macrophages (Brück et al. 1995; Gay et al. 1997). MS features local expression and/or upregulation of markers of T-lymphocyte and macrophage activation (Brück et al. 1995), of class I and class II MHC antigens (Traugott 1987), of chemokines and adhesion molecules in addition to their receptors (Lassmann 1998), and of co-stimulatory molecules (Windhagen et al. 1995).

Diseases with an autoimmune background such as MS or virus-induced inflammatory diseases exhibit a uniform cellular and mediator profile. Unlike MS, lesions associated with viral inflammation of the brain display considerable differences in topography and in their patterns of structural damage. They also vary with regard to the nature of the immune response and its associated cellular tropism. In lesions of virus encephalitis $CD8^+$-lymphocytes abound; in MS lesions both active and inactive $CD8^+$-cells usually outnumber $CD4^+$-cells (Gay et al. 1997).

Virus-infected cells generally evoke a cell-mediated immune response, although humoral mechanisms play a role as well (for review see Esiri and Kennedy 1997). Phagocytosis of infected cells by macrophages can also be promoted by antibodies. Antibody-dependent cell-mediated cytotoxicity (ADCC) is a process in which lymphocytes bearing Fc receptors for IgG lyse virus-infected cells bearing relatively small amounts of surface-bound antibody. The immunological specificity of the reaction derives from the antibody not the lymphocytes, which are not specific and have been designated killer cells. An important cell-mediated specific mechanism for killing infected target cells is provided by virus-specific cytotoxic T-cells. The cytotoxic effect is seen even if an antibody is lacking and is restricted by MHC class I antigens. Viral antigens on the surface of infected host T-cells are recognized by virus-induced cytotoxic T-cells in association with class I MHC antigens. The infected target T-cells are then killed by these T-cells only if they share the same MHC antigens, i.e., the T-cell killing is restricted by MHC (Zinkernagel and Doherty 1974).

Viral infection induces secretion of cytokines within the CNS, either by lymphomononuclear cell infiltrates or infected brain cells. Cytokines play an important role in the induction of MHC molecules. They stimulate humoral and cell-mediated immune responses by acting on immune system cells and neighboring brain cells, evoking the expression of surface recognition molecules such as MHC antigens and antiviral proteins such as Mx (Campbell 1991). Viral infections can provoke or amplify MHC class II expression on the surface of astrocytes and microglial cells, which is important in light of the significance of these antigen-presenting cells in the CNS. This process can occur as a direct effect of the

infection even in the absence of IFN-ɣ, as shown for measles virus-infected astrocytes and the murine coronavirus J. Howard Mueller virus (Massa et al. 1987).

4.4.4.3 Antibody-Mediated Inflammation

In viral and bacterial inflammation, both the cell-mediated immune response and the humoral response are highly important, the latter also usually dominating. Blood-borne dissemination of virus from the primary infection site to other organs is restricted by circulating antibodies, IgG or IgM. Antibodies in tissue spaces can stop the spread of infection from one cell to another by neutralizing extracellular viruses. However, viruses able to fuse cell membranes, such as measles or herpes viruses, can elude this mechanism without ever being exposed to antibody. Viruses can be inactivated by antibodies in a variety of ways. Antibodies can assist phagocytosis by coating the surface of the virion, or they may thwart attachment of the virus to specific receptors on vulnerable cells, or in the case of enveloped viruses they may promote viral lysis via attachment and activation of complement. In the absence of antibody, direct viral lysis can also be produced by complement alone.

4.4.5 Inflammation-Induced Ischemia

Edema can produce an increase in tissue pressure that disturbs the microcirculation of portions of the CNS that are anatomically prevented from swelling by bone or tight meningeal constraints. It is thought that this mechanism contributes to the formation of necrotic lesions in transverse myelitis. The inflammatory process often has a vasculitic component (Gray 1997) that causes occlusion of small veins and venules and is commonly associated with massive tissue damage. Ischemia can contribute to the development of structural damage and functional deficits in inflammatory CNS lesions.

Involvement of arteries and veins is rare in bacterial inflammation but the exudate is frequently accompanied by strands of fibrin. The edematous cortex exhibits large artificial perineuronal spaces and a spongiform neuropil. The cytoplasm of neurons often reveals ischemic cell necrosis and is acidophilic. If the course is subacute, fibrinoid necrosis and thrombosis may appear in a few blood vessels in the exudate, resulting in small foci of cortical necrosis.

4.5 Misinterpretable Findings

In the field of neuropathology both gross and microscopic changes can be misinterpreted. Only a few aspects will be discussed here, each involving routine immersion fixation with 10% buffered formalin, dehydration and embedding in paraffin (see above). A detailed overview of the problems associated with postmortem changes, artifacts, and misinterpretation has been provided by Lindenberg (1982).

4.5.1 Gross Findings

Autolysis, a process involving self-digestion of tissue, can cause slides of the adult brain to be discolored or poorly staining. The morphology of the changes associated with autolysis are identical with those of respirator brain (brain death). They arise if fixation is done too late, i.e., if the interval between intracranial circulatory arrest and autopsy or brain fixation is too long. Depending on the ambient conditions, the brain will liquefy after a certain postmortem interval without fixation.

The brain emits a foul odor if it has undergone microorganism-induced putrefaction, and the central parts of brain slides display a faint pink coloration. Variably large bullous cavities (Fig. 4.25a, b) give an appearance of *Swiss cheese* to large sections of the brain. Such cavities are created by the activation of gas-producing microorganisms due to poor quality formalin.

Macroscopic *necrosis of the cerebellar granular layer* was interpreted by Ikuta et al. (1963) as a postmortem phenomenon, whereas Lindenberg (1982) thought that the necrotic process precedes or accompanies the onset of sublethal hypoxemia, i.e., shortly before death.

Neurons in the substantia nigra and locus coeruleus of the brains of infants and children up to 5 years of age normally possess no *melanin pigment*. This finding is neither an artifact nor pathological.

The spinal cord is especially sensitive to postmortem mechanical injury in an unfixed state. In this manner the so-called toothpaste-artifact can occur (Hughes 1978). If the tissue in a segment of the spinal cord is artificially constricted, proximal portions of the cord are squeezed upward, distal portions downward, thus appearing in histological sections at the wrong level.

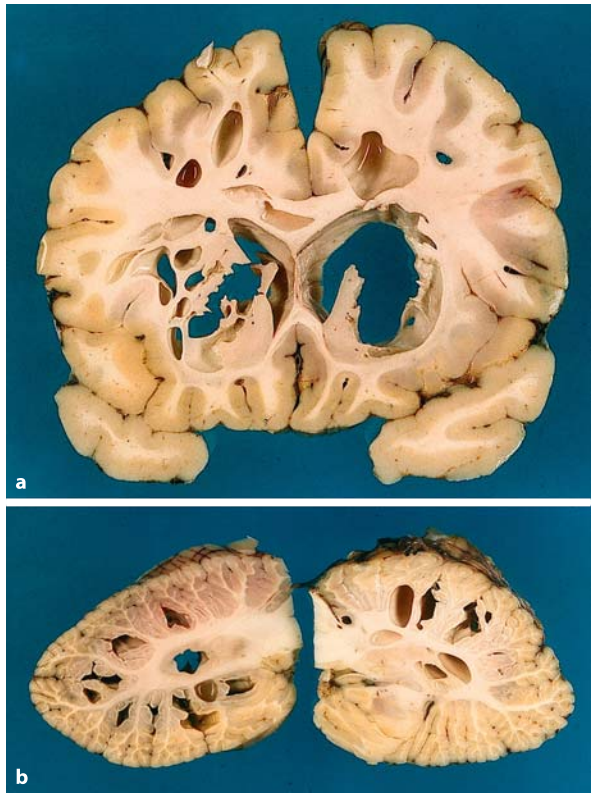

Fig. 4.25a, b. Putrefactive bullous cavities in cerebrum and cerebellum

4.5.2 Microscopic Findings

Any tissue processing produces artifacts that have to be interpreted: fixation procedures as well as staining techniques. The artifacts are dependent on the time periods between death and fixation, the duration of the fixation process, the temperatures, etc. For example the freezing process of (brain) tissue leads to crystalline vacuoles within the tissue sections (Fig. 4.26a, b).

Additionally, the forensic neuropathologist fundamentally needs to be able to reliably distinguish between vital and postmortem changes (cf. Oehmichen 1995). This requires among other things the testing and use of novel histochemical and immunohistochemical staining techniques that can help to establish the length of the postmortem interval.

So-called *dark neurons* (Fig. 4.26c) can appear among otherwise normal neurons. Dark neurons are irregularly contoured, shrunken neurons that are created by excessive pressure on unfixed postmortem tissue (Scharrer 1938; Cammermeyer 1961, 1975). Apical dendrites also have a dark coloration, sometimes in combination with a corkscrew-like appearance. There is a danger of confusing dark neurons with ischemic cell necrosis. In our own investigations (Oehmichen and Gencic 1980a) we could observe that most, but not all dark neurons have a potent albumin uptake, an indication that they represent lesions of neuronal metabolism (and/or membrane).

Animal experiments demonstrate that the following three types of *altered neurons* appear at different postmortem intervals in rats (Oehmichen and Gencic 1980b):

1. Shrunken, hyperchromatic neurons, whose number declines as the postmortem interval proceeds.
2. Swollen and autolytic neurons, with a pale perikaryon and nucleoplasm, and an absence of Nissl bodies. The nucleus can no longer be differentiated from the vacuolized and autolysing cytoplasm. The cells themselves have lost their contours and appear swollen and spherical. The swelling in particular represents the most fundamental postmortem change (whose differential diagnosis is retrograde degeneration).
3. Pericellular spaces surrounding neurons may be caused by postmortem autolytic processes that mimic edema, especially in the gray matter.

Children two years old and younger almost invariably exhibit periventricular and perivenous accumulation of cytoplasm-poor, lymphocyte-like mononuclear cells which suggest an *encephalitis* (so-called pseudoencephalitis). Those cell aggregations consist of neuroblasts as an indication of development, not of an inflammatory process. This age group also regularly shows a *superficial granule layer* of the cerebellar cortex composed of germinal cells (matrix cells). These usually disappear some time between the second and fourth years of life.

In cases of sudden death with brief agony or if tissues have been poorly fixed (Hirano 1981), extensive acute *swelling of oligodendroglia* is common. In addition, a generalized swelling and *clasmatodendrosis of astrocytes* is often seen. These changes are rather slight compared to the neuronal changes. They must also be regarded as non-specific and do not constitute markers of edema.

Lindenberg (1982) points out that the *state of the brain before circulatory arrest* also plays a role. If the agony was brief (healthy person who died within minutes), neurons and glial cells may show marked postmortem ischemic cell injury (vacuolation, homogenization, acute shrinkage associated with nuclear changes). Agony of long duration results in a largely unchanged cytology.

Not only does the architecture of the cells change, but their functional state and/or stainability with various reagents changes as well. Postmortem function and staining are influenced by many factors in addition to fixation procedures (time, temperature,

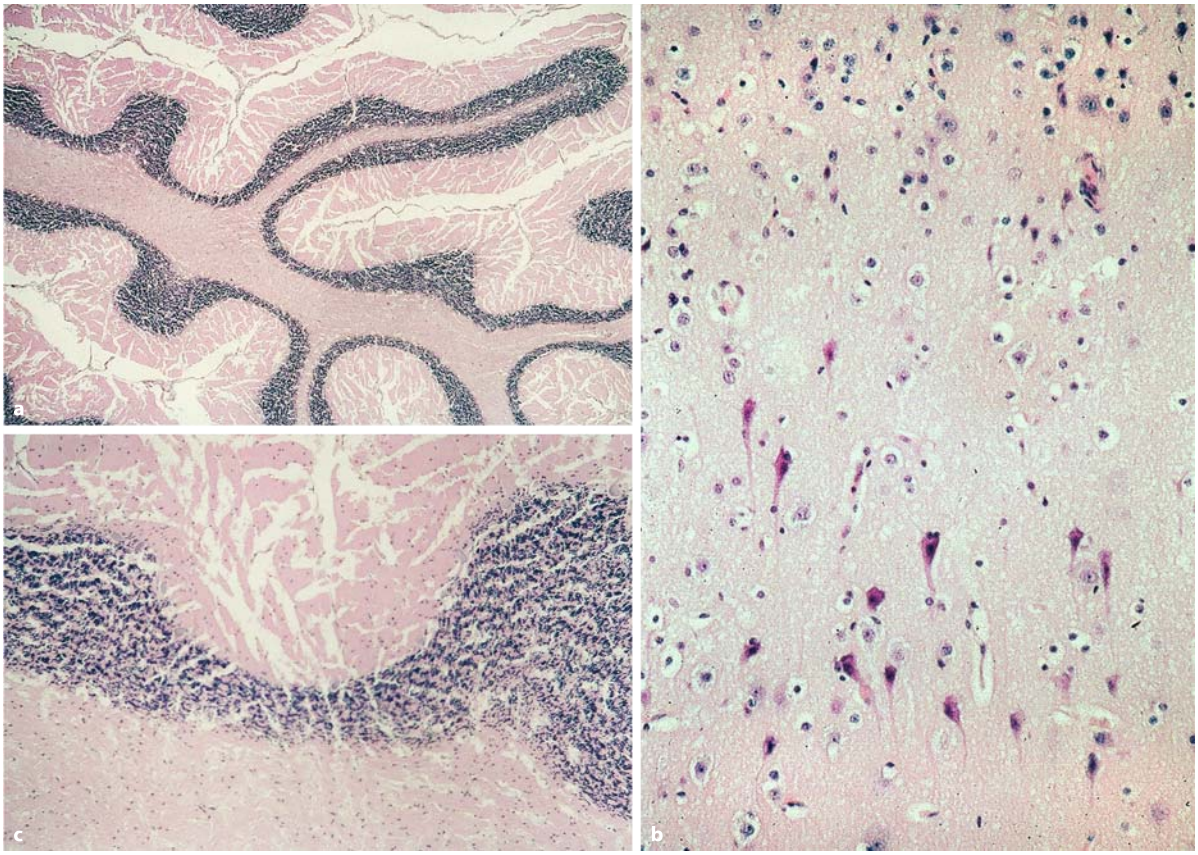

Fig. 4.26a–c. Minsinterpretable findings. **a, c** Crystalline vacuoles as seen within tissue sections after freezing of native brain tissue; **b** dark neurons as a postmortem phenomenon (**a–c** H&E; magnification **a** ×50, **b** ×300, **c** ×500)

and type of procedure). It is further known that the *enzyme activity of cells and tissue* depends in large part on the length of the postmortem interval (for a survey of findings prior to 1980 see Oehmichen 1980).

Numerous variables are known to affect the *immunoreactivity* of cells and tissue in the antigen–antibody reaction for immunohistological demonstration of epitopes (Grizzle et al. 2001). Among these variables are the interval between cellular death and fixation as well as the duration of fixation, the method of tissue processing, the preparation of paraffin blocks, the method of attaching tissue sections to microscopic slides, the interval between cutting tissue sections and immunostaining. To summarize, once findings are obtained by performing the relevant investigations, their proper interpretation requires long experience in the routine practice of neuropathology.

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Methods in Forensic Neuropathology 5

5.1 Macroscopic Examination

5.1.1 Principles of Brain Autopsy

5.1.1.1 Biosafety

Autopsy of the brain must begin by making certain that precautions have been taken to ensure biosafety (Nolte et al. 2002). Contact with droplets and/or direct cutaneous inoculation (percutaneous injury), even after the brain has been fixed in formalin, entails a risk of autopsy-transmitted infection. The overrepresentation of intravenous drug users among the forensic autopsy population means that the prevalence of *hepatitis B virus* (HBV), *hepatitis C virus* (HCV), and *human immunodeficiency virus* (HIV) is disproportionately high. Blood infected with HIV has a 0.3% risk of transmission per exposure, blood infected with HBV a 30% risk (Shapiro 1995), and HCV infected blood a 1.8 to 10% risk (Centers for Disease Control and Prevention 1998). Bodies infected with HIV are infectious for at least 2 weeks postmortem; after being dried and exposed to an ambient environment, HBV in human plasma remained infectious for 1 week (Bond et al. 1981).

Because relatively high risk is associated with autopsies on victims of *viral hemorrhagic fever*, a careful assessment of the risk and benefits should be made before autopsy. Autopsies on victims of Hantaan virus infections are less hazardous than those on victims of other viral hemorrhagic fever infections.

Creutzfeldt-Jakob disease (CJD), *bovine spongiform encephalopathy* (BSE) and other spongiform encephalopathies can be acquired by percutaneous exposure during autopsy. Infectious isoforms of host-membrane sialoglycoproteins known as prions cause transmissible dementias (Johnson and Gibbs 1998). Formalin does not inactivate prions and they retain their ability to be transmitted in paraffin blocks (Brown et al. 1986). Two histology technicians contracted CJD while working in neuropathology laboratories (Miller 1988). Guidelines for safe performance of autopsies, processing and handling tissues, decontaminating work surfaces and instruments are given in Table 5.1 (cf. Schulze-Schaeffer et al. 1998; Nolte et al. 2002). A contamination has to be performed with 1 N NaOH followed by 1 N HCl and rinsed water. Procedures for brain cutting must be carefully performed according to recommendation in Table 5.2.

5.1.1.2 Preserved Native Material

Specimens or liquids obtained at autopsy should be preserved for further investigations on native specimens. Exactly what tissues and how much are preserved depend on the nature of the problem to be solved. Specimens should be examined immediately, frozen or subjected to specific treatment (fixation with special agents). Table 5.3 lists a number of

Table 5.1. Procedures for decontaminating instruments and tables in cases of suspected Creutzfeldt-Jakob disease or bovine spongiform encephalopathy. Source: Nolte et al. 2002

1. Instruments and saw blades are placed into a large stainless steel dish, soaked for 1 h in 2 N sodium hydroxide or 2 h in 1 N sodium hydroxide, and then rinsed thoroughly in water before autoclaving at 134°C [gravity displacement steam autoclaving for 1 h; porous load steam autoclaving for one 18-min cycle at 200 kPa (2 atm) or six 3-min cycles at 200 kPa]
2. The Stryker saw is cleaned by repeated wetting with 2 N sodium hydroxide solution over a 1-h period
3. Any suspected areas of contamination of the autopsy table or room are decontaminated by repeated wetting over 1 h with 2 N sodium hydroxide

Table 5.2. Procedures for tissue preparation and cutting procedures in cases of suspected Creutzfeldt-Jakob disease or bovine spongiform encephalopathy. Source: Nolte et al. 2002

1. Formaldehyde fixation: the brain is examined and cut on the table covered with an absorbent pad with an impermeable backing
2. Samples for histology are placed in cassettes labeled "CJD precautions." Blocks of formalin-fixed tissue can be placed in 96% absolute formic acid for 60 min, followed by fresh 10% neutral buffered formalin solution for at least 48 h. Embedding in paraffin as usual
3. All instruments and surfaces are decontaminated
4. Routine staining:
   a. Slides are processed by hand
   b. Reagents are prepared in 100-ml disposable specimen cups
   c. After placing the coverslip on, slides are decontaminated by soaking them for 1 h in 2 N NaOH
   d. Slides are labeled "Infectious-CJD"
5. Tissue remnants, cutting debris, and contaminated formaldehyde solution should be discarded within a plastic container as infectious hospital waste for eventual incineration

forms of preservation that should be routinely applied in every case.

5.1.1.3 Documentation

Photographic documentation of pathological changes is an established part of macroscopic and microscopic examination in forensic neuropathology. As a means of documentation such pictures are worth many words of dry description. A scaled tape or ruler with clearly visible graduations may be placed within the photographic field to provide information on the size of the pathological finding, especially if it is a laceration, hemorrhage, or cavitation. The camera should be aimed at right angles to the surface of the slide or specimen.

Radiography is especially indicated before autopsy of victims of gunshot or of suspected child abuse. X-ray, CCT, and/or MRI can provide additional documentation for reconstruction as well as information essential to planning the autopsy, especially in cases involving embedded projectiles or old fractures (see pp. 90 ff).

5.1.2 Brain

In the field of forensic neuropathology the same techniques are to be applied as in clinical neuropathology. Therefore, textbooks of neuropathologic techniques are recommended, e.g., Dawson et al. (2003). The following short methodical description gives an introduction and general information on the applied techniques.

5.1.2.1 Fixation Procedures

The brain must not be examined fresh, or roughly 50% of lesions will be missed, compromising further examination, referral, and ultimately the verity of evidence presented in court. Fixation in 10% buffered formalin prior to routine examination by sectioning is thus essential. To be of good quality, fixation of the brain in *formalin* must meet the following requirements:

- The formalin is neutral and buffered
- The quantity is ample (10 times the volume of the brain) and at the right concentration (not less than 10% concentration)
- The fixation time is at least 2 weeks, but does not exceed 4 weeks (formalin becomes acidic at fixation times over 4 weeks)

Two techniques are used for brain fixation: the immersion technique and the perfusion technique. In the *immersion technique* the brain is removed in its

Table 5.3. Types of specimens, handling of body fluids and tissues for different types of examination

Specimen	Handling	Type of examination
Cerebrospinal fluid	Native/freezing	Electrocytes
		Toxic agents
	Native	Infectious agents
Brain tissue	Native/freezing	Toxic agents
		Neurochemical diagnosis (lipidoses)
	Native	Infectious agents
	Native/freezing	Histochemistry
	Formalin or other fixatives	Immunohistochemistry
		Molecular biology
	Glutaraldehyde	Electron microscopy
	Native/freezing	Molecular biology
	Formalin	Histology (routine)

natural state prior to any fixation. This has the advantage that untreated tissue and cerebrospinal fluid (CSF) can be obtained. The drawback is the risk of artificial wounding to the brain during removal and a fixation time lasting at least 14 days. There are two ways to avoid the creation of artifacts during fixation of the brain in formalin: table salt can be added to the formalin, which allows the brain to float freely in the solution; or, the brain can be suspended from a string tied to the basilar artery.

The *perfusion technique* achieves optimal fixation of the brain in situ within 2–3 h. Formalin is infused into the brain via carotid artery stumps. Perfusion is especially advisable if autolysis of the brain has already begun but not advanced far enough to prevent fluid flow. This technique minimizes the risk of artificial lesions being created during removal from the skull. Further macroscopic examination can be performed immediately thereafter.

5.1.2.2 Examination during Autopsy

Before the brain is removed the dura mater should be inspected for lacerations, punctures, external and subdural hemorrhage, thrombosis of the venous sinus, surgical wounds, etc. External examination of the brain begins at autopsy and provides information regarding subarachnoid hemorrhages, tumors, inflammatory processes, etc. If a basilar aneurysm has ruptured, the brain requires further preparation before fixation since it is easier to remove subarachnoidal blood and expose the aneurysm in the unfixed brain.

The CSF should also be removed prior to fixation of the brain. It can be drawn off either from the large basal cisterna during removal of the brain, or by lumbar puncture through the intervertebral disks in the area of the lumbar spine on the ventral side after removal of the internal organs from the abdominal cavity. For toxicological analysis native brain tissue should be removed from a region with no pathological changes, from the occipital lobe for example.

5.1.2.3 Sectioning of the Formalin-Fixed Brain

When obtaining brain sections a uniform procedure should be used to allow consistent written and/or photographic documentation of any external and internal lesions. The formalin-fixed brain should first be weighed, followed by a detailed description of the outer structure of the dura mater, the large external vessels, leptomeninges convolutions and any signs of brain swelling (herniation of the cerebellum and/or hippocampus, flattening of the gyri, etc.). The procedure should proceed as outlined by, for example, Vonsattel et al. (1995).

Parallel sections are then cut through the cerebral hemispheres once the cerebellum and brain stem have been excised cutting through the cerebral peduncles (Fig. 5.1a). Sections of the cerebellum and brain stem (Fig. 5.1b–d) can also be obtained along the frontal plane, the cerebellum and brain stem thus being cut together with the cerebellar peduncles. This demonstrates the fourth ventricle to best advantage, useful in cases of subarachnoid hemorrhage, for example. Alternatively, sections can be cut longitudinally through the vermis of the cerebellum up to the fourth ventricle; the cerebellar peduncles are then excised to isolate both cerebellar hemispheres near the brain stem. Frontal incisions are then made through

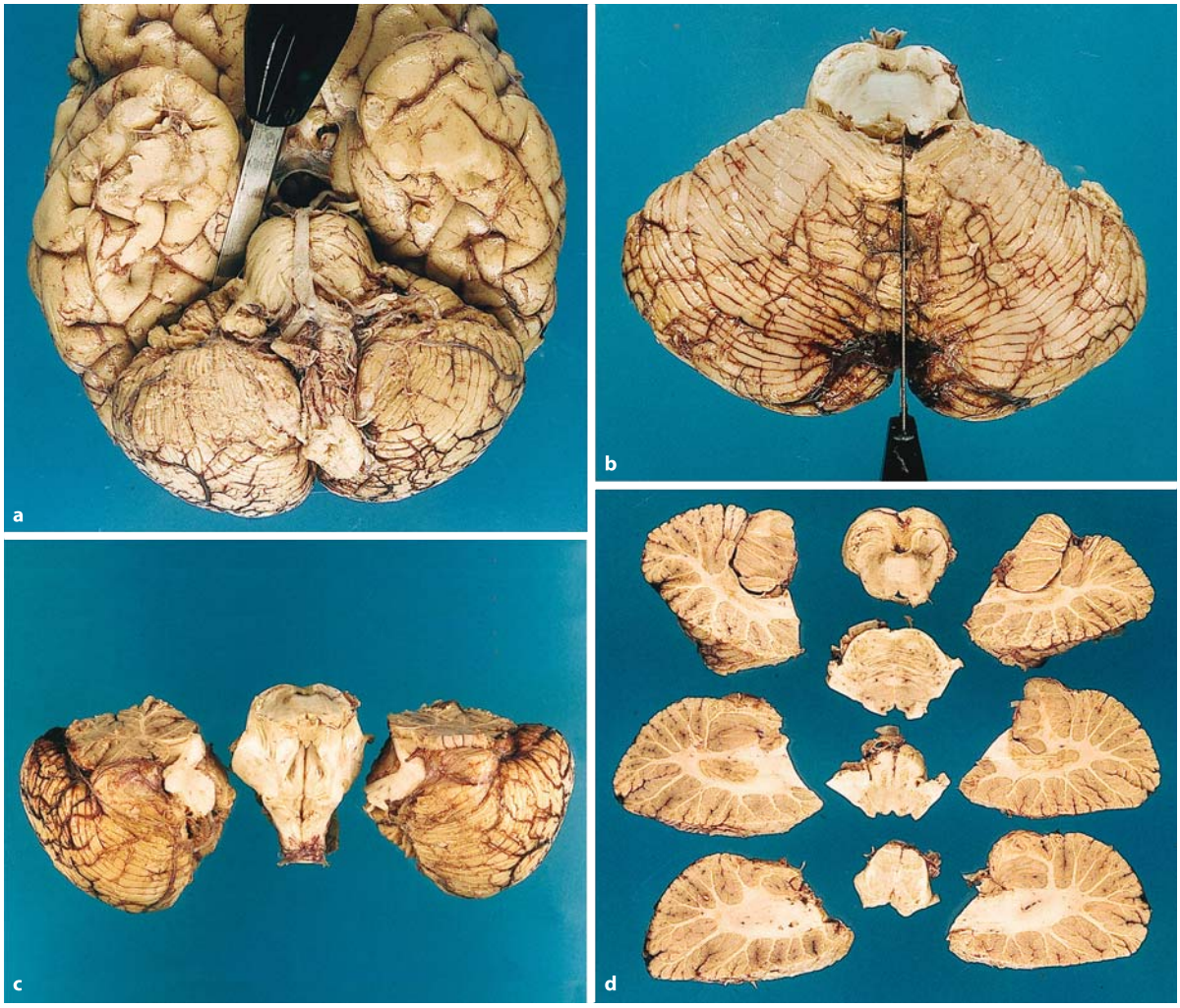

Fig. 5.1a–d. After inspection and documentation of the brain surface the cerebellum and brain stem have been excised cutting through the cerebral peduncles (**a**), cutting through the cerebellar vermis (**b**), separating both the cerebellar hemispheres (**c**) and making parasaggital incisions through the brain stem as well as parasagittal sections through the cerebellum (**d**)

the brain stem, medulla oblongata, and superior cervical cord. Parasagittal sections are then cut through the cerebellar hemispheres parallel to the cut surface of the cerebellar vermis. This method demonstrates alcoholic superior vermal atrophy to best advantage. The method of cutting the cerebellum should thus be tailored to the case. In degenerative or alcoholic disease of the cerebellum, cutting in the parasagittal plane will best demonstrate the lesions, whereas in conditions dilating or impinging on the fourth ventricle, cutting the cerebellum attached to the brain stem will best preserve the relations that need to be seen.

The sections of the cerebrum can be cut in the frontal (coronal) plane, corresponding to the classical procedure of clinical neuropathology (Fig. 5.2). Or they can be cut parallel to the hat line (Fig. 5.3), the cut surfaces thus correlating with clinical images of axial CCT or MRT (Matsui and Hirano 1978). A large knife held at right angles to the base of the brain or the frontal pole can be used to cut sections. The sections should be no more than 1 cm thick. This can be achieved freehand, using a pair of specially designed brain angles or even using pipettes across which the knife is rolled. These techniques will obviate the appearance of knife lines across the surfaces of the cut sections, aiding the presentation appearance of photographic evidence.

5.1.2.4 Block Selection for Microscopy

If gross lesions are found during sectioning of the brain, selecting blocks becomes relatively easy. If a *tumor* is involved, a correct impression of the cytology and architecture can usually be obtained from

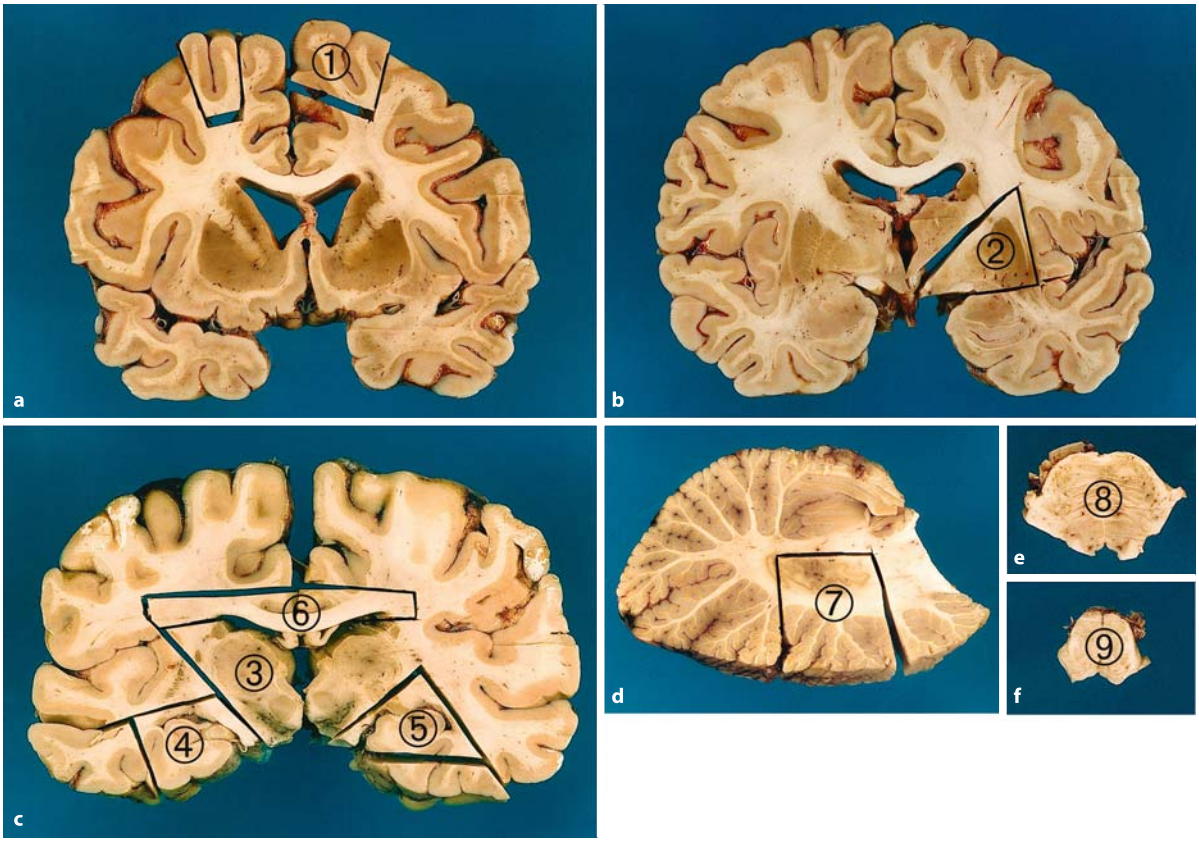

Fig. 5.2a–f. Frontal sections through the cerebrum and block selection. The sections were cut parallel to the frontal plane and *marked blocks* are selected for histological examination

blocks obtained from a well-defined border of the lesion. In the case of *cortical contusion injuries* or vascular lesions, it is necessary to take a sizeable block extending the entire width of the glass slide and including at least one edge of the contusion injury and adjacent cortex. If there has been *hemorrhaging* in the brain, the presence of possible degenerative or inflammatory changes in the vessels can only be determined if the blocks originate from the ganglionic or medial side of the lesion and from the contralateral portion of the brain. The hemorrhagic margins in such cases should be scrutinized for small, easily overlooked anomalous vessels.

Proper selection of blocks is more difficult in brains with no apparent gross lesions. The clinical record can sometimes provide information on the topography of the lesions (Courville 1964). If the deceased has suffered from mental deterioration, cortical-subcortical blocks should be obtained from the midfrontal area; if there was known paralysis, blocks should be taken from the contralateral motor cortex or the motor pathways; blocks from patients with epilepsy should include the motor cortex, uncus or hippocampus; if there was documented visual failure, tissue from the calcarine cortex, optic chiasm, and optic tract must be examined; in cases of ataxia, blocks from the cerebellar cortex (including dentate nucleus), medulla (including olivary nucleus), and spinal cord are needed; if the victim has died of sudden death in a febrile state, blocks should be made of the upper spinal cord, pons, medulla, thalamus, and midbrain.

If the clinical record indicates no specific area of the brain and no gross lesions are present, multiple blocks may be necessary. They can be of various sizes and shapes (triangular, rectangular, elongated, square, etc.) and should enable identification of the topography on the histological slide, as described by Courville (1964). Notches can be made on the block to distinguish the right and left hemispheres. Our own experience with routine cases has shown that the following areas of the brain must be preserved for microscopic examination (see Figs. 5.2, 5.3):

1. Frontal cortex (first and second frontal gyrus including white matter)
2. Lenticular nucleus
3. Thalamic nuclei
4. and 5. Hippocampus (right and left)
6. Corpus callosum (including caudate nuclei)

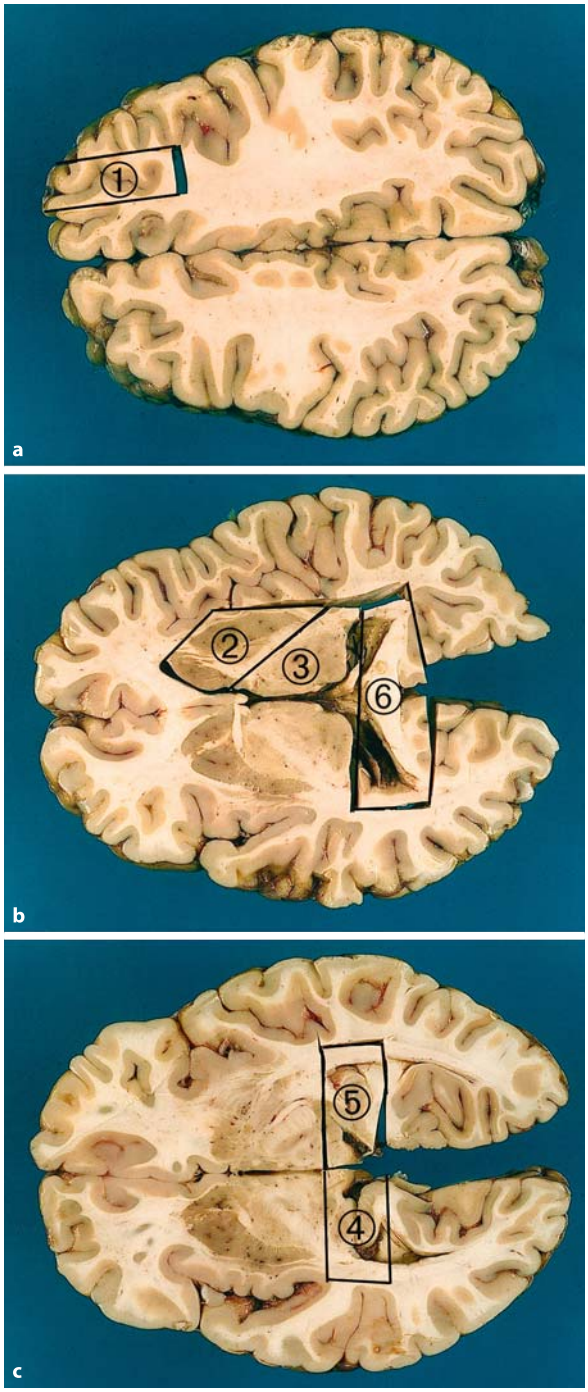

Fig. 5.3a–c. Sections cut parallel to the hat line. The *marked blocks* are selected for histological investigation

7. Cerebellum (including cortex and dentate nucleus)
8. Pons
9. Medulla

If brain tissue from a region is embedded in paraffin, tissue from the same area should also be preserved in formalin. Frozen sections may subsequently be needed for metallic methods or special stains.

5.1.2.5 Paraffin Embedding

The *paraffin-embedding* procedure must avoid too rapid a dehydration or overheating of paraffin, which can induce shrinkage of neuropil and cells, artefactually giving rise to vast empty spaces around blood vessels and neurons. We recommend the following paraffin-embedding procedure:

- 6 h in ethanol (70%), +40°C
- 4 h each in ethanol (80%, 90%, 3×100%), +40°C
- 2 h each in xylol, 3×, +40°C
- 1 h each in paraffin, 3×, +60°C
- 3 h in paraffin, +60°C

5.1.2.6 Special Problems

Identification of CNS Tissue. Forensic practice requires not only the personal identification of tissue samples, for which DNA techniques are indicated, but also the identification of specific types of tissue, whether, for example, a particular piece of tissue derives from the brain or some other organ. For this purpose morphological criteria (Oehmichen 1984; Oehmichen et al. 1984) can be applied as well as immunohistochemical methods using antibodies specific for the brain, or specific for glial or neuronal epitopes.

Kimura et al. (1995) showed that the ratio between the non-muscle myosin heavy chain isoforms M II A and M II B differs from tissue to tissue. They developed a highly sensitive ELISA to quantify each heavy chain isoform of myosin and establish the traits of different types of brain tissue.

Brain Tissue of Mummies. Only a few investigators have examined the brain tissue of mummies. Gerszten and Martínez (1995) investigated the brains of 15 naturally mummified humans dating from 1,000 BC to 1,500 AD and excavated from the deserts of northern Chile. Macroscopically the cerebral hemispheres, cerebellum, dura mater, and spinal cord of several cases were found to be relatively well preserved. Five mummies exhibited signs of intracranial disease, three of external injury. One mummy had evidence of subarachnoid, one of intracerebral hemorrhage. The brain parenchyma exhibited on light microscopy vascular structures against an eosinophilic staining background but few cellular elements. The architecture of the dura mater consisted, as is normal, of collagen fibrils.

5.1.3 Spinal Cord

The spinal cord including the dura mater is carefully removed from the spinal canal according to recommendations made elsewhere (Hill and Anderson 1988). If a Rokitansky evisceration has been done as part of the general autopsy, then the spinal cord can easily be removed anteriorly by cutting the laminae with a Stryker saw. Posterior removal of the spinal cord is more laborious, involving posterior laminectomy. Posterior removal is essential, however, in cases where the cervical spinal cord must be seen in situ and relationships determined, such as Arnold–Chiari malformation or the presence of prior surgery in the cervical region. Whether removed by the anterior or posterior route, the cord should be preserved in a hanging position in such a manner that preserves the dura mater.

Macroscopic examination should begin with inspection of the outer and inner surfaces of the dura mater, followed by examination of the leptomeninges and leptomeningeal vessels. The spinal cord is then cut into pieces and cross sections scrutinized. Blocks should be made from the various segments of the spinal cord.

The *cervical spine* including the occipitocervical junction must be removed in cases of mechanical brain injury (MBI) or any case involving mechanical injury of the neck, e.g., during strangulation, to acquire supplementary biomechanical information regarding the cause of death. Berzlanovich et al. (1998) have described the technique for dissecting the cervical vertebral column. The removed sample is fixed in 4% formalin for at least 14 days. After fixation, a circular saw is used to cut the cord in the sagittal direction along the midline. Cartilaginous and bony tissues are evaluated for fractures, tumor, hemorrhages, necrosis, etc. The spinal canal is inspected for cord compression and/or stenosis. For evaluation of dural hemorrhages, the spinal cord and spinal dura are removed. The isolated spinal cord is cut into multiple cross sections and the cut surfaces examined for spinal hemorrhage, necrosis, cysts, and/or inflammation.

Preparation and documentation of the cervical spine must focus on the following structures:

- The vertebral body (degenerative alteration?; fracture?; luxation?; presence and extent of hematopoiesis?)
- The intervertebral disc (laceration?; hemorrhage?; complete or partial transection?)
- The spinal canal (cord compression?; stenosis?)
- The spinal dura (extradural or subdural hemorrhage?)
- The spinal cord (softening?; hemorrhage?; scarring?)

If macroscopic examination discloses pathological findings, soft tissues, bones, and vessels must be removed for embedding and histological examination. In cases such as unexplained cerebellar infarction, where vertebral dissection is suspected (Auer et al. 1994), particular attention must be paid to the vertebral arteries for signs of trauma and/or thrombosis. After fixation in formalin, the vertebral arteries on both sides must be removed by bilateral excision. Longitudinal and cross sections from the spinal cord are embedded and examined microscopically, especially for signs of axonal injury or a cell reaction.

5.1.4 Peripheral Nerves

Peripheral nerves need only be inspected if disease or injury is suspected. Material is garnered from peripheral nerves that could be of clinical or forensic interest.

Diagnosis of mechanical, poisoning or ischemic insults depends in large part on the morphological examination of peripheral nerves. The morphology remains optimally preserved if the tissue is fixed immediately in glutaraldehyde and embedded in plastic. Success often depends on early fixation of the nerve. Semithin and/or ultrathin sections are cut. In routine forensic neuropathological practice, any one of a number of stains and/or antibody reactions are used on 5-µm sections of paraffin-embedded tissue, among them the following:

Table 5.4. Histologic demonstration of different tissue structures in peripheral nerves by different staining techniques

Axonal injury	Silver stain
	β-APP expression
Collagen fibers	Trichrome stain
Macrophage activation	CD 68 expression
Myelin injury	Klüver–Barrera stain
	Basic myelin protein expression
Neuronal injury	H&E stain
	Nissl stain
Oligodendrocytes/ Schwann cells	Carbonic anhydrase II expression

Most institutes of forensic pathology are as ill equipped for the investigation of peripheral nerves

as they are for investigation of muscles. Forensic pathologists also often lack the necessary experience for their proper examination. Difficult cases, therefore, must be referred to clinical neuropathological colleagues.

5.2 Microscopic Examination

As a rule, the *thickness of paraffin sections* should not exceed 5 µm. The most common stain for paraffin sections is hematoxylin and eosin stain (H&E). Blue hematoxylin, a base, stains acidic cell structures such as nuclei, nucleoli, and Nissl bodies, while the acidic eosin stains basic components, mainly proteins, of cytoplasm, red blood cells, glial cell fibers, and collagenous fibers.

A number of *special stains* are used in classic neuroanatomy and neuropathology, which will be only briefly listed here together with their target tissue (for an overview see Luna 1960; Rális et al. 1973; DeLellis 1988; Böck 1989):

Table 5.5. Routine techniques which demonstrate different structures of the CNS

Neurons: cresyl violet stain (Feigin and Cravioto 1961)

Myelin: Luxol Fast Blue

Neurons and myelin: cresyl violet/Luxol Fast Blue (Klüver and Barrera 1953)

Axons: silver techniques (Bielschowsky, – see Hirano and Zimmermann 1962)

Glial fibers: silver technique (Holzer 1921)

Astrocytes: silver technique (Cajal 1913)

Microglia: silver technique (Naoumenko and Feigin 1963)

Oligodendrocyte: silver technique (Conn and Darow 1943)

Polymorphonuclear (neutrophilic) leukocytes: histochemistry – naphtol-AS-D chloracetate esterase (N-AS-DCIAE – see Böck 1989)

Reticulin fibers: silver technique (Gomori 1937)

In recent years numerous antibodies have been developed for *immunohistochemical techniques*. These antibodies are capable of highly specific staining of cells, fibers, etc. The entire spectrum will not be presented here, only antibodies known to be selective for specific cells and fibers of interest to forensic neuropathology. The expression of an epitope sometimes only provides information on the current functional state of a cell. Activated astrocytes, for example, are GFAP and/or vimentin positive, activated microglia CD68 positive, whereas in a resting state they are partly GFAP negative and CD68 negative (see above).

Surveys of immunohistochemical methods have been published by Sternberger (1979) and, more recently, by DeLellis (1988). Only a few antibodies used for routine demonstration of cytological and histological structures will be described here (Table 5.4). Details on the numerous other staining methods can be obtained from the relevant volumes dealing with histological techniques (Luna 1960; Böck 1989). Here the following *histochemical methods* will be described:

- Demonstration of glycoproteins using periodic acid
- Demonstration of iron III (hemosiderin as a catabolic product of hemoglobin) using Prussian blue reaction
- Fat (lipid) demonstration using oil red O or Sudan solution

5.3 Postmortem Imaging

Radiographic study of MBI, of gunshot wounds of the head in particular, has long be used for localization and documentation of skull fractures as well as of bone and missile fragments in the brain (Lorenz 1948; Metter et al. 1989; for review see Brodgon 1998; Brodgon and Lichtenstein 2000). Cerebral computed tomography (CCT) is often employed in forensic investigations of, for example, gunshot wounds of the head (Schumacher et al. 1983a, b, 1985, 1987; Karger et al. 1998) and hanging (Wallace et al. 1994). CT should commonly be applied in forensic traumatology for biometric analysis and reconstruction (Donchin et al. 1994; Farkash et al. 2000; Thali et al. 2001). Such studies, like those of MBI (Schumacher et al. 1987; Wallace et al. 1994), are sometimes performed on isolated, formalin-fixed brains (Chance et al. 1998). Helical CCT scan, by contrast, has been used for 3D imaging of skull fractures (Myers et al. 1999). The brain can also be studied with magnet resonance imaging (MRI), whose findings correlate closely with neuropathological findings and are highly reproducible in isolated, formalin-fixed brains (sensitivity, 83.39%; specificity, 76.6%) (van den Hauwe et al. 1995). Several authors have shown that postmortem imaging findings correlate with known neurological disease patterns (Nagara et al.

Table 5.6. Selected antibodies for identification of specific cell types, their processes and/or specific types of injury

Target	Epitope	Author
Neuron	Neuron-specific enolase (NSE) (Dako)	Reynolds et al. (1994)
Axons		
(Normal)	Neurofilament protein (NFP) (Binding site)	Perez et al. (1990)
(Pathologic)	β-Amyloid precursor protein (β-APP) (Chemicon)	Gentleman et al. (1993)
Dendrites	Microtubule-associated protein (MAP) (Dianova)	Li et al. (1997)
Myelin	Myelin basic protein (MBP) (Dako)	Hardy et al. (1996)
Synapses	Synaptophysin (Binding site)	Reynolds et al. (1994)
Astrocyte	Glial fibrillary acidic protein (GFAP) (Dako)	Galou et al. (1996)
	Vimentin (Dako)	Reynolds et al. (1994)
	S 100 protein (Binding site)	Reynolds et al. (1994)
Oligodendrocyte	RIP (Sigma)	Friedman et al. (1989)
	Carbonic anhydrase II (CA II) (binding site)	Cammer et al. (1977)
Microglia		
(Normal)	F4/80 (Serotec)	Gordon et al. (1992)
(Pathologic)	CD68 (Dako)	Esiri and McGee (1986)
Endothelial cells	Factor VIII (F VIII) (Dako)	Sehested and Hou-Jensen (1981)

1987; Wind et al. 1988; Bisset 1998; Erly et al. 1999). Harris (1999) demonstrated the utility of such imaging studies for forensic pathology (Oehmichen et al. 2003, see also Chapter 8) (Figs. 8.15–8.18).

Continued technical improvements have increased the sensitivity of imaging procedures in postmortem examinations (Gean 1995; Gilman 1998; Gulyas and Lestar 1999). These techniques are increasingly in demand as society grows less tolerant toward the conduction of autopsies. Even if autopsy remains the „gold standard" of pathologic-anatomical diagnosis and forensic investigation, imaging procedures can be the source of valuable supplementary information. In cases where they are able to produce results superior to those of other methods, imaging procedures should be applied on a regular basis. They can be used in the quality control of the results of postmortem examination and its documentation, by for example localizing foreign objects (bone splinters, projectiles, and other types of foreign object). 3D reconstruction using digital imaging enables among other possibilities biomechanical reconstruction of a traumatic event postmortem (cf. Wind et al. 1988).

When does CCT/MRI imaging provide useful information for the forensic neuropathologist?

1. Providing information on the brain in surviving victims of gunshot injury. Such findings, for example, are sometimes needed for court proceedings.
2. The pathologist may review the imaging together with the radiologist after a patient has died in surgery that has resulted in excision of the relevant portions (in the case of gunshot wounds: entrance, exit, dura, bone, and portions of the injured brain) of the deceased's head.
3. Review of the imaging with the radiologist can be helpful if a patient has survived an injury for weeks, months or years and the brain at death exhibits only repair and scarring.
4. Review of *premortem* imaging can be helpful if the brain has undergone autolysis in situ, as happens in „respirator brain," for example, which results in the bullet descending through the liquefying brain to the lowermost intracranial location.
5. Postmortem CCT/MRI may help in the examination of bodies burned so severely that bony entrances have been obscured, damaged or obliterated altogether.
6. Imaging of facial fractures so as to obviate the need of disturbing the features by dissection.
7. Examination of embalmed, exhumed bodies in which entrances, exits, and trajectories are altered.

In light of these advantages there can be no question of the importance of imaging procedures for evaluation in neurotraumatology, above all for the examination and documentation of gunshot wounds of the head. The value of imaging techniques for postmortem documentation of gunshot injuries of the head is evident, especially if bone or projectile fragments have been displaced at autopsy. Biometric reconstruction using the digital data obtained with imaging procedures on the isolated, formalin-fixed brain is able to replicate the position of the brain in a standing individual (see pp. 167 ff).

These observations allow the following conclusions:

- CCT and MRI are no substitute for autopsy in medicolegal cases. Rather they should be used to supplement other findings in cases where survival or interventions have altered the original wounds.
- 3D imaging in most cases is based on spiral CCT volume data sets and is able to establish the direction in which the missile traveled in gunshot injuries, tracing the missile track, and distinguishing between entrance and exit wounds. Commercially available software is able to process the biometrically relevant data. Lesions along the missile track such as edema and hemorrhage can be distinguished by MR imaging of the brain parenchyma, thus providing important information on primary and secondary changes caused, for example, by gunshot wounds of the head.
- CCT is especially helpful in locating opaque foreign objects in the brain which are sometimes difficult to locate at autopsy, objects such as bullet and bone fragments.
- Although autopsy on the isolated, formalin-fixed brain can also demonstrate opaque fragments and the missile track, it is usually not able to determine the direction of travel, making biometric classification difficult or impossible.
- CCT-obtained 3D imaging is positively indicated if there is uncertainty regarding the location of entrance and exit wounds, or where the bullet and/or bullet fragments have lodged in the brain, and if documentation of the in situ locations of bone and projectile fragments is needed. CCT-obtained 3D imaging is relatively indicated if photographic documentation is impossible.
- Imaging procedures have the disadvantage compared to autopsy of being less able to detect microscopic signs of a preexisting disease process or hypoxic changes to neuronal tissues. They are also unable to assist in assessing the vitality of gunshot wounds or of survival time.

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Physical Trauma II

Basic Principles of Mechanical Trauma 6

6.1 Classification

The term "*trauma*" generally implies "wound" or "injury," whether physical or psychic. Physical injury/wound means damage inflicted to tissue of the body by an external force. Synonymous with trauma and injury is "tissue damage" as the sequelae of external violence inflicted on the body. The action or process leading to trauma, injury, wound or tissue damage in Germany is called "traumatisieren," which is translated as "traumatization," i.e., "wounding," "hurting," "lesioning" or "injuring," which may be replaced by the following verbs: to injure, to bruise, to hurt, to damage, to lesion. The term "trauma" is used in common and scientific language synonymously to name the process of wounding as well as the effect of wounding. We will differentiate the nomenclature in the following text according to *Dorland's Medical Dictionary*. Therefore, we will avoid the term "traumatic brain injury" and use the term "mechanically caused brain injury" (MBI) instead.

Damage of the brain due to mechanical loading of the head is differentiated according to whether the injury is penetrating or non-penetrating, i.e., the coverings of the brain are penetrated including the dura mater or not, and the result is called *open* or *closed skull-brain injury* or *open/closed craniocerebral injury* respectively. A closed brain injury is characterized by an intact dura mater; in contrast, an open brain injury usually is characterized by a laceration of skin and dura mater as well as a fracture of the skull. *Penetrating skull-brain injury* is caused by bullets or other flying objects, by sharp or pointed implements or bar-like weapons and by blunt traumatic violence; *closed brain injury* results from the impact suffered in traffic or sports accidents, falls or explosions, from violent blows delivered by hands and feet/shoes, weapons, or objects falling on the head. With regard to their possible consequences, mechanical *injuries of the coverings*, e.g., injuries to the scalp, skull, dura, and leptomeninges, must be distinguished from *injuries of the brain parenchyma*. Whereas scalp injuries entail the risk of complicated wound healing processes, which may prove fatal if secondary bacterial infection reaches intracranial structures, skull injuries involving bone fractures and/or bleeding can lead to space-occupying processes with shifting of the brain and herniation, sometimes accompanied by brain stem hemorrhage.

A distinction must also be made between trauma caused by *local impact* (contact force) and trauma associated with head motion, i.e., with *acceleration*, *deceleration*, and *rotational movements* (non-contact or inertial force). Impact-induced injuries of the brain are commonly associated with cortical hemorrhages on the side of impact (homolateral = "coup" contusion injuries) and/or focal hemorrhages on the opposite side (misleadingly called "contrecoup" contusion injuries), both known as "contusion" or "contusional hemorrhage" as well. Coup and contralateral cortical hemorrhages are characterized pathologi-

cally by perivascular cortical hemorrhages. Injuries of the dura and leptomeninx may be associated with both impact and inertial forces: rapid alterations in linear motion of the head or a rapid change in its direction of motion can result in stretching, shearing, and pressure of brain structures, or cause tangential movements of the brain's surface relative to the interior of the skull (Al-Bsharat et al. 1999). Distinction must also be made between *focal* and *diffuse injuries*, as well as between *primary mechanical injury* and *secondary changes*, especially hypoxia, ischemic anoxia, and brain edema.

Moreover, we have to classify mechanical *spine injury* or spinal cord injury according to the same criteria as mechanical head injury, and we have to differentiate mechanical injuries of the CNS from injuries of the *peripheral nervous system* (PNS).

Last but not least, we have to sum up other types of physical trauma beside mechanical trauma: the last chapter of Part II (Chap. 12) will deal with neuropathological features induced by different physical influences.

6.2 Epidemiology of Mechanical Brain Injury

The available epidemiological data on mechanical brain injury (MBI) and spinal cord injury (SCI) come mainly from the USA (USA in 1974 – Kalsbeek et al. 1981; San Diego County in 1981 – Kraus et al. 1984). The data indicate that about 50% of all deaths following mechanical injury result from damage to the central nervous system (CNS). Reports from Australia (Selecki et al. 1982), Southern Australia (Simpson et al. 1981), and Virginia (Rimel 1981) show that about 10% of fatal injuries of the CNS involve damage to the spinal cord (see Kraus et al. 1984). In 1990, the National Health Interview Survey on brain injury frequency (Collins 1990) reported approximately 373,000 hospital discharges annually associated with a diagnosis of MBI, while 75,000 MBI-related deaths were registered in the USA from 1985 through 1987.

A more recent study, Trauma Facts 1992, has provided evidence that an estimated 500,000 adult Americans are admitted to a hospital with MBI each year: of these, an estimated 75,000–90,000 die; while 70,000–90,000 of those surviving endure life-long debilitating loss of function; an additional 2,000 continue to exist in a persistent vegetative state. Another evaluation shows that acute brain injury accounts for nearly 40% of all traumatic deaths in the USA (Waxweiler et al. 1995). Typically, the victim of a MBI is a young male aged 15–24 years and at the beginning of his productive life (Torner and Schootman 1996). The mortality rate of MBI in children is estimated to vary from 9% to 35% (James 1985). Direct costs are estimated to be US$ 4 billions annually, and indirect costs may exceed 10 times that amount (Johnston 1989).

In 1992, the most common cause of fatal MBI in the USA was injury secondary to firearm use (Sosin et al. 1995). From 1979 through 1986, gunshot wounds accounted for at least 14% of all MBI-related deaths (Sosin et al. 1989). In the same period, the annual rate of motor vehicle-related MBI mortality was 9.5 per 100,000 for men and 3.9 for women. Falls accounted for between 20% and 30% of head injuries; the number of head injury-related deaths was 16.9 per 100,000 residents.

The data from West Germany are meager and mainly outdated. Franke (1972) assumed that about 30% of all cases of accidental injury treated in hospital involved MBI. At that time, about 35,000 fatal accidents occurred in the former Federal Republic of Germany (FRG) annually and it can be assumed that more than 10,000 of those victims had suffered MBI. Among the more recent German studies (Jennett 1996; Lehr et al. 1997), that of Bouillon et al. (1999) is worthy of special note even though it is restricted to a single city (Cologne) with a population of 1 million inhabitants. From 1990 to 1996, 49% (n=93) of the victims of severe brain trauma had suffered multiple injuries. The overall mortality rate was 46.6%. Sixty percent of the deaths occurred in a pre-clinical setting.

Data on file at the Federal Office of German Statistics reveal the following: of the approximately 250,000 patients hospitalized in 1998 with a diagnosis of "skull fracture and intracranial injuries," 8,000 died. Half of these patients may well die in the preclinical phase, the other half in the clinic (Personal Communication, Systemanalyse der präklinischen und frühen klinischen Versorgung beim schweren Schädel-Hirn-Trauma, February 2001 from A. Baethmann, BMBF-Verbund Neurotraumatologie und Neuropsychologische Rehabilitation München).

6.3 Forensic Aspects

MBI may be an auxiliary finding at autopsy, but it can also be found to be the primary cause of death or a major contributor to the lethal process. Every incidence of death subsequent to MBI must be classified as a "death due to unnatural causes" since it must follow an accident, a suicide, or a homicide, each of which poses its unique forensic problems.

The neuropathologist must not only establish the cause of death. He must also try to reconstruct the external event of violence and the internal mechanisms which have produced an injury. Moreover he has to realize the processes leading to the sequelae

of this injury. This requires knowledge of the biomechanics and pathophysiology of injuries (Gurdjian 1975; Breig 1978; Sances et al. 1986; Stahlhammar 1990, 1991) as well as the clinical features and the physical and psychological sequelae. In some cases, the question arises as to whether the victim was still alive or already dead when the mechanical trauma was induced (*wound vitality*). If the victim was alive at the time of event, the *survival time* of each injury must be determined to enable reliable reconstruction of the temporal sequence of the traumatic events.

The extent of *secondary changes* (e.g., edema, hemorrhage, ischemia, thrombosis) occurring after impact partly are dependent upon time of survival. These alterations may in turn induce further changes (ischemia, anoxia, acidosis, embolism). *Functional deficits* may occur with no direct evidence of structural damage, but these deficits may themselves induce further functional changes. *Angiospasm*, for example in subarachnoid hemorrhage, can lead to disturbances in blood flow and infarction, but spasm is not a demonstrable postmortem phenomenon. An associated mechanical injury of the heart can also, for example, develop a disturbance in *intra-atrial conduction*. An *epileptic seizure*, which may induce circulatory cardiovascular failure, usually lacks discernible morphological equivalents. A *neural shock* – especially spinal shock – must be considered as a possible cause of death (White and Panjabi 1978; Unterharnscheidt 1993) even in the absence of specific morphologic changes associated with shock in the lung or other organs. Lastly, neurocardiac deaths may be unaccompanied by morphological findings.

The severity of an injury of the nervous system, and thus its potential to cause death, depends not only on the site and amount of the energy released by the external force for its immediate result, but also on other factors. These include the victim's age (Kirkpatrick and Pearson 1978), the ambient temperature, chemical influences (e.g., drugs and alcohol; Flamm et al. 1977), or injuries of other organs (e.g., cardiorespiratory trauma), which can lead to cerebral ischemia, cerebral fat embolism, etc. Finally, it is also dependent upon the clinical sequelae of an injury and the time span between the traumatic event and the first attempts at life-saving therapy. The morphologist must also confront the question of *prognosis*, both with regard to survival and to possible handicaps/functional deficits, which are evaluated according to the Glasgow Scale (Jennett et al. 1981; Dick 1992).

Moreover, the questions of *causality* in regard to the injury, the possibility of avoidance of the traumatic event, and/or neuropathological sequelae to adequate medical treatment and their secondary influences must be addressed in assessment of the outcome following an accident. *Differential diagnoses* must be considered as well as determination made of the presence of possible *preexistent* acute or chronic CNS *disease*, along with assessment of the possible role of *drugs* and *substances of abuse* in influencing the traumatic event or the subsequent *therapy*. In cases of mechanical trauma, the degree and timing of *incapacitation* must be estimated to establish, whether and for how long the victim was able to ward off further injury, to flee, or to be otherwise active.

6.4 Biomechanical Aspects and Pathomorphology

6.4.1 Physical Quantities

The following physical quantities and units of measure are used in describing the biomechanics of injury of the head and/or brain (International System of Units = SI units):

- Linear velocity, measured in m/s (meters per second)
- Linear acceleration, measured in m/s^2, especially gravitational acceleration, which implies the acceleration toward the earth's center, g=9.81 m/s^2
- Force, measured in N (Newton), equivalent to kg m/s^2
- Mass, measured in kg (1 kg=2.2 lb)
- Energy (work), measured in J (Joule), equivalent to N m. Energy can appear as kinetic energy (associated with a moving object) or potential energy (associated with the position of an object). The kinetic energy is described as $E=1/2\ mv^2$ (m=mass, v=velocity). The potential energy of an object in the gravitational field of the earth is described by $E=m\ g\ h$ (h = height above the ground, measured in meters)
- Angular velocity, measured in rad/s (radians per second, 1 rad=180°/π=57.3°)
- Angular acceleration, measured in rad/s^2

6.4.2 Mechanical Forces

Nerve and vessel disruption as well as fractures and lacerations are explainable according to the laws of physics (Thibault and Gennarelli 1985). The brain injuries may be caused by a violent impact to the head, or it might be that the head strikes or is struck by an object, e.g., by falling to the ground or being thrown against the dashboard of a car or by receiving a hammer blow. The resulting mechanical loading of the head and the resulting contact and inertial forces to the brain induce local near and remote strains and

Table 6.1. Types of injury caused by different biophysical mechanisms

Types of injury	Contact forces	Non-contact forces	
		Translational acceleration	Rotational acceleration
Skull fracture	+++		
Epidural hemorrhage	+++	+	+
Subdural hemorrhage	++	+++	+
Subarachnoid hemorrhage	+	+	+++
Cortical hemorrhage	Homolateral	Contralateral	
Intracerebral hemorrhage		+++	+++
Intraventricular hemorrhage			+++
Gliding contusion injury			+++
Diffuse axonal injury		+	+++
Concussion injury			+++

local and global movements generating vascular and brain tissue damage, causing focal and diffuse brain injuries (Gennarelli and Meaney 1996).

The basic mechanisms causing the different types of mechanical head injuries can be summarized as follows (cf. Table 6.1):

- *Impact injury* (deformation injury) – with local effects resulting from contact between the head and an object (**contact forces**):
  - Abrasion, contusion, and laceration of the scalp
  - Skull fracture
  - Epidural hemorrhage
  - Subdural hemorrhage
  - Cortical hemorrhages (contusion of the brain)
- *Acceleration injury* (head – positive or negative – acceleration) – with resultant production of intracranial pressure gradients and shearing and tensile forces (*inertial forces* = **non-contact forces**) to the brain:
  - Subdural hemorrhage
  - Subarachnoid hemorrhage
  - Intracerebral hemorrhage
  - Gliding contusion injury
  - Diffuse axonal injury (DAI)
  - Cortical hemorrhage (cavitation)

In addition the following types of mechanical loading to the head and brain are theoretically distinguished. In reality, as a rule, combinations occur, and impulsive loading usually results from (large, slow, blunt) impact. However, in some cases one or the other mechanism is predominant.

1. Static loading
   The head is slowly compressed causing fractures of the vault and base of the skull, often occurring while consciousness is preserved. In severe cases deformation and laceration of the brain appear with fatal consequences (Gennarelli and Meaney 1996).
2. Impact loading or contact
   An object strikes the head or the head strikes an object. If the object is massy, flat, and slow moving, its impact sets the head in motion. If the object is small and rapidly moving, its energy is highly concentrated at the impact point (contact force) and used to produce strongly localized fractures (perforations) to the skull and coup contusions to the brain and does not cause the head to move.
3. Impulsive loading or non-contact
   The head is set into sudden motion without significant contact when force or a change of speed is applied to the torso or neck, but not directly to the head. This causes the tethered neck and head to swing due to the inertia of the mass. Whiplash is one consequence, i.e., the head moves rapidly in one direction, is then restrained by the neck and bounces back with the result of high angular acceleration loading to the brain (Bandak and Eppinger 1994; de Jager and Sauren 1994).
4. Linear acceleration
   These types of loading are caused by a rapid change in translational motion (anterior-poste-

rior or lateral) of the head, the different biomechanical properties of the head structures (skull – dura mater – leptomeninx – brain parenchyma) creating tensile traction and a compressive load within the interior of the skull. These forces also cause tissue acceleration, hemorrhage-inducing lacerations, and positive or negative intracranial pressure. The results include lacerations, vessel ruptures and DAI. This type of head movement can also injure the cervical spine, including the spinal cord and/or the spinal nerve roots.

5. Rotational (angular) acceleration
   Rotational acceleration occurs when the head is rotated about its center of mass. Usually there is a combination of linear and rotational acceleration and angular acceleration occurs when the head swings in a sagittal or frontal plane. Because of its attachment to the neck, movement is permitted only in the form of an arc. This is the most common movement of the head and the most injurious brain loading. It occurs most frequently and it combines the injurious mechanisms of both translational and rotational motions. For example Clarke et al. (1971) investigated the resultant loading to the head with shoulder-harness-restrained volunteers on sleds during exposure to sled deceleration of 9.5 *g*. As maximum values they found 555 rad/s^2 angular acceleration, 445 rad/s^2 angular deceleration, 18.5 rad/s angular velocity, 1.3 rad angular displacement and 20 *g* front head linear acceleration. The resulting mechanisms and loadings of the brain are:
   - Rotation of the brain around the cervical axis, i.e., the brain stem, may place a compressive, tensile or shearing load on collagenous fibers, blood vessels, axons, and cells. The result is diffuse brain damage, which can lead *to coma or other lapses of consciousness*. This type of damage is known as "diffuse axonal injury" (DAI).
   - Swirling brain movements laterally across the orbital and petrous ridges and the sphenoid wings cause *lacerations*, usually in *the frontal and temporal lobes*.

Events leading to the creation of such mechanisms (e.g., traffic accident, blow) always produce a combined biomechanical effect, pure rotation being as unlikely as pure translation. Gennarelli et al. (1972) observed the effects produced by the different types of mechanical force in experiments on squirrel monkeys. *Pure translation* of the head at peak positive accelerations ranging from 665 to 1,220 *g* (6–8 ms duration) did not generate cerebral concussion in a single animal, whereas *pure rotation* of the head at peak positive tangential levels at center of gravity ranging from 348 to 1,025 *g* (5.5–8 ms duration) produced concussion in all (n=13) animals. Both groups suffered visible intracranial lesions, but they were more frequent and severe after rotation. The relation (rotation versus translation) of different injuries in both groups were as follows: subdural hemorrhage 20:8, subarachnoid hemorrhage 27:1, intracerebral hemorrhages including petechial hemorrhages 22:4, cerebral contusions 5:6.

6.4.3 Types of Mechanical Brain Injury

The aforementioned biomechanical loadings can cause the following types of tissue destruction of the brain:

1. Strain or tension injuries
   To strain or create tension in a tissue with the result of damage means to pull, draw or stretch it beyond tolerable limits with the result of an injury. The results of this type of injury are undetectable using MRI, CT (Barth et al. 1986), or light microscopy, but require electron microscopy.
2. Shearing injuries
   Shearing forces are created when part of the brain moves at a different speed or angle than surrounding tissues. As different planes or areas of different strength pass each other, fibers are stretched and may suffer reversible or irreversible loss of function (Zhou et al. 1994). The resultant diffuse brain damage may be minor in each area, but clinically significant in its overall effect on consciousness and ability to function normally (Meaney et al. 1995; Miller et al. 1998; Brands et al. 2002). DAI and petechial hemorrhages can be demonstrated by MRI, but not by CT (Gean 1995).
3. Torsion injuries
   Torsional stress is created when one part of an object is twisted in one direction while another part remains motionless or is twisted in another direction. In the brain, the result is parenchymal laceration and hemorrhage such as gliding contusional injuries, both of which can be demonstrated by MRI or sometimes by CT.
4. Cavitation injuries
   An acute stopping of a moving head or a hard, rapid, broad impact of sufficient intensity leads to temporary high pressure at the pole of impact and short duration negative pressure at the antipole region opposite to impact. By falling short of the critical vapor pressure within liquids (e.g., blood or liquor) small gas bubbles (cavitations) are formed which, in collapsing after negative pressure has vanished, produce vessel damage and focal cortical hemorrhages. This mechanism has been verified experimentally by Nahum et al. (1977) and Lubock and Goldsmith (1980) and confirmed by mathematical modeling (Ruan et al. 1993; Young and Morfey 1998).

6.4.4 Pathology

The following types of morphological changes can be observed following mechanical loading the head and brain:

1. Skull deformation and fractures
   Deformation of bones of the skull is caused by the force of impact (fall or blow) to the head. Depending on the velocity, mass, contact area, and hardness of the impacting object, there may be perforation fracture, depressed fracture, linear fracture, or skull deformation without fracture. The fixed head is more vulnerable to fracture than the freely moving head.
   Skull fracture is a contact injury. If the impact involves a small area of contact (<13 cm^2) releasing a large amount of energy, the result may commonly be a *perforation fracture* or *depressed skull fracture* (Melvin and Evans 1971). If it occurs over a large surface area of contact it can inflict a *linear skull fracture* (Yoganandan et al. 1995). Linear skull fractures are usually caused by falls and not by blows.
   Basilar skull fractures are differentiated according to the site of impact: temporo-mandibular loading in conjunction with cervical tension (McAlhany et al. 1995) and occipital impact (Gurdjian et al. 1950) (for detailed information, see pp 117 ff).
2. Cortical hemorrhages
   Cortical hemorrhages (Adams et al. 1985; Graham et al. 1987) are focal damages of the surface of the brain. Sometimes they extend into the white matter in the form of extravasated blood, but without rupture of the pia-arachnoid membrane. There are local areas of swelling and capillary hemorrhage resembling bruises. Cortical hemorrhages are associated with local nerve cell body and axonal damage, multiple punctate hemorrhages, and edema.
   Mechanical cortical hemorrhages induced by contusion of the brain (contusional injuries) are caused by impact of short duration (blows and falls), as well as rotation or deformation of the skull. They are typically located in the frontal and temporal poles, usually frontopolar, orbitofrontal, anterotemporal, or lateral temporal, and on the inferior surfaces of the frontal and temporal lobes. Posterior fossa hematomas, especially cortical hemorrhages of the occipital lobe or of the cerebellum, occur almost always as a result of direct impact proved by occipital bone fracture. Cortical hemorrhages of the brain in the posterior fossa induced by opposite impact are extremely rare.
   More *severe cortical hemorrhages* tend to be associated with a fractured skull. They are less severe in patients with DAI but they are often more severe at the point of impact than at a site diametrically opposite, as illustrated by the fact that patients with frontal injuries have more severe contusional injuries in the frontal lobes. On the other hand, however, impact to the parietal, temporal or occipital part of the head generally produces more severe contralateral than ipsilateral hemorrhage of the brain.
3. Parenchymal lacerations
   Lacerations are actual tears, not only in the cortex but also in the white matter.
   Gliding contusional injuries to the white matter occur on the superior surfaces of the cerebral hemispheres, especially in the first parietal gyrus, when the medial parts of the temporal lobes are pressed against the dura mater and the cerebellum against the foramen magnum at the time of loading. This type of wounding is commonly caused by the shearing forces generated by acceleration.
4. Diffuse axonal injury (DAI)
   DAI and the accompanying tissue tear hemorrhages are considered to be due to high levels of local shear and tensile strains as well as strain rates as a result of rotational and translational head acceleration (Povlishock and Christman 1995). These acceleration-induced tissue strains are associated with local brain displacements within the deep white matter measured by Hardy et al. (2001) and calculated by Kleiven and Hardy (2002). At peak angular speeds of the head ranging from 17 to 22 rad/s, peak accelerations of 10–150 *g* and peak angular accelerations of 1,000 to 8,000 rad/s^2, the authors recorded local motions of the brain with respect to the skull, generally following loops or figure-of-eight patterns with peak displacements on the order of +/-5 mm.
   DAI is manifested clinically as traumatic coma lasting more than 6 h. Biomechanically, it is characterized by a non-contact trauma caused by inertial forces as a result of abrupt cranial deceleration or sudden angular motion of the head. In real-world situations head contact is commonly necessary to produce linear or angular accelerations sufficient for cerebral tissue damage to occur. Therefore, contact injuries are often superimposed. DAI usually requires "rotational" acceleration of the brain (Ommaya and Gennarelli 1974). The resulting severe primary diffuse brain injury is dominated by widespread axonal injury.
   DAI, as a special type of shear injury, is macroscopically characterized by small focal hemorrhages and salient cerebral swelling. Microscopically, axonal injury is seen in the corpus

callosum and the rostral brain stem. DAI often coexists with subdural hemorrhage and other indicators of cranial acceleration, especially gliding contusional injuries (Gleckman et al. 1999). DAI involves damage to the white matter or tracts connecting groups of cells, with temporary or permanent loss of function, but without mass lesions or ischemia (Gennarelli 1987). Axonal injury is seen even following simple contusion (Langfitt and Zimmerman 1985) and causes disability following minor head injury. Soft cranial impacts are especially capable of generating rotational velocity and the acceleration of sufficiently long duration which is necessary for the formation of DAI. Experimental results obtained from animals (Thibault et al. 1990) may lead one to suspect an injury threshold for DAI at an angular acceleration of about 15,000 rad/s^2 with a duration of ~10 ms.

5. More severe white matter damage
   If the impact is severe, injury of the corpus callosum, fornix, brain stem (ascending and descending tracts), cerebellum, etc. can result (Adams et al. 1977). Impact can inflict such damage even in the absence of high intracranial pressure or hypoxic brain damage.
6. Inflammatory response
   The laceration and hemorrhage induce an acute emigration of leukocytes, i.e., neutrophilic granulocytes and macrophages, partly as an indication of a scavenger reaction which predominantly will be transient. This phenomenon will be of forensic interest with regard to the expression of vital reactivity or to the estimation of the survival time (comp. p. 190). Moreover, long-term inflammatory responses are discussed (Gentleman et al. 2004) as a persistance of inflammatory process in the brain which may explain subsequent neurodegeneration and cognitive decline in later life (Jellinger 2004).

6.4.5 Secondary Lesions

All of the above named primary injuries are capable of giving rise to secondary lesions, the most common being *brain swelling* and *hypoxia*. Brain swelling and hypoxia via secondary edema lead to an *intracranial space-occupying volumetric increase*, which can lead to brain herniation and trigger a (tertiary) brain stem hemorrhage culminating in death. The brain itself can be affected secondarily without suffering primary injury: mechanical injury to other organs can induce a generalized hypoxia with hypovolemic shock or transient asystole. The brain is also susceptible to the sequelae of cerebral fat embolism, pulmonary embolism, etc. (see pp 208 ff). Mechanical trauma of the CNS entails a threat of secondary injury of all vital organs, the loss of function of which can lead to death.

1. Increase in intracranial pressure
   Reestablishment of equilibrium after increases in intracranial pressure is impossible within the narrow confines of the capsule of the cranial cavity. The inevitable consequence of either an intracranial space-occupying hemorrhage and/or an edema-induced intracranial increase in volume due to perifocal edema (penumbra) or hypoxic edema is displacement of the brain parenchyma in a caudal direction. If there is a supratentorial increase in volume at the medial cortex of the hippocampal area and/or a supra- and infratentorial increase in pressure, the resultant herniation of the brain stem at the foramen magnum can cause a decrease in or arrest of respiratory activity and/or a tachycardia that may show a transition to bradycardia. Administration of artificial respiration can permit the development of respirator brain syndrome (non-perfused brain).
2. Central nervous system engendered shock
   Paralysis of the peripheral vessels is more commonly caused by spinal injury than by MBI. The paralysis leads to dilation of the peripheral arterial vessels and redistribution of the blood to the periphery. A relative hypovolemic shock is the consequence, with reduced blood flow to all organs, including the brain.
3. Endocrine mechanisms (Baron 1993)
   Secretion of catecholamines may increase due to afferent impulses arising from damaged tissue. Catecholamines in turn promote increased secretion of corticotrophin-releasing hormones, which stimulate secretion of adenocorticotrophic hormone (ACTH) and thus of cortisol, the principal glucocorticoid hormone. Impulses from damaged tissue also trigger the secretion of antidiuretic hormone (ADH: vasopressin) and cytokines, chief among them interleukin-1 (IL-1), tumor necrosis factor (TNF), and acute phase protein (Wilcockson et al. 2002). There is also a release of free radicals and an induction of nitric oxide (NO) synthase (Orihara et al. 2001). NO can in turn contribute to brain tissue destruction via free radical mechanisms, or preservation via vasodilatation. The hypometabolic phase as a response to MBI is gradually supplanted by a second catabolic phase, which is followed by an anabolic third phase.
4. Aspiration
   Fracture of the base of the skull entails a risk of hemorrhage and vomiting; aspiration of the vomit or blood can lead to asphyxiation. This is especially likely if the victim is comatose and unable to swallow.

Table 6.2. Glasgow Coma Scale (*GCS*). Source: Bastos et al. 1993

Eye-opening (*E*):	Spontaneous	4
	To voice	3
	To pain	2
	No response	1
Best motor response (*M*):	Obeys commands	6
	Localizes	5
	Withdraws (flexion)	4
	Abnormal flexion (posturing)	3
	Extension (posturing)	2
	No response	1
Verbal response (*V*):	Oriented conversation	5
	Confused, disoriented	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
Score = *E*+*M*+*V*		

5. Other complicating factors
   Among the other complications of MBI are infections and malnutrition. If the hypothalamic-pituitary axis is damaged, especially the posterior pituitary, a hyponatremia-promoting diabetes insipidus can arise. Since MBI is often associated with polytrauma involving other organs, secondary phenomena such as hypovolemia, fat embolism (Mellor and Soni 2001), thromboembolism, hypoxemia, and air embolism can be expected.

6.5 Clinical Features

6.5.1 Somatic Symptoms

MBI can give rise to both generalized and focal symptoms. The severity of the clinical symptoms depends largely on the magnitude of the forces and ranges from transient slight disturbance of consciousness to long-term loss of consciousness (coma) or long-term disorientation, short- or long-term retrograde amnesia, seizures, etc.

Impact to the head often leads directly to loss of muscle tone, the victim dropping to the ground with loss of consciousness, reflexes, and respiration. Breathing soon returns. Autonomic dysfunction accompanied by nausea, vomiting, hypothermia, and alterations of pulse and blood pressure often occur. The patient becomes restless, begins to regain consciousness, appears irritable, apathetic and confused, occasionally becoming uncontrollable and abusive. Headaches are common.

These diffuse functional disturbances lack a concrete morphological correlate such as hemorrhage, DAI, edema or generalized hypoxic and/or ischemic injury and, thus, their causes remain largely uncertain (Graham et al. 1995). However, if the impact and secondary hemorrhages or ischemia cause destruction of local brain structures, focal symptoms corresponding to the site of injury will occur. Focal symptoms always indicate injury of the brain parenchyma.

Quantitative assessment of the clinical sequelae to injury, of coma in particular, is commonly performed according to the Glasgow Coma Scale (Bastos et al. 1993; for review see Stein 1995a, b; Tables 6.2, 6.3). The value of this instrument, often in modified form, has been demonstrated in routine practice in clinics around the world (see below, pp 177 f).

Table 6.3. Glasgow Coma Scale (*GCS*): score, clinical signs and severity of the MBI. Source: Bastos et al. 1993

Severity	Category	Score	Clinical Signs
Minimal	(1)	15	Temporary confusion, no loss of consciousness (LOC), no amnesia
Mild	(2)	13–15	Amnesia, or brief LOC (<5 min), or impaired alertness or memory
Moderate	(3)	9–13	LOC >5 min, complete amnesia and focal neurological deficits
Severe	(4)	5–8	
Critical	(5)	3–4	Respirator brain

MBI has been reported by some authors to cause primary neurogenic tumors such as gliomas (for review see Unterharnscheidt 1993), but no reliable evidence has yet emerged to establish such a link (Herrmann 1991). Since an expert opinion must rely on the application of established criteria (Manuelidis 1972) drawn from well-documented cases (cf. Annegers et al. 1979), a causal connection between MBI and such tumors must be negated at present.

6.5.2 Neuropsychological Impairment

Closed brain injury with loss of consciousness is often followed by *retrograde amnesia*: the victim is left with no memory of events leading to the traumatization. The length of the time interval between the last memory before the traumatic event and the moment of wounding itself correlates with the severity of the brain injury.

MBI may also induce *anterograde amnesia*, which can be explained in part by the loss of consciousness. The victim sometimes regains consciousness and appears lucid to bystanders but later retains no memory of this period during the so-called stage of irritation (Russell and Nathan 1946).

MBI-induced loss of consciousness may be followed by a *transitional posttraumatic phase* characterized by confusion, loss of orientation, alertness, and lack of arousal. This phenomenon is especially common after MBI associated with traffic accidents and sometimes accounts for the victim leaving the scene of the accident. These psychopathological changes however only follow MBI severe enough to produce disorientation, confusion, and amnesia in the transitional posttraumatic phase. The presence of such psychopathological phenomena allow a differentiation between somatically induced involuntary and psychologically initiated intentional actions following a traumatic event.

The psychopathological changes associated with "posttraumatic confusion" are described as a *traumatic state of semi-consciousness* (Mifka and Scherzer 1963; Straube 1963), sometimes known as a "transient amnestic episode" (Bender 1956). Actions initiated prior to traumatization are resumed, leading witnesses to assume the victim is performing meaningful intentional activity of his own volition. The victim, however, retains no memory of these actions.

Delayed psychopathological alterations associated with MBI include epilepsy, aphasia, belligerence, and cerebral personality disorders. These give rise to anxiety and stress as well as loss of psychodynamic reactivity, intellectual functioning, efficiency, and control. Some cases include acute *traumatic psychoses* as a complication (Pauleikhoff and Mester 1974). These psychoses can be: (1) merely coincidentally associated with the MBI, (2) triggered by the traumatic event, or (3) the cause of the accident. The few published case reports have failed to establish an actual causal connection between the MBI and psychosis (Unterharnscheidt 1993, p 614 ff).

Long after the original traumatic event, the victim can suffer from the psychopathological phenomenon known as *posttraumatic stress disorder* (Breslau et al. 1991; Harvey and Bryant 1998). The defining characteristic of the traumatic event in such cases is its capacity to provoke fear, helplessness or horror in response to the threat of injury or death (American Psychiatric Association 1994). The salient manifestation of posttraumatic stress disorder is the victim's involuntary re-experiencing of the traumatic incident in images, nightmares or flashbacks. The victim will also avoid reminders of the event, and an anamnestic hyperarousal of at least 1 month in duration is described (Yehuda 2002). This state of hyperarousal is typically manifested in physiological symptoms such as insomnia, irritability, poor concentration, hypervigilance, and increased startle reactions (Kessler et al. 1995).

Epidemiological studies and retrospective autopsy data provide evidence that a late cognitive and neurodegenerative decline may occur after severe MBI (Gentleman and Graham 1997). After experimental MBI the long-term accumulation of amyloid β peptide suggests that the neurodegeneration is influenced by apolipoprotein E∈4, and after human brain injury both amyloid β deposition and tau pathology are seen, even in younger patient. Therefore the influence of the apolipoprotein E genotype on the prognosis of MBI is under discussion (Jellinger 2004) (see also: pp. 188 f).

6.6 Outcome

The severity of the mechanical loading is the main determinant of the outcome of MBI. Careful documentation of the type of loading and the symptoms is important for the determination of prognosis and for settling questions regarding insurance claims, finally also as a basis of expert medicolegal evaluation particularly in regard to questions of culpability.

A *mild brain injury* is characterized by a period of unconsciousness lasting 20 min or less with a Glasgow Coma Scale score of 13–15. It induces no focal neurological deficit, and can leave no sign of contusion or hematoma (cf. Levin 1995). Post-concussional symptoms usually arise within the first week: headache (71%), fatigue (60%), and dizziness (53%). Although symptoms decrease within 3 months, slight residual complaints may persist. Rutherford et al. (1977, 1979) reported that 14.5% of their patients still complained of at least one symptom after 1 year: headache, irritability and/or dizziness.

Patients admitted to the hospital with a Glasgow Coma Scale score of 9–13 have been categorized as having *moderate brain injury* by Stein (1995). About 30% of such patients are found to have intracranial lesions on CT scan; almost half require a second CT scan for clinical reasons, and one-third exhibit delayed or progressive cerebral lesions. Between 4% and 10% require a craniotomy. Mortality during initial hospitalization ranges from 0.9% to 2.5%. Fifteen percent of patients require extended care, and only 60% make a good recovery during the first 6 months after the traumatic event. Nearly 70% are unable to return to work within 3 months.

Severe brain injury is denoted by a Glasgow Coma Scale score of less than 9 (Marion 1995). The duration of the coma and subsequent amnesia correlate with the incidence of long-term neuropsychological sequelae. Common effects include cognitive disabilities, especially memory deficits, behavioral disturbances, etc. Severe MBI can induce increasing edema or space-occupying intracranial hemorrhage, ultimately leading to the clinical state known as apallic syndrome or persistent vegetative state (Chap. 14, p. 312) or brain death (respirator brain, non-perfused brain) syndrome (Chapter 15, pp. 319 ff) (Kaufman 1995).

6.7 Medicolegal Principles

The forensic expert is expected to report on the type and severity of the impairment caused by an external mechanical event. In cases of surviving victims, consideration must be given to possible *concurrent functional disturbances* and to the likelihood of *future and permanent disabilities* as they bear, for example, on the victim's ability to continue to work or pursue a profession, or his need for long-term care (Schönberger et al. 1984).

If a survivor of MBI has residual physical or mental impairment that renders unfitness to drive, *driving privileges* must be revoked. After MBI or brain surgery, the victim is generally unfit to drive all classes of motor vehicle for at least 3 months. An exception can only be made if organic brain impairment is proven on medical examination to be no longer present.

If MBI is followed by death of the victim, the *precise cause of death* has to be determined and/or whether there was a causal *link* between the traumatic event, the brain injury, and the death. The presence of the pathological features of MBI does not in itself constitute an explanation of the death. In general, (minor) brain hemorrhage is not invariably lethal and should not be indiscriminately regarded as responsible for a death if found postmortem. Even a depressed fracture does not always lead directly to death or to neurological deficits. The brain injury itself must be severe enough to explain the death from the external event; if it is not, another cause of death must be sought.

In most cases cerebrocranial injury is accompanied – especially following traffic accidents – by multiple injuries involving numerous organs. These injuries can lead to secondary brain damage via brain edema and/or ischemia. In such cases of indirect brain damage, there may be a legally relevant causal connection between the traumatic event and the brain injury leading to death.

The causal link may be difficult to establish in cases with preexistent diseases such as atherosclerosis, cardiac decompensation, etc. as well as in cases with a long survival period. Decisions can be made possible by a detailed analysis of the case history as well as the injuries and careful scrutiny of information on the period after the traumatic event including therapy.

If injuries result from the act of another person, it is necessary to establish whether the perpetrator could have been able to foresee the consequences. This applies to traffic accidents just as to violent assault.

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Injuries of the Brain's Coverings 7

Four layers of tissue protect the brain from the effects of mechanical loading: the scalp, the skull, the dura mater, and the arachnoid mater (leptomeninx) (Fig. 7.1). These layers are liable to injury from contact and – partly and exceptionally – from non-contact loadings, which leads to tissue lacerations and/

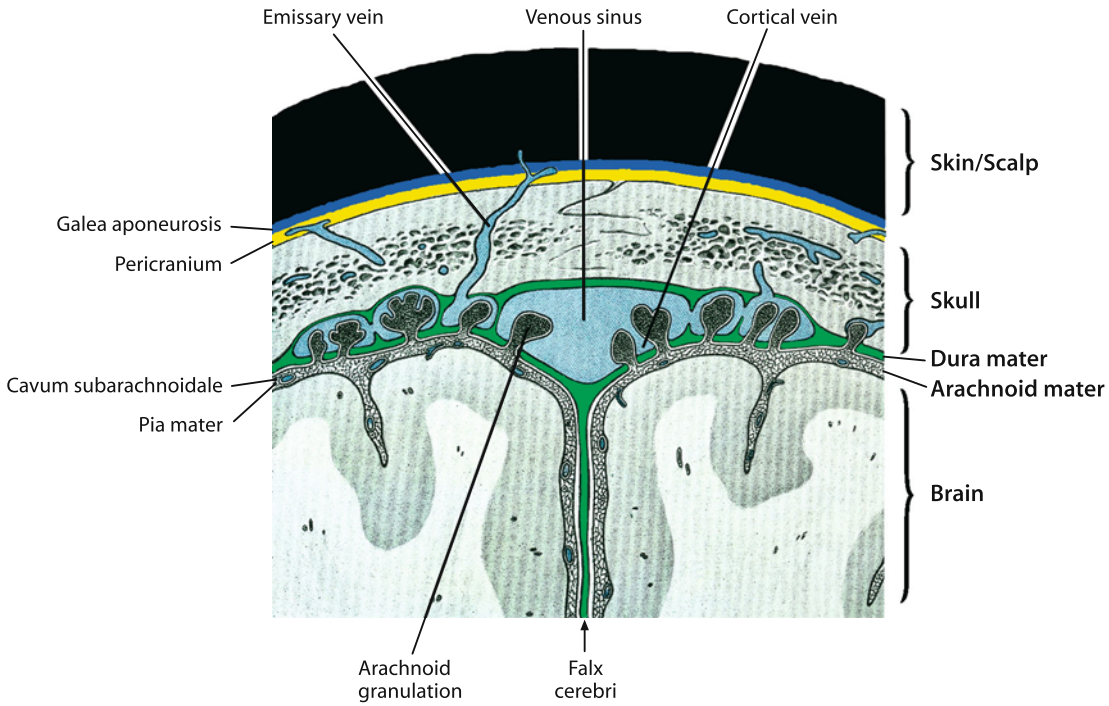


Fig. 7.1. The anatomy of the brain's coverings

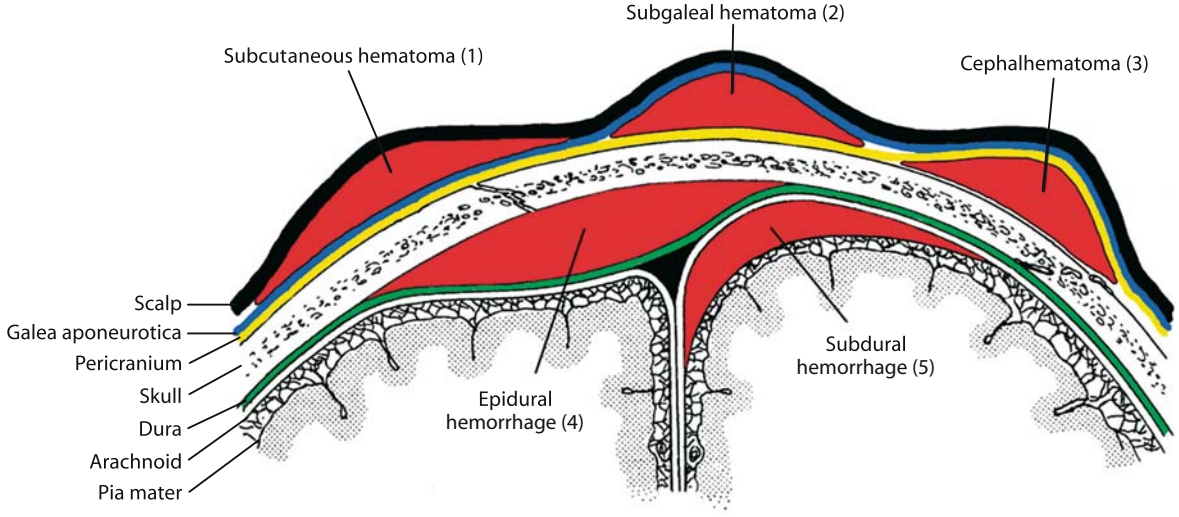


Fig. 7.2. Hematomas and hemorrhages in different spaces of the brain's coverings caused by mechanical injury: subcutaneous (1) and subgaleal hematoma (2), cephalhematoma (3), epidural (4) and subdural hematoma (5)

or bone fractures as well as to rupture of vascular walls with the sequelae of corresponding hemorrhages within the spaces between the layers. We have to differentiate the five types of hemorrhage according to the different spaces, which are demonstrated in Fig. 7.2:

- Subcutaneous hematoma (1)
- Subgaleal hematoma (2)
- Cephalhematoma (3)
- Epidural hemorrhage (4)
- Subdural hemorrhage (5)

7.1 The Scalp

7.1.1 Anatomy

The scalp varies in thickness from 3 to 7 mm. It extends anteriorly from the eyebrows to the superior nuchal line posteriorly, and laterally from one temporal line to the other. The scalp has five layers: an epidermal layer, a layer of dense connective tissue (dermis), a subcutaneous layer, a layer of loose connective tissue, and the periosteum (pericranium). The subcutaneous layer is highly vascular and contains anastomotic vessels, subcutaneous fat, epithelial adnexal structures, and septa of the superficial fascia which bind the skin tightly to the underlying galea aponeurotica. The galea aponeurotica, situated between the occipital and frontal muscles, is the layer of greatest strength in the scalp. The subaponeurotic layer of connective tissue contains loose areolar tissue with small arteries and emissary veins. Superficial veins of the scalp communicate with intracranial venous sinuses through this layer. The innermost layer, the periosteum, comprises the pericranium.

Both the galea and the muscles associated with it are loosely connected to the pericranium by areolar tissue, which facilitates separation of the scalp from the pericranium. Survival of hair follicles depends on preservation of the fat on the undersurface of the detached scalp.

7.1.2 Pathophysiology

The scalp and hair protect the skull from fracture. Injury of the scalp, soft tissue, and face are usually caused by contact forces. Due to its high mechanical stability, the scalp is able to dissipate much of the energy released by the mechanical force of an impact, e.g., >35% of the energy of a blow (Gurdjian 1975). Scalp injury entails a risk of bacterial infection that may spread into the intracranial cavity and cause intracranial abscess or suppurative meningitis. Hematomas, abrasions, and lacerations of the scalp are indicators of the location, severity, and number of impacts to the head, as well as of the shape and type of impacting object. This must be qualified in infants and small children (for details see Chap. 24, pp. 471 ff), who rarely bruise (Sugar et al. 1999) and in whom the location of subgaleal hematoma does not always reflect the site of cranial impact (Arnholz et al. 1998). In infants and small children, moreover, blood loss more readily entails a risk of life-threatening hemorrhagic shock, with increased heart and respiratory rates.

7.1.3 Pathology

Cerebral trauma in children and adults is nearly always accompanied by injury of the skin or soft tissue of the face or scalp. One important exception in infants is the shaken baby syndrome, in which pure acceleration forces induce subdural hemorrhage (SDH) (see Chap. 25, pp. 493 ff). Shaking as a special type of pure acceleration force has also been described as a cause of SDH in adults, without having yet been conclusively proven (Pounder 1997). In all other forms of mechanically induced functional disturbances of the brain, injury of the scalp, face or chin may be visible, either in the living patient on occasion of clinical diagnostic procedures or on occasion of autopsy. As a rule, any visible injury of the head is a marker of a traumatic event and may lead to immediate or delayed functional disturbance of the brain. If, therefore, injuries are found on the skin of the head of a living victim, the victim's brain function must be monitored for a period of 24 h, to ensure timely therapeutic intervention if needed (see below). By the same token, if a patient is known to have suffered a fall or blow, the physician must examine the head carefully for signs of injury which may be hidden by hair. For the forensic pathologist, this means that in the absence of visible or palpable bruises and edema of the face or scalp the hair must be carefully shaved away to expose the scalp for careful examination and documentation. Moreover it is important to know that a fatal bleeding from a single scalp injury can occur under special conditions (Bratzke and Gilg 1987).

In regard to *localization* of scalp injuries, the following rule of thumb may be applied for an upright person: a scalp injury located above the line of the hat brim, i.e., toward the top of the head, was probably caused by a blow; a scalp injury situated below the hat brim was probably incurred in a fall on an unwrinkled or smooth plane (Fig. 7.3). Scalp injury on the top of the head may be associated with depressed fracture of the skull; injuries below the hat line, with linear fracture of the skull.

Moreover, it may be of forensic importance to determine whether an injury was incurred while the victim was still alive, or after death. If an injury occurred during life, the question arises of its survival time, i.e., its age before death. The vitality of an injury can be confirmed by the presence of leukocytes at the margin of the wound. Wound age is determined as described elsewhere (Oehmichen 1990, 1998; Betz 1996; Oehmichen and Kirchner 1996).

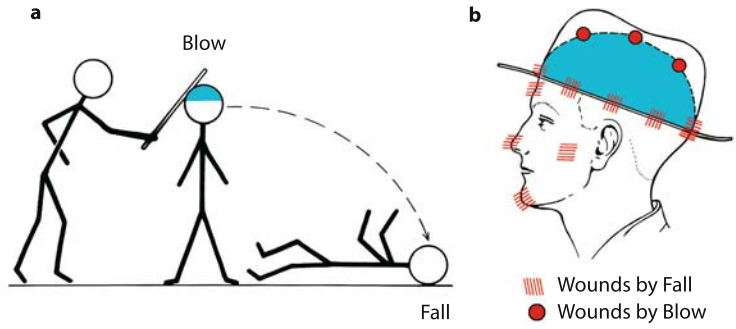


Fig. 7.3a, b. Differentiation between fall and blow. Scalp wounds located above the line (blue) of the hat brim area probably caused by blow (**a**) while wounds located below this line were probably incurred in a fall on an unwrinkled or smooth plane (source: Ponsold 1967)

The following types of injury of the skin and scalp of the head are differentiated, each caused either by blow or fall.

7.1.3.1 Abrasion Injury

Abrasion wounds caused by impacts perpendicular to the scalp often leave imprints that can provide evidence as to the type of weapon used (blow) or the nature of the object/surface struck (fall). Additional abrasions may also be found on the scalp opposite the site of impact if the head has been pressed forcefully against the ground or other object.

7.1.3.2 Contusion Injury

Contusion injury (Fig. 7.4a, b) marked by pronounced swelling occurs at the site of impact. The swelling is due to edema and/or bleeding within the subcutaneous tissue and sometimes beneath the aponeurosis. If the force of the impact is sufficient, all layers of the scalp may be affected. The weapon or object striking the head sometimes may leave an imprint on the surface of the scalp.

7.1.3.3 Hematoma

At impact, the scalp shifts in relation to the surface of the skull or galea. The movement may cause tearing of connecting blood vessels in the scalp and between the scalp and the skull, resulting in a subcutaneous or subgaleal hematoma (Fig. 7.4c) associated with an apparent laceration and/or bruising wound of the scalp. The severity of bleeding depends largely on the intensity of impact and may involve isolated epidermal bleeding, subcutaneous bleeding, or bleeding within all the layers of the scalp.

In newborns, scalp hemorrhages are differentiated according to the type and cause of injury: caput succedaneum, subgaleal hematoma, and cephalhematoma (for details see Chap. 24, pp. 441 ff).

7.1.3.4 Laceration Injury

Laceration wounds (Fig. 7.4d) of the scalp generally involve total separation of tissue continuity surrounded by a zone of bruised tissue. The tear may be either partial or complete, i.e., penetrate some or all of the layers of the scalp. Acute angled or tangential bruising may cause partial avulsion of the scalp. The worst injury occurs when avulsion involves a large area of the scalp (see below). Bleeding from a laceration wound is diffuse and if profuse or prolonged may culminate in fatal hemorrhagic shock. The laceration injury may be linear, stellate, or Y-shaped.

Experiments with unembalmed cadaver heads and rigid free-fall impactors (total mass: 1–1.2 kg, impacting surface area: 3 cm^2, impacting velocity: 4.5–5 m/s) resulted in a lower limit of about 12 Nm impacting energy or about 2,000 N impacting force for producing a laceration injury. Janssen (1963) in agreement with Gadd et al. (1970) estimated the approximate tolerance of the scalp against compressive loading to be between 1,980 N and 2,700 N.

In most cases the different types of *wounds are combined* because of the different forces which likewise influence the biomechanics of scalp wounding. Figure 7.4e shows the result of a blow by a hammer, i.e., a combination of contusion injury, hematoma, and laceration wound.

7.1.3.5 Avulsion Injury

Pulling of the hair or shearing forces applied to the scalp may detach the scalp from the skull (Fig. 7.4f), almost always along the loose subaponeurotic layer. If the hair is pulled from behind, the skin in front will tear first, if pulled from the front, the occipital region tears first. If the hair on the top of the head is pulled, the skin will yield at the vertex and tear above the ears. Bleeding from the avulsion wound may be profuse at first, but usually ceases before shock supervenes, often stopping spontaneously from vascular spasm.

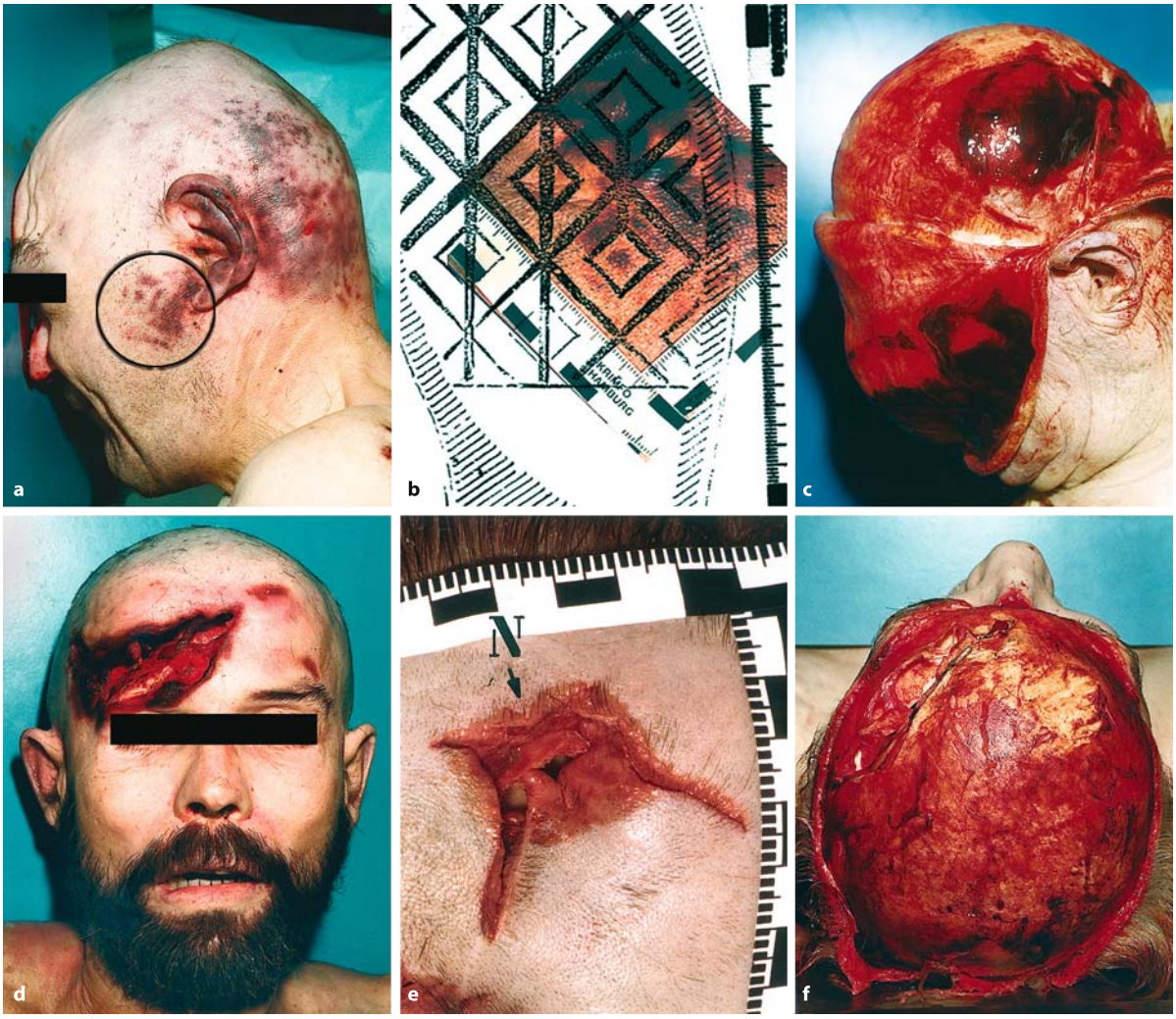


Fig. 7.4a–f. Different types of scalp lesions. **a, b** Contusion injury as a result of stamping with shoes, which could be adapted to the sole structures; **c** subgaleal hematoma as a contact injury resulting from a vehicular accident; **d** laceration in combination with contusion injury by fall; **e** formed direct bruising wound by hammer blow associated with indirect radial lacerations (*N* nail notch); **f** avulsion injury as a consequence of a vehicular accident associated with a depressed fracture

7.2 The Skull

7.2.1 Anatomy

The skull forms the bony framework of the head and has two main regions, the brain case or cranium, and the facial skeleton. The cranial bones enclose and protect the brain. They have for the most part flat surfaces with outer and inside layers of solid compact bone, and an interior layer of less dense (spongy = trabecular) bone. The compact bone is surrounded by a periosteum of dense fibrous and elastic tissue which is divided into an outer fibrous layer and an inner more vascular cambial layer composed of loosely arranged osteogenic cells. The external layer of compact bone is usually well mineralized. When mature it consists of secondary osteons with a central Haversian canal containing a neurovascular bundle and surrounded by concentric lamellae of bone tissue. The inner layer of spongy bone is made up of a meshwork of calcified trabeculae.

The cranium is composed of seven bones. The anterior, superior, and posterior portions and much of the lateral surface of the cranium are comprised of the broad and convex frontal bone, occipital bone, and the parietal bones. The posterior part of the base of the cranium is formed by parts of the occipital bone. The base of the cranium is made up of three levels or platforms: the anterior cranial fossa (base of the frontal lobes of the brain), the middle cranial

fossa (base of the temporal lobes), and the posterior cranial fossa (base of the cerebellum and the pons). The interior aspect of the skull, especially of the temporal bone, is supplied with arteries (middle meningeal artery and its branches). Injury of these arteries by cranial fracture can result in hemorrhage (extradural hemorrhage).

7.2.2 Biomechanical Aspects

Compact bone is more rigid than trabecular bone and can withstand greater pressure, but less tension stress. Trabecular bone is highly elastic and is well able to store and release energy. Whereas the ultimate strain limit of cortical bone is a 2% change in initial dimensions, trabecular bone can withstand as much as a 75% strain deformation before fracture (Carter and Hayes 1976).

Skull fractures are the morphological result of contact violence, and only exceptionally of non-contact forces. The skull's morphology and biometry, and thus its stability to external mechanical forces, vary with age. Direct forces generated by local impact can cause cranial fractures, or, if they affect the base of the skull, basal skull fractures. Indirect forces released by a bullet can produce burst or tear drop fractures via the transfer of energy. Differences in fracture morphology can be attributed to differences in the underlying biomechanics.

The types and severity of skull fracture inflicted by a given traumatic violence depend to a large extent on the following factors (Di Maio and Di Maio 2001):

1. The physical characteristics of the head:
   - Thickness of the scalp and hair covering
   - Thickness and configuration of the skull
   - Elasticity of the bone
2. Physical characteristics of the impacting object:
   - Shape and size of contact area
   - Mass
   - Consistency, surface structure, rigidity, sharpness of the edges
3. Kinetics of contact:
   - Velocity of the head
   - Velocity of the object
   - Angle of incidence

The fracture mechanisms and physical tolerances are described below.

When the head is loaded by blunt force of relatively high intensity, such as a blow or by reactionless fall of an upright person to the ground, the impact induces strains and deformations of the skull. If the impact energy exceeds the elastic deformation capacity of the skull, either in a local sector with a small contact area and a short duration time (hard impact), or in general by broad contact and longer impact times (soft impact), fractures of local and/or global extent will be produced. The local fractures close to the impact point are called *direct fractures*; the global ones, remote from the impact area, are called secondary or *indirect fractures*.

The most important strains for blunt impact are tensile strains in the case of pure tension load and a combination of tensile and pressure strains in the case of bending. The highest tensile strain is always on the surface of the locally convex deformed side (bending-tension side), and the maximum of pressure strain is induced on the surface of the locally concave deformed side (bending-pressure side). Since the skull bends inwardly at the point of impact and outwardly in the surrounding segments, a bending fracture may be indicated on either the external or the internal surface of the skull.

Since bone material generally can take much more pressure than tensile loading before losing continuity (Evans and Lissner 1957), a fracture always starts (perpendicular to surface) on the bending-tension side and extends asymptotically to the bending-pressure side. Therefore bending fracture lines at the inner and outer compact layer are systematically displaced to each other. In skull loads by blunt impact, bending is always a locally induced mechanism at and around the contact area and is predominant, if this area is small (<15 cm^2). This is the field of penetration and depressed fractures.

If the contact area is large (>15 cm^2) a perforation of the skull rarely occurs because the whole skull is put under stress, deforms as a whole and bursts, while local deformation stays relatively small, and no or only a superficial (circular bending) fracture of the outer bone table is created. Because of the symmetrical state of stress (tensile stress on the inner and on the outer side of the skull bone) bursting fracture lines at the inner and outer compact layer are not displaced relative to each other. Since the formation and propagation of a fracture occur perpendicularly to the local tensile strain direction, the typical outward appearance of a bursting fracture is linear and finely jagged, exceeding radially from the impact region and/or extending far from it, while the fracture lines of bending fractures are normally arched and smooth, circularly surrounding the contact area.

In the case of a low velocity broad contact blow to the head or a fall on a hard surface, the amount of energy necessary to produce a single linear calvarial fracture, a stellate fracture, or multiple linear fractures is 45–100 Nm absorbed by the skull and the surrounding soft tissue in 1.2 ms (Evans et al. 1958; Lissner and Evans 1958). After a free fall from a height of 1.8 m, a head with a mass of 4.5 kg impacts with a velocity of approximately 6 m/s (=22 km/h),

producing an energy of 80 Nm, and therefore a skull fracture may just be produced.

If an object striking the head – or the ground in the case of a falling victim – is deformable, the energy of impact is dispersed. Kinetic energy levels of 360–790 Nm and impact velocities of 13 m/s (=47 km/h) to 20 m/s (=70 km/h) are required for a deformable object to induce a skull fracture (Evans et al. 1958 – see also Melvin and Evans 1971), always dependent of course on the elasticity of the object. Differences in the impact tolerance of different areas of the skull have been described in detail by Nahum et al. (1968).

If a rigid object with a small, flat surface area (5 cm^2) strikes the head, the average energy consumed during the creation of a fracture (duration time 4 ms), e.g., in the temporo-parietal region, was measured to about 25 Nm with an average fracture force of 5,000 N (Allsop et al. 1991).

According to their anatomic location, specific form, and mechanism of generation, we can classify the following *specific types of fractures*.

7.2.2.1 Linear Calvarial Fracture

Linear calvarial fractures (Fig. 7.5a) are bursting fractures resulting from stress distributed over the entire cranial vault. The skull cap is deformed as a whole and fractures as a whole, usually just exceeding, but remote from, the impact region. Longitudinal compressing loads induce transverse tension and therefore longitudinal fractures, just as transversal large blunt impacts produce transverse burst fractures. Impact to the vertex tends to produce linear skull fractures that are widest at areas remote from the impact site (Yoganandan et al. 1995). Bursting of the cranial vault as a way to reduce induced tension stress may also be realized by diastasis of suture lines even at a distance from the point of impact.

7.2.2.2 Depressed Calvarial Fracture

Depressed fractures (Fig. 7.5b, c) are direct bending fractures and result from the local impact of a blunt object to a small area of contact such as that from a blow with a hammer. The skull will be loaded highly directly under the impactor. If its energy is low and exceeds just the local capacity of elastic deformation, the outer table is bent inwardly, and a dent fracture results as a superficial indentation of the outer table. The inner table is bent inwardly as well and tears. With increased impact energy there results a depressed fracture with a dislocated, impressed area of the outer compact layer, frequently formed by the impacting instrument, surrounded by closely parallel fracture lines at the border region, which are called *terrace fractures* or *stair-step fractures*. The diploë layer collapses, and the inner table's compact bone caves in deeply and fractures under the high tensile stress. Comminuted fractures are formed at the inner table, and a splinter pyramid always results there, which projects into the interior of the skull, usually perforating the dura and penetrating the subjacent brain. In instances of high energy impact and a small instrument, the injuring object perforates the skull bone completely. Since a two-dimensional bending fracture spreads out in a funnel-shape from the exterior to the interior of the skull, a cone-like fragment is punched out and propelled into the brain. This results in a hole in the skull, shaped like the perforating instrument. Fractures like these are called penetration type depressed fractures, *penetration fractures* or *hole fractures*.

7.2.2.3 Combined Fractures

Combined fractures (Fig. 7.5d, f) are fracture systems consisting of combined bending and bursting, direct and indirect, near and remote fractures. If energy remains after local absorption has produced a bending or depressed fracture, this residual energy will be exhausted in the generation of circular bending fractures around the impacted area and linear burst fractures radiating in a star-like fashion from the center. The result is a fracture system called *spider's web fracture*. With increasing impact area of the striking object the degree of depression may be minimal or nearly absent. A subarachnoid hemorrhage and a laceration of the brain structures beneath the contact area will be the result of this fracture system (Fig. 7.5e).

If there are several impacts, the fracture systems might form a network, and according to "Puppe's rule" (Fig. 7.5f), the later fractures will not cross the earlier ones but will terminate at the earlier ones, a reliable indication that the latter preceded the former (cf. Knight 1996).

7.2.2.4 Basilar Skull Fracture

Basilar skull fractures (Fig. 7.6) are normally bursting fractures, and the causal mechanisms are the same as in linear calvarial fractures, which often extend into the base or conversely start there because of the lower fracture tolerance which is the result of the numerous local weak points of the structure of the skull base. The causal load can be a fall to the ground or being driven over by the wheel of a vehicle, a blunt impact to the neck, mandibular or facial impact, or an impact to parts of the occiput and almost any type of diffuse impact to the vertex of the head.

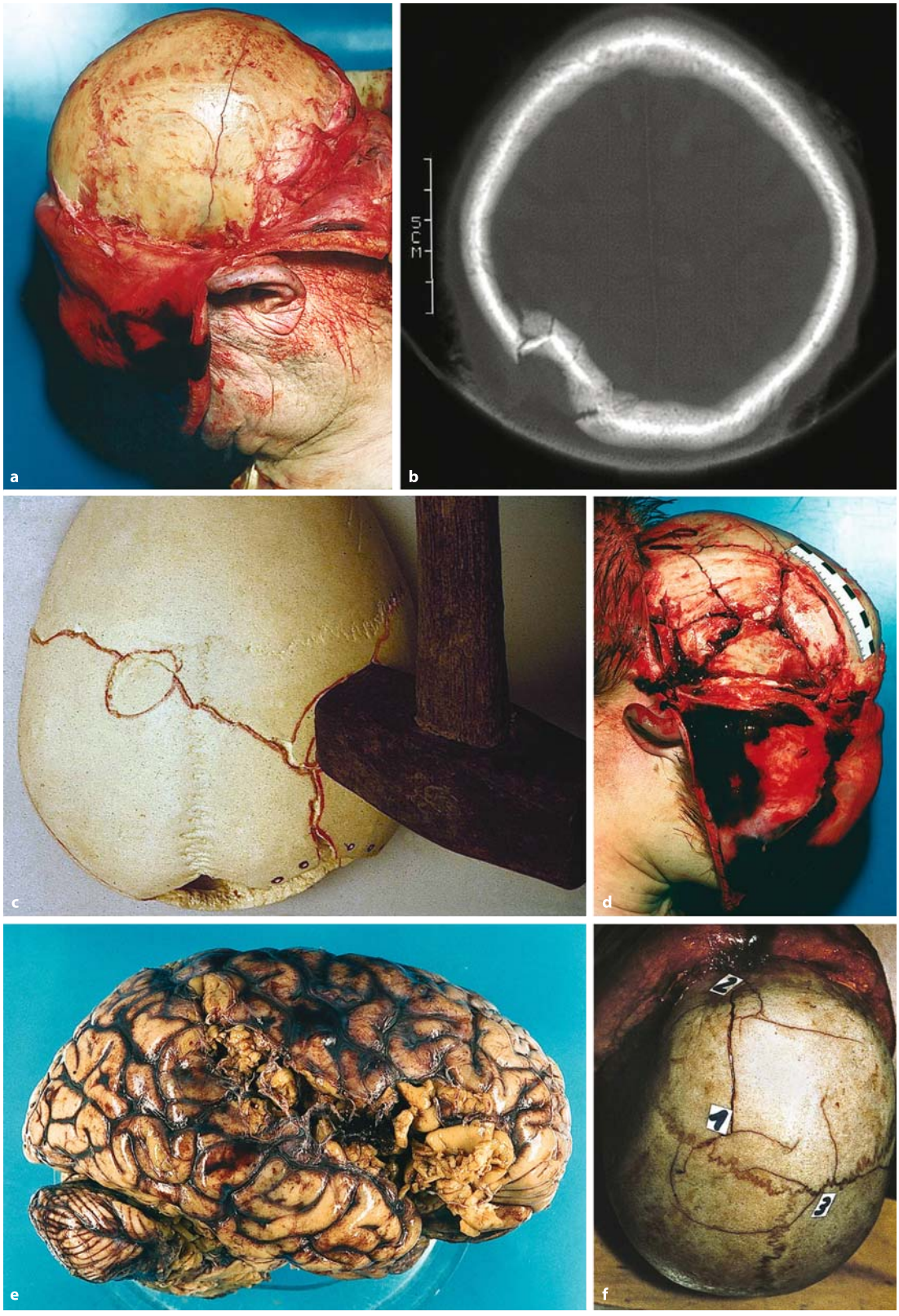


Fig. 7.5a–f. Types of calvarial fractures. **a** Linear fracture caused by broad contact violence on occasion of a vehicular accident; **b, c** depressed fracture caused by a blow with a hammer; **d** combined fracture caused by a fall with circular bending fracture of the parietal and temporal parts of the skull and secondary (burst-caused) linear fractures, associated with **e** tissue laceration of the brain structures located beneath the center of impact; **f** Puppe's rule which gives information on the sequence of impacts (see text)

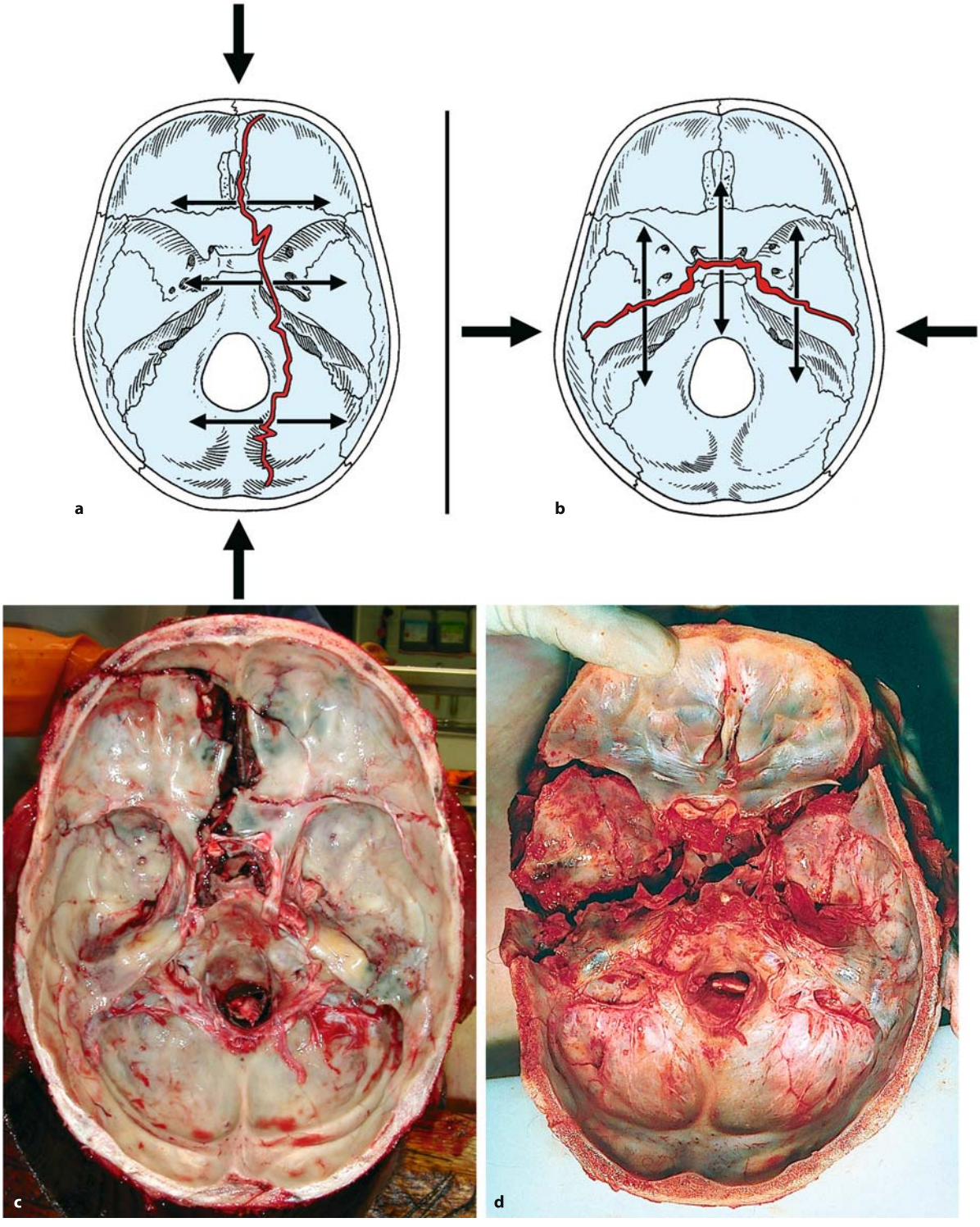


Fig. 7.6a–d. Basal skull fracture. The fracture lines usually run from side to side, transverse to the base of the skull: **a, c** a sagittal fracture is the result of a load on the longitudinal axis and **b, d** a transverse fracture of a load on the transverse axis. The figures (**a, b**) were kindly provided by Professor Dr. D. Leopold, Leipzig

If impact occurs on a relatively thick region of the skull, the stress radiates outward from the site of impact to thinner parts of the skull, which may fracture if their elastic deformation capacity is exceeded. The fracture lines usually run from side to side, transverse to the base of the skull: a sagittal fracture

at the base of the skull is the result of a load on the longitudinal axis (Fig. 7.6a, c). In contrast, a load on the transverse axis (lateral load) gives rise to a transverse fracture (Fig. 7.6b, d). The force transmitted to the base of the skull can cause lateral fractures that extend from the posterior foramen magnum to both occipital condyles, continuing along the inferior petrosal sinus and into the dorsum sellae (McElhaney et al. 1995).

A *transversal basilar fracture* which involves the petrous bone frequently leads to bleeding from the external auditory canal and can be manifested by this symptom.

A basilar fracture of specific form and generation is the *basilar skull ring fracture* around the foramen magnum, which is a special type of bending fracture, created by axial tension or pressure as a local response resulting from contact or non-contact loading. The contact may be a mandibular impact or striking the ground with the top of the head. Non-contact loading may be an acceleration of the head away from the restrained body or striking the ground with the lower end of the spinal column, e.g., by fall from a height.

7.2.2.5 Facial Skull Fracture

Facial skull fractures are direct and indirect bending and bursting fractures of the mandible or other facial bones. If the intensity of the causal impact is very high, additional basilar fractures might be produced. Most fractures of the facial bones are caused by blow, fall or traffic accidents.

7.2.2.6 Growing Skull Fracture

Growing skull fractures are peculiar to childhood and are described in Chap. 24 (pp. 474 ff).

7.2.3 Clinical Features

Skull fractures do not necessarily entail neurological sequelae, such as loss of consciousness, paralysis or vegetative symptoms, even though there may be simultaneous injury of the brain. Fractures of the base of the skull may involve injury of the cranial nerves and the blood vessels at the base of the skull, which often is characterized by a hematoma of the periorbital soft tissue (monocular or binocular hematoma) as well as bleeding within the external auditory canal, with the attendant risks of air embolism, aspiration of blood, liquorrhea, etc.

7.3 Dura Mater

7.3.1 Anatomy

The dura mater is made up of two coalesced membranes of thick tough connective tissue. The outer endosteal layer, composed of a dense network of collagenous fibers, constitutes the internal periosteum of the cranial bones. The inner so-called meningeal membrane apposes the arachnoid mater. This layer of the cranial dura is continuous with the spinal dura at the foramen magnum thus forming a continuous dural covering *of the intracranial and intraspinal space*. The intracranial space is subdivided into compartments by inwardly projecting folds of the dura, known as the *falx cerebri* and the *tentorium cerebelli*. The dura mater contains arteries, which run within the periosteum along the inner surface of the calvaria. The majority of the large venous blood vessels, the sinuses, are located at the base of the dural foldings. *Bridging veins* connect the vessels of the pia with the dural sinus. The space between the dura and skull is termed the epidural space; that between arachnoidea and dura is known as the subdural space.

Fluid and proteins of the cerebrospinal fluid (CSF) can cross the space enclosed by the dura and arachnoid at the passage of the nerve cell roots and in the vicinity of the arachnoidal villi (Pacchionian bodies). Aging arachnoid villi grow in size and eventually become arachnoid granulations also known as Pacchionian bodies. CSF, proteins, corpuscles, and cellular components can be reabsorbed and/or removed via this route.

7.3.2 Pathology

The "open-brain injury" caused by skull fracture-induced disruption of the dura will be addressed separately (see Chap. 8, pp. 151 ff). A more common result of skull fracture is *hemorrhage* into the epidural and/or subdural spaces. Such bleeding itself can lead to *intracranial displacement* of the brain, generally laterally and/or caudally with consequent direct injury of the cerebral parenchyma and (secondary) herniation syndromes (see Sect. 7.3.3) as demonstrated in Figs. 7.7, 7.8.

Dural hemorrhages can be induced by both contact and non-contact loading. An isolated dural hemorrhage resulting from external mechanical force is not invariably accompanied by additional direct injury of the brain, especially if the hemorrhagic source is not cortical. Although most patients exhib-

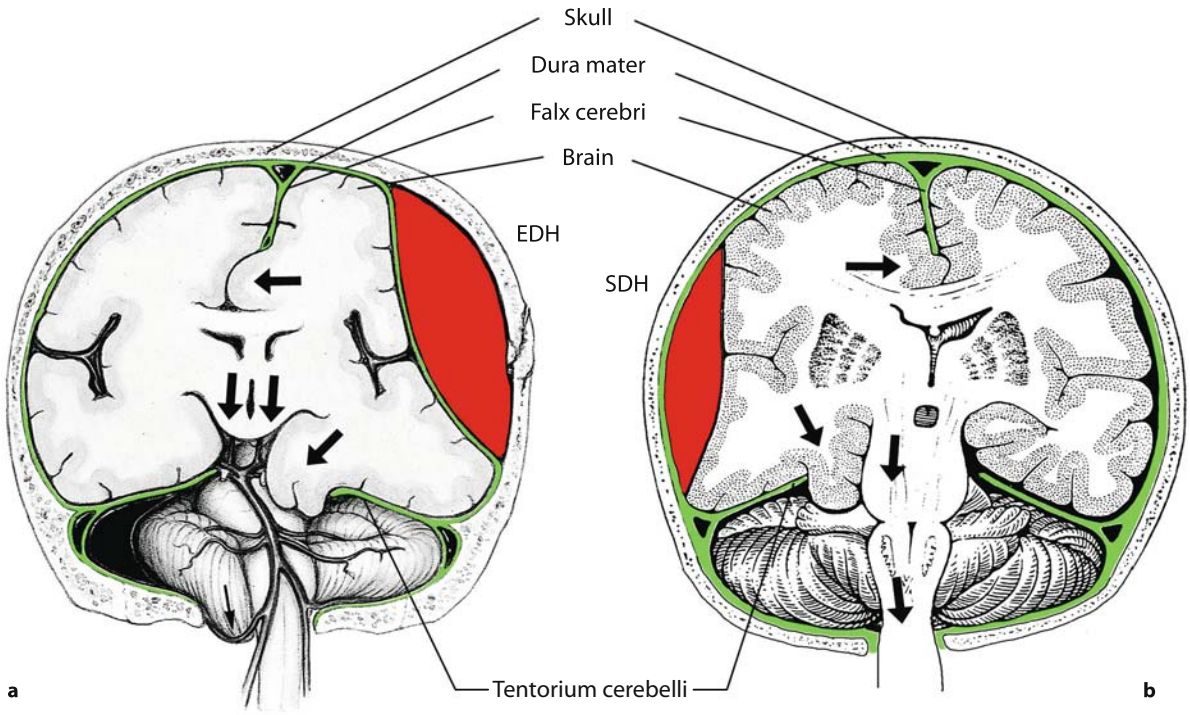


Fig. 7.7a, b. Schematic demonstration of the sequelae of mass shifting by epidural and subdural hemorrhages – the different types of herniation are demonstrated by arrows. **a** Epidural hemorrhage (*EDH*); **b** subdural hemorrhage (*SDH*)

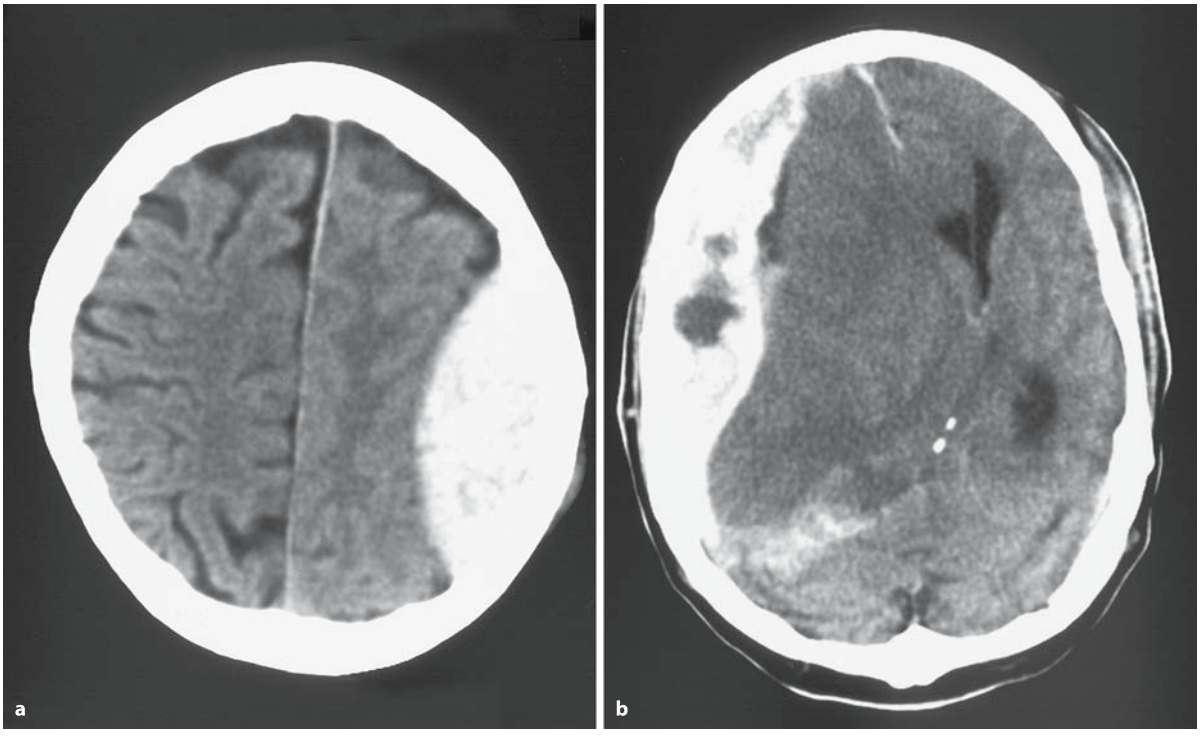


Fig. 7.8a, b. Different features of epidural and subdural hemorrhages as demonstrated by MRI. **a** Epidural hemorrhage; **b** subdural hemorrhage. The figures were kindly provided by Professor Dr. H.-B. Gehl, Lübeck

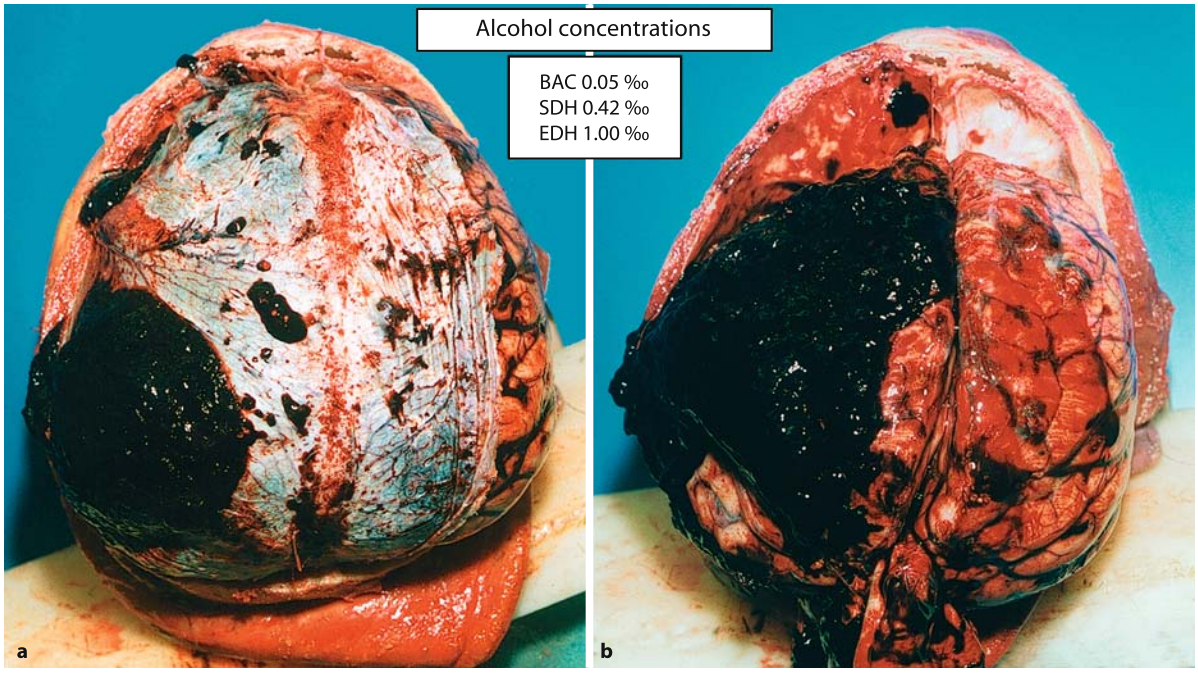


Fig. 7.9a, b. Blood alcohol concentrations in different compartments of blood of the same victim. **a** Epidural hemorrhage (*EDH*) = 1.0‰; **b** subdural hemorrhage (*SDH*) = 0.42‰, while the concentration in peripheral blood (*BAC*) was 0.05‰

it neurological deficits as symptoms of accompanying subarachnoid or cortical hemorrhages, in some instances of mechanical injury there are no apparent *clinical*, *i.e., neurological, symptoms* of any kind. Epidural hemorrhages in particular are unlikely to be accompanied by foci of cortical bleeding. If there is a gradual displacement of the brain caused by space-occupying bleeding, secondary *clinical symptoms* will be *delayed*, i.e., occur after a *symptom-free (lucid) interval*, the length of the delay depending on the rate and amount of bleeding. Morphological changes in the brain itself are mainly due to its displacement and compression and are associated with clouding of consciousness and/or hemiparesis.

The findings of microscopic examination of the hematomas are greatly dependent on survival time (see below): signs of coagulation appear first, followed by evidence of a blood cell reaction, and resorption and/or organization (see below). Subdural hemorrhages (SDHs) in particular are likely to involve intradural bleeding but do not involve a complete breach of the dura, as evidenced on histological examination.

Morphologically (and clinically) significant lesions of the brain are secondary in nature and characterized by damage to the brain parenchyma. The sharp edges of the dura mater may cause lacerations if the brain is pressed against them. Two types of influence may cause the brain to be pressed against the dura mater:

1. *Acceleration forces* may press the brain against the dura, causing cutting or bruising of the brain (median part of the hippocampal area, corpus callosum).
2. A *hemorrhage* as well as an *edema-induced increase in brain volume* may force the brain against the dura, resulting in herniation of brain tissue with consequent structural distortion, stretching, and compression injuries (see Sect. 7.3.3 on secondary lesions).

Often – especially after rotational acceleration – a hemorrhage is found in the white matter of the first frontal lobe gyrus, i.e., a so-called *gliding contusion injury* (see below). Moreover axonal injury can almost always be demonstrated in cases with survival times of >2–3 h (Oehmichen et al. 1997), most frequently in both the corpus callosum and the rostral portion of the brain stem as an indication of diffuse axonal injury (DAI) (Graham and Gennarelli 1987).

Examination of the alcohol concentration (AC) in the dura hematomas in comparison with the peripheral blood will be of special diagnostic value. The AC will give evidence of the time course of the bleeding process and the dying process as demonstrated in Fig. 7.9. In this special case a contact mechanism caused an epidural and subdural hemorrhage. While the blood alcohol concentration (BAC) was 0.05‰ at the time of death, the concentration in the SDH was 0.42‰ and in the epidural hematoma (EDH) 1.00‰. These differences give evidence of the velocity of

bleeding and some information on the duration of the agony.

The *outcome* in EDH and SDH was found to be predominantly influenced by the preoperative state of consciousness, associated brain lesions, and, in comatose patients, the duration of the time interval between onset of coma and surgical decompression. When this interval exceeded 2 h, mortality from SDH rose from 47 to 80% (good outcomes 32 and 4%, respectively). In acute EDH an interval under 2 h led to 17% mortality and 67% of good recoveries compared to 65% mortality and 13% of good recoveries after an interval of more than 2 h (Haselsberger et al. 1988).

7.3.3 Secondary Lesion (Herniation Syndrome)

Supratentorial brain herniation exhibits the following major patterns: subfalcine, central transtentorial, uncal, and tonsillar as demonstrated in Fig. 7.7. If untreated, it can culminate in total intracerebral circulatory arrest (brain death syndrome). In any case, the prognosis depends on the size of the hemorrhage as well as on the speed of the space-occupying bleeding.

An expanding mass lesion may cause a compression of one hemisphere (Fig. 7.10a) and a medial shift of the ipsilateral hemisphere, forcing the cingulate gyrus beneath the falx cerebri (*subfalcine herniation*) (Fig. 7.10b) and causing local hemorrhage in the ipsilateral gyrus cingulus and/or in the center of the corpus callosum. Herniation of this type may lead to compression of the ipsilateral anterior cerebral artery. The result is often cerebral ischemia and possible (hemorrhagic) infarction of the medial posterior frontal and parietal lobes supplied by this artery.

Supratentorial hemorrhages, either subdural or epidural, may cause *central transtentorial herniation*. Such lesions displace the cerebral hemispheres and basal nuclei downward, pushing the diencephalon and adjacent midbrain through the tentorial notch. The clinical symptoms reflect bilateral progressive injury of the diencephalon. They include drowsiness, agitation, and impaired upward gaze, the latter secondary to compression of the quadrigeminal bodies at the level of the superior colliculi. If herniation continues to progress, stupor and coma rapidly follow.

Uncal herniation (Fig. 7.10c) results from lesions expanding in the lateral middle fossa or temporal lobe, displacing the medial edge of the uncus and hippocampal gyrus medially and over the ipsilateral edge of the tentorium cerebelli. Compression of the midbrain occurs, as well as compression or stretching of the contralateral or ipsilateral third cranial nerve. In its classic form, uncal herniation syndrome entails compression of the posterior cerebral artery and ipsilateral cerebral peduncle and stretching of the ipsilateral oculomotor nerve. The resulting symptoms include diminished consciousness, contralateral hemiparesis, and a dilated ipsilateral pupil that is unreactive to light. Compression of the opposite cerebral peduncle against the contralateral edge of the tentorium (Kernohan's notch) will induce hemiplegia ipsilateral to the mass lesion. Progression to coma then rapidly follows pupillary dilation.

Such secondary changes, which are common to all types of intracranial space-occupying processes, can produce focal hemorrhages in the corpus callosum, cingulate gyri, hippocampal gyrus, and in the brain stem.

Tonsillar herniation (Fig. 7.10d) is caused by compression of the cerebellar tonsils into the foramen magnum. The clinical symptoms reflect the brain stem compression with the result of bleeding within the midbrain or pons (Fig. 7.10e) and the clinical features of apnea and bradycardia, respiratory and cardiac arrest.

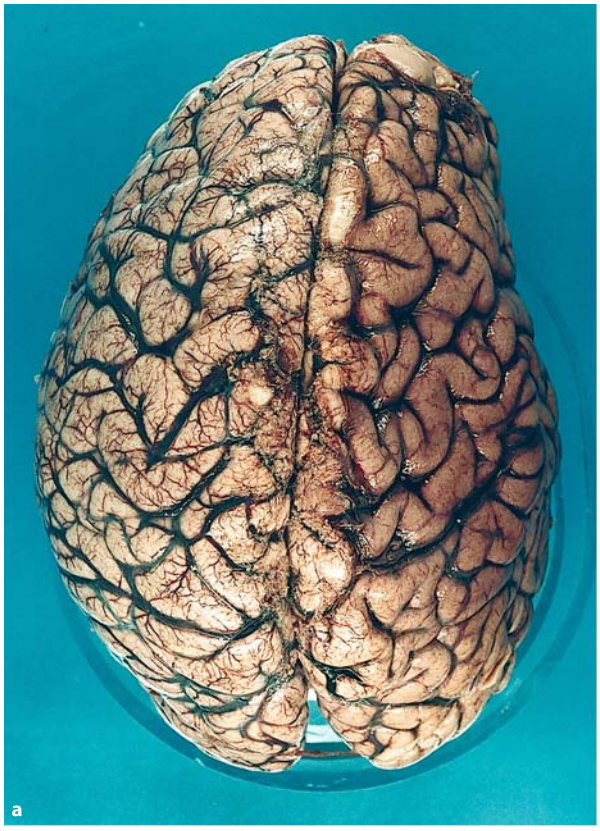
7.4 Epidural Hemorrhage

7.4.1 Classification

Epidural hemorrhage (EDH), bleeding between the skull and the dura mater, is most commonly related to traffic accidents, and much less frequently encountered than SDH. It is especially rare in children under the age of two and in the elderly. EDH usually involves arterial bleeding (>50%). If the mechanical loading does not induce immediate central nervous symptoms, the lucid interval between the generation of injury and appearance of the first symptoms is commonly shorter than for SDH, in most cases lasting not more than a few hours (delayed EDH). In very rare cases, however, the interval can last up to days. The delayed form of EDH has been reported in up to 30% of cases (Poon et al. 1992). The mortality of EDH is markedly higher than that of SDH, even given optimal neurosurgical intervention. Chronic EDH is rare and more likely to result from venous than arterial bleeding (Iwakuma and Brunngraber 1973).

7.4.2 Biomechanical Aspects

Unlike SDH, EDH is caused by local impact loading of the head and is, thus, nearly always associated with contact injury. EDH arises from injury of the middle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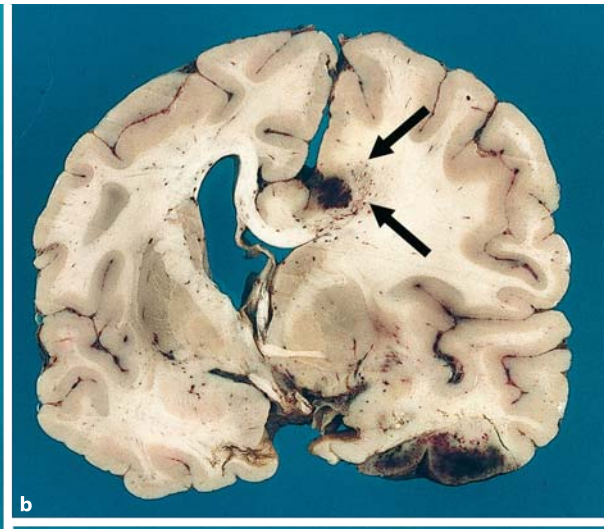
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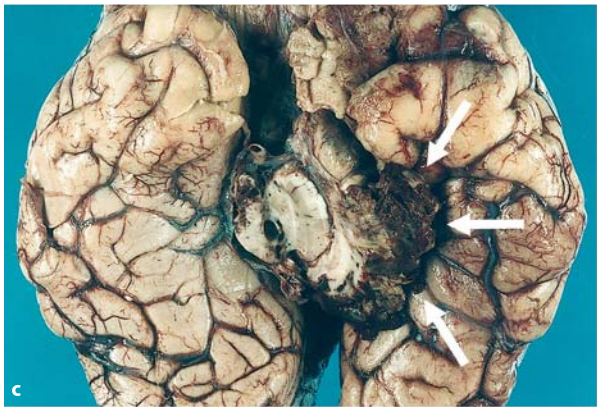
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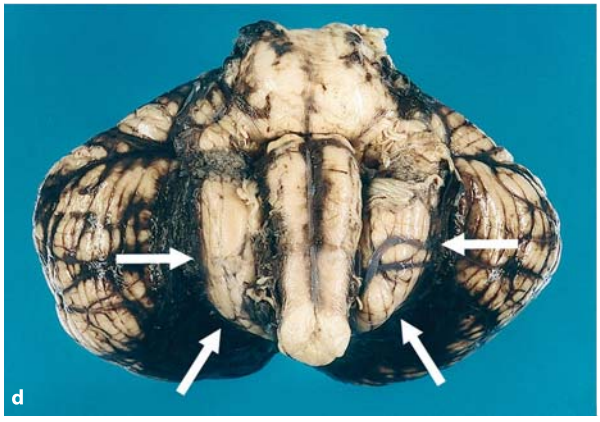
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meningeal artery and its branches near the impact site. In a typical case, EDH occurs when a fracture crosses the middle meningeal artery, which adheres tightly to the inner surface of the temporal bone. About 24% of all instances of skull fracture are associated with EDH (Edna 1983); only about 1% of EDH are not associated with a fracture (Galbraith 1973). Edges of fractured bone can cause laceration of underlying dural arteries and, less frequently, veins. In rare cases, EDH is caused by lacerations of one or more branches of the venous sinuses or emissary veins. EDH rarely occurs spontaneously. Bilateral EDH is uncommon. Bilateral EDH in the absence of fracture has been reported in a few children under 10 years of age (Cooper 1987). Deformation of the elastic skull in children can strip the dura from the inner table and lacerate the adherent vessels (Mealey 1960; Freytag 1963).

Fracturing of the skull absorbs much of the impact energy itself. Consequently, EDH is less likely to produce cerebral contusion injuries than SDH. Only 25% of patients suffering EDH exhibit associated parenchymal lesions of the brain (Bricolo and Pasut 1984; Guillermain 1986). If a parenchymal lesion does occur, it may produce a concomitant SDH.

7.4.3 Pathology

EDH is characterized by the presence of a hematoma between the dura and skull. It attaches tightly to the skull and dura mater at the borders of the sutures and has a thick lenticular, convex appearance (Fig. 7.11b, c). The volume of blood varies greatly, but amounts to at least 100 ml in most fatal cases (Lindenberg 1971; Leestma 1988).

The EDH is usually located beneath the fracture in the cranial vault (Fig. 7.11a), i.e., on the side of the impact, in most cases in the region of the temporal bone (see Table 7.1). EDH rarely develops contralateral to the impact site. Although a primary, mechanically induced, intracerebral hemorrhage involving the brain parenchyma rarely occurs, disseminated axonal injury is often seen in the brain parenchyma, especially in the corpus callosum and brain stem, sometimes without attendant hemorrhage. A space-occupying EDH will displace the brain (Fig. 7.11c, d), resulting in compression of the brain stem (herniation syndrome). The cytological and histological features resemble those of SDH and vary according to the survival time (see below).

7.4.4 Clinical Features

If there is concomitant injury of the brain parenchyma, clouding of consciousness with neurological deficits will develop either immediately (in approx. 25–30% of cases) or after an interval of minutes or hours (usually within 4–8 h – Auer et al. 1989), typically with focal ipsilateral mydriasis and hemiplegia. As already mentioned, skull fractures may be associated with EDH, the incidence of EDH being 20 times higher in cases with skull fracture than in cases without fracture (Auer et al. 1989). If a skull fracture is suspected, CT should be performed to confirm or exclude an incipient EDH. The typical appearance of EDH in CT is the presence of a biconvex hyperdense mass.

7.4.4.1 Prognosis

Prognosis depends on the interval between onset of the space-occupying EDH-induced cerebral compression and the start of surgical decompression; this means that timely diagnosis and treatment are essential to a favorable prognosis. The patient's life can only be saved by early surgical decompression. If performed early enough, this can achieve a complete recovery. The mortality of EDH varies between 0% (Paterniti et al. 1994), 5% (Poon et al. 1992) and 43% (Seelig et al. 1984). Early surgical intervention does not guarantee the patient's survival or complete recovery. The possibility of mistaken diagnosis is just as likely in EDH as in SDH and is discussed below (see p. 130).

Fig. 7.10a–e. The herniation sequelae of space-occupying intracranial (subdural) hemorrhage. **a** Compression of one hemisphere (*right*) and compression of the contralateral hemisphere (*left*) in a formalin-fixed brain after removing the subdural hemorrhage; **b** extreme hemispheric shifting as a result of a (*right*) subdural hemorrhage characterized by a flattening of the lateral parts of the hemisphere with discrete lesion of the corpus callosum and hemorrhage in the right gyrus cingulus (= subfalcine herniation); **c** extreme basal brain herniation causing hippocampal hemorrhage (= uncal herniation); **d** tonsillar herniation; **e** herniation-induced pontine hemorrhage

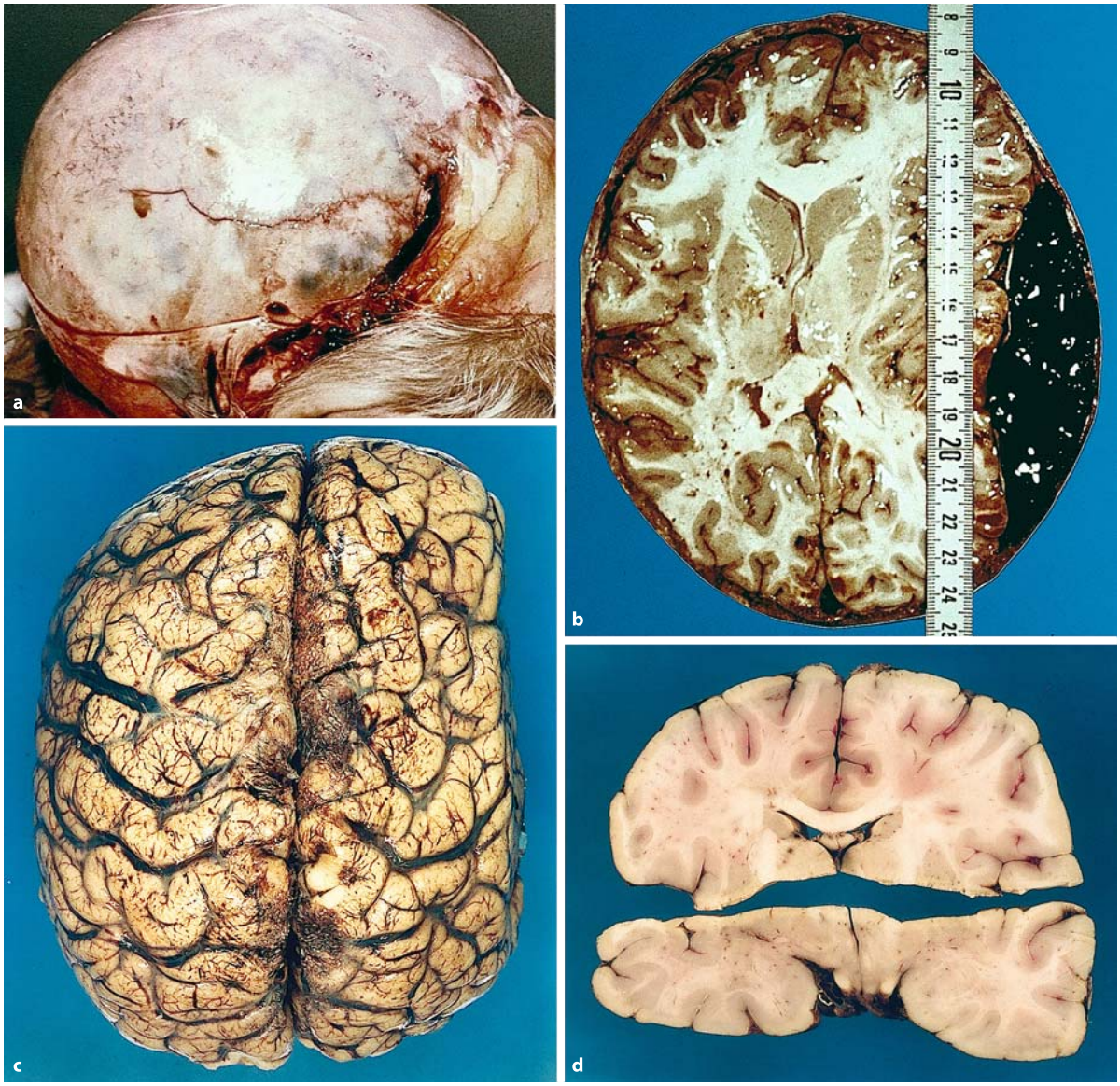

Fig. 7.11a–d. Epidural hemorrhage (*EDH*). **a** Fracture of the temporal and latero-parietal bone can be associated with a laceration injury to the medial meningeal artery with the sequelae of an epidural hemorrhage; **b** EDH compress the right hemisphere as the result of a space-occupying process; **c** EDH leads to an intracranial displacement of the brain parenchyma with **d** a midline shift from right to left

7.5 Subdural Hemorrhage

Subdural hemorrhage (SDH), bleeding into the space between the dura and the arachnoid, is commonly associated with mechanical brain injury and has a correspondingly high mortality rate. It is most frequently found in elderly and alcoholics, often in connection with a fall. SDH tends to be initially overlooked in the absence of fractures, intracerebral hemorrhage, or early neurological symptoms.

7.5.1 Classification

SDH is 3–5 times as common as EDH. Acute, subacute, and chronic *courses* can be *clinically* and *morphologically* differentiated. Special forms of SDH are *hemorrhagic internal pachymeningitis* and subdural hygroma. SDH can occur bilaterally or unilaterally, in isolation or in combination with skull fractures, with or without cortical hemorrhage.

Table 7.1. Localization of epidural hemorrhages (*n*=23). Source: Guillermain 1986

Location	Percentage
Temporal	70–90
Frontal	5–25
Parietal	1–3
Occipital	3–14
Posterior fossa	3–12

The *source of the bleeding* may be arterial or venous. According to Krauland's (1982) survey of his own cases and cases in the literature, the sources of SDH are, in order of frequency, as follows:

- Cortical hemorrhage (contusion injury) (60–70%)
- Tear in a bridging vein (2.5–20%)
- Arterial injury (cortical part of the middle cerebral artery) (2.5–10%)
- Sinusoidal injury (4–9%)

In 4–11% of cases the source cannot be found, either because there is no visible, accompanying local SAH or because the traumatic event is too long past and scarring has obliterated clear signs of the source.

7.5.2 Biomechanical Aspects

Each of the four different sources of bleeding has its particular underlying mechanism. The different types of SDH are summarized according to their pathogenetic features:

1. Recurrent "*spontaneous*" *SDH* undoubtedly exists (Matsuyama et al. 1997), although its pathogenesis has been questioned (Maxeiner 1997). Most spontaneous SDH are arterial in origin caused by a hypertensive peak in blood pressure or preexisting damage to an arterial wall (e.g., arteriosclerosis). A compromised vessel can also tear spontaneously. Spontaneous SDH is also associated with hematological or hepatic coagulation disorders and with anticoagulation therapy. A (secondary) SDH may result from the rupture of a cerebral arterial aneurysm or an intracerebral angioma into the subdural space. Friede's (1971) electron microscopic studies of the dura showed that a subdural neomembrane may form even in the absence of a traumatic event due to a proliferation of dural endothelial cells; a secondary spontaneous SDH is possible in such cases (Friede and Schachenmayr 1978; Schachenmayr and Friede 1978).
2. *Contusion-induced SDH* arises when intracerebral pressure causes tearing of, e.g., small cortical veins. The cavitation theory (see Chap. 9, pp. 179 ff) does not adequately account for such arterial tearing. Additional distortion of the vessels – such as that caused by an acceleration event – is required for tearing to occur.
3. *Cortical lacerations associated with fissures, linear fractures or depressed fractures of the skull* can cause SDH when arteries or veins are torn by sharp bone edges. Attendant lesions of the arachnoid will result in bleeding into the subdural space. In most cases, laceration or contusion injuries of the scalp are found at the site of impact.
4. *Acceleration/rotational mechanisms* (Fig. 7.12): SDH is less likely to be near the impact site than a contusion injury (even in the presence of a fracture). Thus, inertia is probably responsible for some instances of SDH (Ommaya and Gennarelli 1974; Gentleman et al. 1992). Gurdjian (1975) created experimental loading conditions that initiated rapid acceleration without impact to the head to show that acute SDH can be induced without contact. Biomechanical conditions sufficient to cause SDH can also be generated by a blow (assault) or fall. About 30% of all cases of SDH involve isolated SDH without associated skull fracture or cortical hemorrhages (Unterharnscheidt 1993; Graham and Gennarelli 1997; Maxeiner 1998), generally caused by acceleration (Gennarelli and Thibault 1982) or a blow.

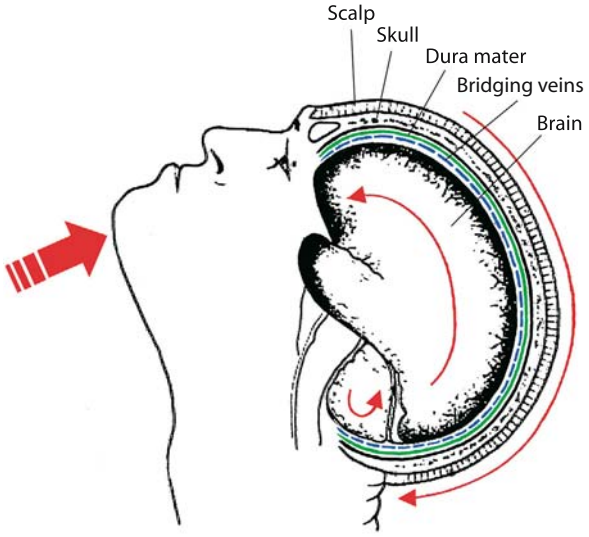

Fig. 7.12. Acceleration mechanism of the head which causes a tearing and stretching of the (*blue colored*) parasagittal bridging veins connecting the arachnoid and the dura (source: Wilson 1946; see also Sellier and Unterharnscheidt 1963)

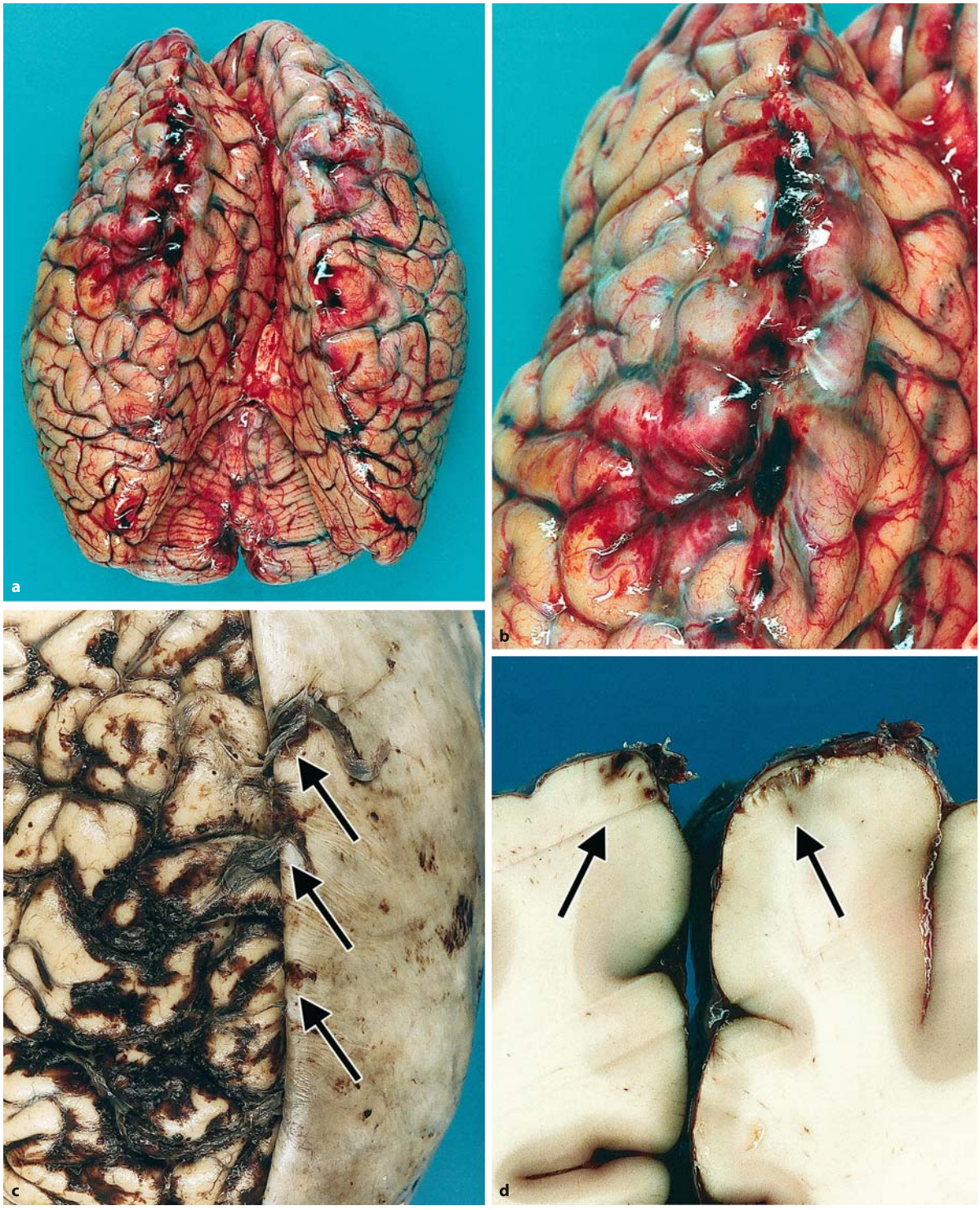

Fig. 7.13a–d. Rupture of bridging veins along the sagittal fissure. **a, b** Seen at autopsy on the surface of the left brain hemisphere and – a second case – **c** after formalin fixation demonstrating the bridging veins (*arrows*) connecting the arachnoid and the internal lamina of the dura on the left hemisphere; **d** the vessel's rupture (*arrows*) on the crest of the first frontal gyrus of the right and left hemisphere is demonstrated on the frontal section

Non-contact mechanisms usually produce no injury of the scalp. A blow to the chin, however, can induce rotational movement sufficient to cause tears of the bridging veins and/or cortical and basal arteries (Krauland 1982; Unterharnscheidt 1993). The resulting SDH may be bilateral or occur on the same or contralateral side of the impact. SDH may be induced in infants by shaking with or without accompanying impact (see Chap. 25, pp. 493 ff). In the elderly, SDH may occur without apparent or negligible head injuries.

Most SDH are located over the cerebral convexities, associated with cortical hemorrhages, and result from associated (indirect) tearing and stretching of the parasagittal bridging veins (Krauland 1961; Jamieson and Yelland 1972) that drain the surface of the cerebral hemispheres and the CSF into the dural venous sinuses. Parasagittal bridging veins are highly vulnerable to rupture from brief, high-velocity angular acceleration of the head (Gurdjian 1975).

If angular acceleration is low and of long duration, as often happens in traffic accidents, strains are propagated deep within the brain and cause diffuse axonal injury (DAI). Increased acceleration can result in acute SDH combined with DAI and torn-tissue hemorrhages (Gurdjian 1975). Such acceleration can be produced by falls in which the head strikes a hard surface or a blow, with broad impact and induced rotation. Seventy-two percent of acute SDH on file at the University of Pennsylvania Head Injury Center Data Bank had been attributed to a fall or blow, only 24% to motor vehicle accidents (Gurdjian 1975; Maxeiner 1998).

Rotation is most likely to cause tearing of the bridging veins along a transverse or diagonal-frontal axis, the greatest displacement of the skull relative to the brain occurring along the midline (Krauland 1982). If there is rotation around a transversal axis, which is often associated with translational acceleration, the brain is rotationally displaced against the skull in the parietal region, injuring the cortical arteries and inducing parietal cortical hemorrhages.

The macroscopic picture is dominated by the intracranial shift of brain tissue and edema, usually becoming apparent in the contralateral hemisphere through obliteration of the gyral sulci and flattening of the gyral crests. SDH is often attended by extensive subarachnoid hemorrhage (SAH). A circumscribed SAH may indicate the site of the torn bridging veins (Fig. 7.13).

7.5.3 Clinical Features

Clinical symptoms of SDH, which commonly involve venous hemorrhage, often arise after a lucid interval, developing more slowly and later than in EDH. A hemorrhage is regarded as subacute if it takes longer than 48–72 h after the traumatic event to become clinically relevant. The mortality rate of SDH is very high; it is even higher if the SDH is associated with a parenchymal lesion (Becker 1986).

7.5.3.1 Types and Causes of SDH

- In the *perinatal period*, birth trauma can occur mainly in premature babies including SDH associated with a tentorial tear. Clinically there may be a symptom-free interval of 2–3 days followed by symptoms of increased intracranial pressure (p. 504).
- In *infants*, SDH is usually the result of a fall or associated with shaken baby syndrome (pp. 493 ff), a consequence of child abuse. Death ensues after cerebral injury results in increased intracranial pressure, edema, secondary hypoxia, and shock caused by the loss of blood (Schiefer et al. 1968 – see pp. 502 f).
- In *adults*, the correct diagnosis of SDH is usually easy when there is a clear temporal relationship between the traumatic event and the appearance of clinical symptoms. Early diagnosis can be difficult, however, if no such readily apparent connection exists, when for example a minor head injury in an alcohol-dependent man has given rise to a chronic SDH. If the SDH is bilateral rather than confined to a single hemisphere, diagnosis can be even more difficult (Jacobsen and Farmer 1979).
- In *the elderly*, the clinical presentation is often dominated by an organic psychosyndrome rather than by hemiparesis and disturbed consciousness secondary to tissue displacement. A relatively minor head injury can cause SDH in the elderly. This brings with it the danger of incorrect diagnosis with serious consequences, especially when bilateral subdural hematoma is mistaken for a degenerative process intrinsic to the brain.

7.5.3.2 Prognosis

The prognosis for SDH is generally somewhat better than that for EDH. It is largely dependent upon the period of time between onset of the neurological deficits and neurosurgical intervention, i.e., early diagnosis is crucial to a favorable outcome. If decompression surgical treatment is effected within 4 h after the traumatic event and/or at the time of onset of neurological deficits, mortality falls significantly. Decompression surgery, however, is only necessary if clinical symptoms develop. If the victim exhibits the symptoms of herniation with intracranial circulatory arrest, it is already too late for neurosurgical intervention. Therefore, the indications for neurosurgical intervention depend upon clinical criteria.

7.5.3.3 Diagnosis

Diagnosis of SDH and EDH is usually based on *cranial computed tomography (CCT)*. Even discrete *neurological symptoms* expressing a GCS <15 – see Rieger et al. 2002) appearing after blunt impact to the head constitute an absolute indication for this procedure. The symptoms of SDH-induced increase in intracranial pressure include headache, somnolence, nausea, vomiting, and disturbances of consciousness as well as papilledema. The finding of CSF xanthochromia caused by hemosiderin-laden macrophages can support the diagnosis, since an SAH (possibly discrete) almost always accompanies an SDH (Oehmichen 1976). *Radiographically*, an expanding mass lesion is indicated by shifting of the pineal shadow.

In every instance of sudden onset of hemiparesis of unknown origin, the *differential diagnosis* must include an external mechanical force. Physical examination must include a careful inspection of the scalp for a hematoma which, if found, is an indication for early CCT. The differential diagnosis of an apparently age-related *organic psychosyndrome* in the elderly must include SDH.

An overlooked SDH – or EDH – is a common, but not in all instances excusable, *mistaken diagnosis* with fatal consequences. Late diagnosis can have fatal consequences. Although the failure to detect or correctly diagnose may be understandable in cases of chronic SDH, it should never happen in acute or subacute SDH. The misdiagnosis or late recognition is commonly due to the absence of (severe) clinical deficit symptoms in the immediate aftermath of the traumatic event. Every blunt impact to the head – even minor – entails a risk of SDH. This applies especially to the elderly with external brain atrophy and to chronic alcoholics, who also tend to suffer from external brain atrophy with possible additional coagulation disturbances secondary to liver damage.

Homeless persons in poor physical condition and reeking of alcohol are at particular risk for misdiagnoses. The patient's disorientation and confusion are attributed to simple alcohol intoxication and a thorough physical examination is not made. The overlooked blow or fall-induced hematoma of the scalp may only be discovered at autopsy.

Hematoma or laceration injury of the scalp is a marker of traumatic impact to the head entailing possible injury of the skull, dura, and/or brain. The risk of SDH is always present, even if there are no primary clinical symptoms. Early CT and/or close monitoring of the patient's state of consciousness and other neurological features including cranial nerve function for 24 h following the traumatic event can prevent misdiagnosis of SDH.

Should the patient die of SDH, the *forensic question* arises as to whether the death could have been averted by immediate neurosurgical intervention (trephination). In lieu of generally accepted guidelines, the answer must depend on expert assessment of the circumstances of the individual case. Arguments against neurosurgical intervention may be the age of the patient, an interval of more than 6–8 h between fixed pupils and craniotomy, compression of basal cisterns, and absence of upper brain stem reflexes (Sakas et al. 1995). Although fatal progression of an SDH can usually be forestalled by early intervention, in cases of non-accidental MBI the clinical (prognostic) consequences of delayed therapeutic intervention cannot be proven.

7.5.4 Pathology

7.5.4.1 Acute SDH

Fresh coagulated blood between the arachnoid and dura mater is characteristic of acute SDH and can be diagnosed by clinicians or pathologists in the first 3 days following the traumatic event (Figs. 7.14, 7.15). The loosely coagulated blood drains off at autopsy, leaving no – or only minimal – visible residues on the inner surface of the dura and brain after formalin fixation. An SAH and/or displacement of the cerebrum with unilateral flattening of the hemispheres are present in most cases. A rapidly developing SDH becomes life threatening in adults once its volume has attained 50 ml (Di Maio and Di Maio 2001). If the SDH develops slowly, a considerably larger volume can be tolerated. Most cases of SDH are accompanied by laceration and/or contusion injuries of the cerebral cortex (Maxeiner 1998: 42 versus 30 of 166 cases investigated).

The ruptured vessel can be detected in some cases of acute, or even subacute SDH (Krauland 1982; Maxeiner 1997). On removal of the brain, an operating microscope and contrasting agents or dye may be applied for demonstration of the rupture (Maxeiner 1997). The site of a venous (or arterial) rupture often exhibits small focal SAH, which should be examined microscopically to confirm (or exclude) primary vascular disease, especially if non-accidental injury is suspected.

A concomitant old SDH is often found, especially if the victim was an alcoholic (or in shaken baby syndrome – see p. 502). Spontaneous or mechanically induced rebleeding into an old SDH is not uncommon. The bleeding has its source in the sinusoidal vessels of the granulation tissue organizing the preexisting hematoma. The presence of hemosiderin-containing macrophages or of macrophages of different ages in different layers of the bleeding are an indication that multiple bleeds have occurred at different times. A

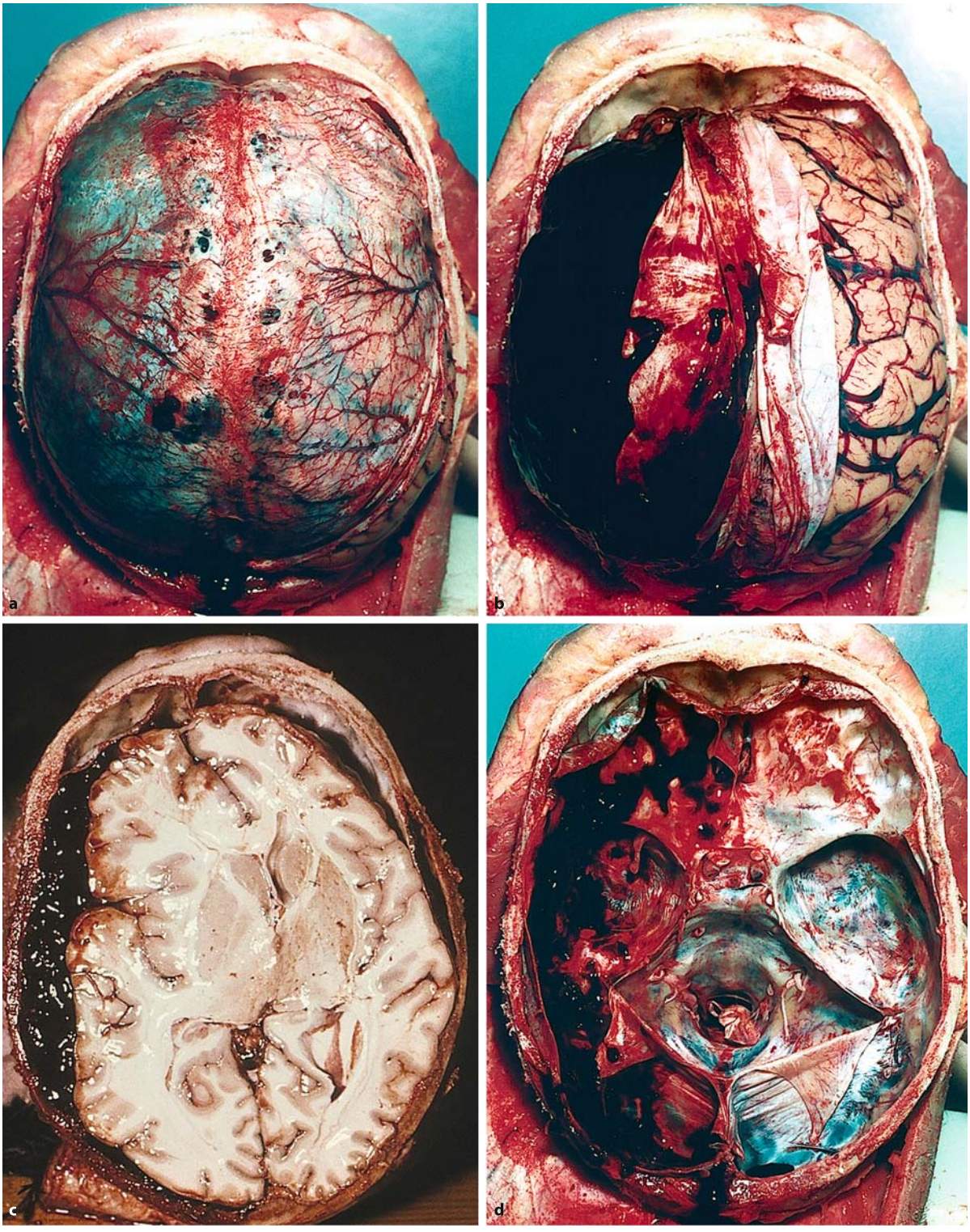

Fig. 7.14a–d. Acute subdural hemorrhage at autopsy. **a** Beneath the dura mater the left-sided hemorrhage is translucent as a blue-colored alteration; **b** after removal of parts of the dura the hemorrhage is exposed while the right hemisphere is characterized by an extreme flattening of the gyri as an indication of brain compression and swelling as well as **c** mass shifting; **d** the hemorrhage may extend to the basal subdural space of the cerebrum

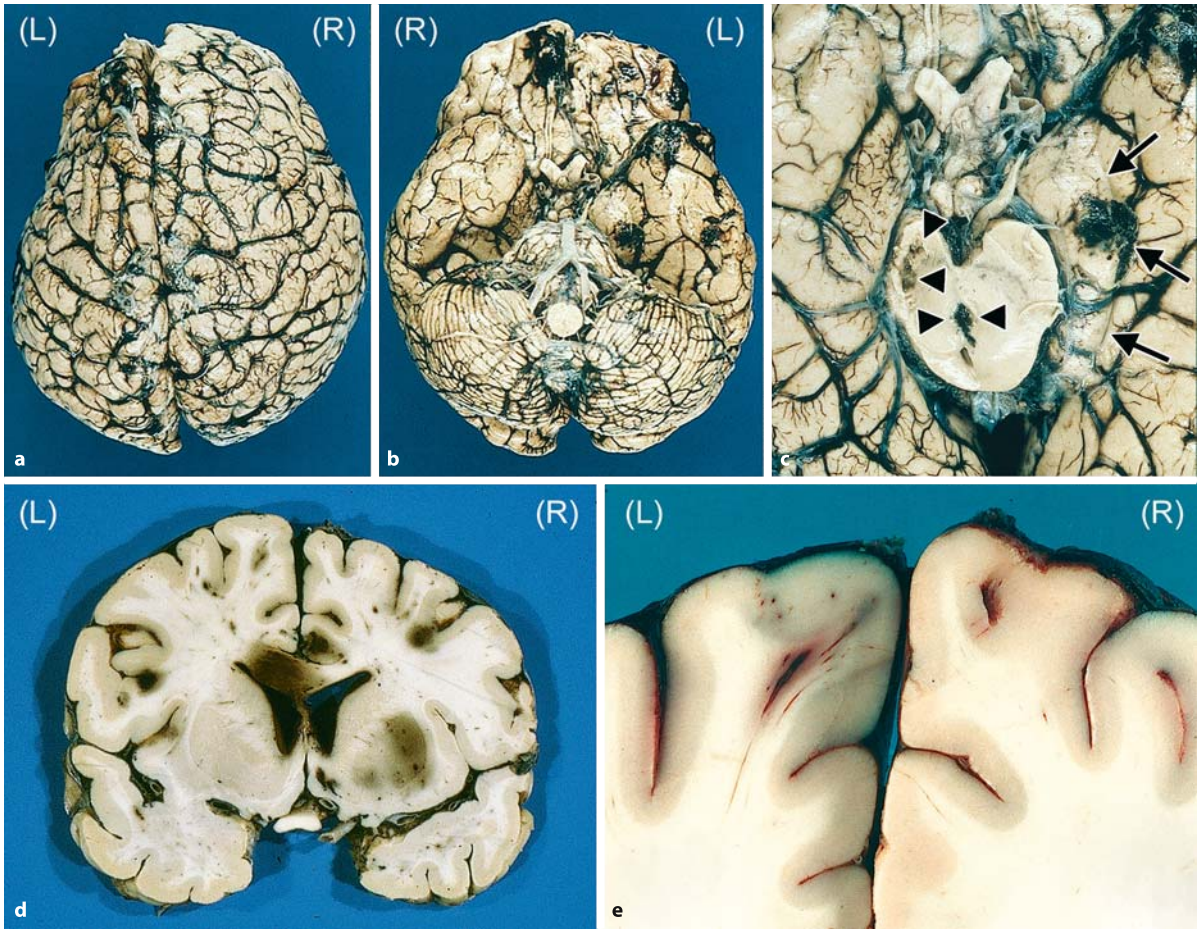

Fig. 7.15a–e. The cerebral sequelae of an acute subdural hemorrhage after formalin fixation. **a, b** The brain hemispheres are marked by a left-sided (*L*) parenchymal compression (caused by the already removed SDH) associated with left-sided minor cortical hemorrhages at the temporal pole and right-sided (*R*), more distinct cortical (frontoabasal) hemorrhages; **c** (left-sided) uncal herniation (*arrows*) with bleeding associated with (central and right-sided) midbrain hemorrhage (*arrowheads*); **d** on the frontal section: multiple hemorrhages (right-sided) because of the shifting process, especially in the left part of corpus callosum, the right gyrus cingulus as well as a (ischemic induced) dark-colored right putamen; **e** hemorrhages within the white matter of the first frontal gyrus which gives evidence of gliding contusions as the result of acceleration

Prussian blue reaction for stainable Fe should be carried out even on an apparently fresh SDH (for details see Oehmichen et al. 1981).

7.5.4.2 Subacute SDH

As stated above, an SDH is classified as subacute if the clinical symptoms take more than 48–72 h, but less than *3 weeks* to appear (Fig. 7.16a). Coagulation of the blood has usually occurred, with signs of leukocyte emigration, ingestion of erythrocytes, and/or digestion as demonstrated by Fe-containing macrophages, plus the formation of granulation tissue comprised of fibroblasts, collagenous fibers, macrophages, and endothelial cells. A dense network of precipitated fibrin holds the hematoma together.

7.5.4.3 Chronic SDH

Chronic SDH requires a survival time of about *3 weeks or more* to develop. It expands very gradually due to successive bleeding, so that clinical symptoms develop very slowly. The *morphology*, which is largely characterized by resorption and organization, varies according to the survival time. Chronic SDH is characterized by a clearly delineated collection of a clot between the dura mater and arachnoid. The SDH is typically encapsulated by a neomembrane (Figs. 7.16d, c, 7.17) formed by the dura mater as a non-specific reaction to blood or its degradation products (Apfelbaum et al. 1974). Whereas the outer membrane contains giant neovessels, the inner membrane is only poorly vascularized.

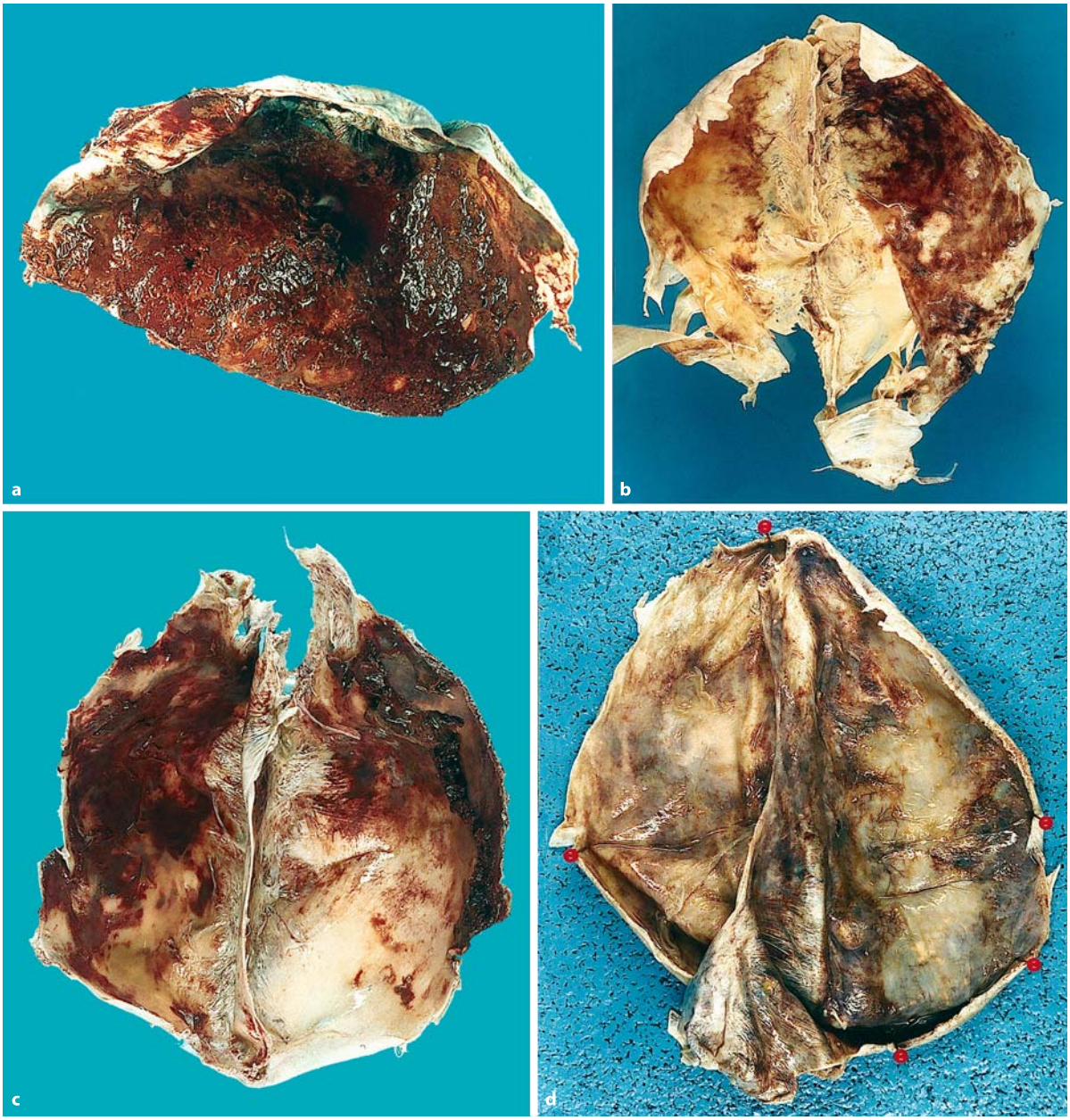

Fig. 7.16a–d. Subacute and chronic subdural hemorrhages. **a** Subacute and **b, c** chronic, non-space-occupying subdural hematomas; **d** bilateral neomembranes in an old man without a history of traumatic event and without morphological signs of an old hemorrhage (no hemosiderin containing macrophages)

The neomembrane (Fig. 7.16d) that forms on the inner aspect creates a small space or a cavity into which recurrent bleeding may occur. The rebleeding phenomenon can make it difficult or nearly impossible to determine the age of an SDH. Bleeding that recurs after a single traumatic event must be distinguished from multiple episodes of bleeding caused by one or several, temporally distinct, traumatic or spontaneous events. Though most neuropathologists suggest that any neomembrane will result from subdural hemorrhages, we have to accept that neomembranes are seen in newborn infants as well as in the elderly without any morphological indication of former hemorrhage and without a traumatic event.

Under clinical conditions in the elderly, chronic SDH can present diagnostic problems. The brain atrophy often associated with advanced age is a well-recognized factor facilitating development of SDH (Fogelholm et al. 1975; Spallone et al. 1989). Chronic SDH, though present, is often not suspected in elderly patients for a number of reasons: the neurological symptomatology is frequently protean and slow

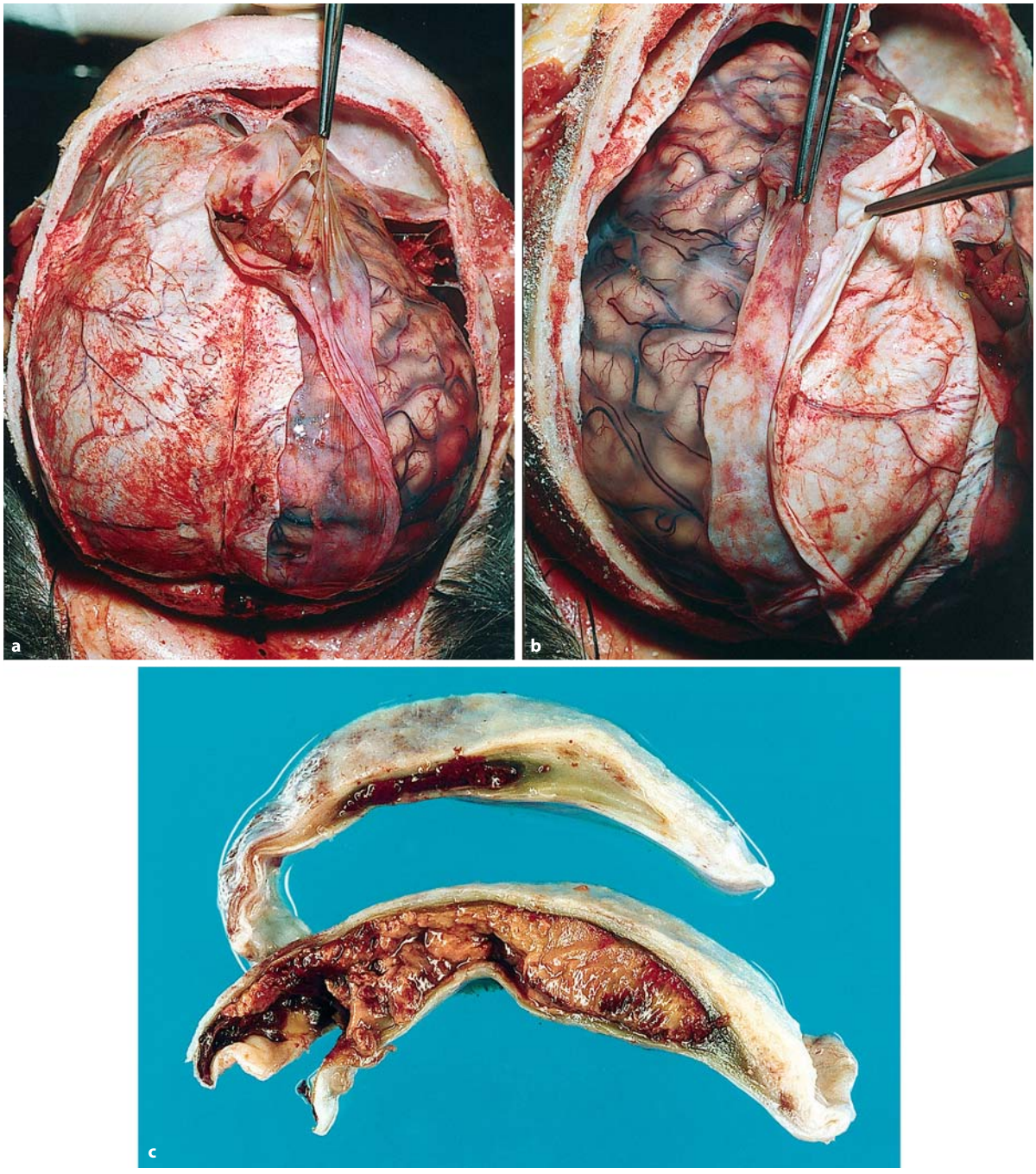

Fig. 7.17a–c. Chronic subdural hematoma associated with age-related external brain atrophy. **a** The external lamina of the right part of the dura is still removed and parts of the internal lamina are visible; **b** within this secondary (intradural) space the hematoma is located; **c** a transverse section of the hematoma gives evidence of the membrane structure, the color, and consistence of the hematoma

to progress, and may closely mimic cerebrovascular disease; the causative traumatic event may have been so mild, such as walking on irregular ground or stepping into a gopher hole, as to elude the notice of even the victim.

A special problem may be the question of why chronic SDH continues to grow slowly and does not coagulate. Murakami and his colleagues (2002) evaluated thrombomodulin expression and stated that thrombomodulin is expressed on the sinusoidal vessels and, thus, the blood coagulation system is inhibited in the hematoma. As a result, bleeding from the sinusoidal vessels may persist and the hematoma may grow slowly and fail to coagulate.

7.5.4.4 Internal Hemorrhagic Pachymeningitis

A variant of chronic SDH in the elderly is the so-called internal hemorrhagic pachymeningitis, which is often associated with mild MBI and almost always develops bilaterally. Atrophy of the brain may contribute to the etiology as the space-occupying lesion expands between the dura mater and arachnoid. Impact to the head causes strain and tearing of the bridging veins due to differential acceleration of the skull/dura and brain/leptomeninges. Morphologically the surface of the brain and the inner aspect of the dura display a hematoma that is one to several centimeters thick, and often rust-colored. In a fixed state, the brown-colored contents of the space-occupying hematoma appear friable and oily; the acute-angled bleeding extends to the normal dura. In rare instances, there is liquefaction, the cyst being filled with a watery fluid resembling that seen in hygromas (see below).

7.5.4.5 Hygroma

A hygroma is a *fluid-filled cyst on the interior side of the dura* that occurs mainly in children (pp. 479 f) (Fig. 24.5). The age distribution and *clinical picture* of mechanically induced subdural hygromas resemble those of chronic SDH. In individual instances, however, a hygroma obviously can arise as early as 4 h after the traumatic event (Oka et al. 1972).

Pathophysiology. The early occurrence casts doubt on the osmotic fluid shift theory, which assumes a slow breaking up of the hematoma by CSF invasion. Studies have shown that no significant differences exist in the osmolarities of the hematoma liquid, venous blood, and CSF (Voigt et al. 1977). Hygromas are more likely a result of a valve-like arachnoidal tear than of SDH (Oka et al. 1972). In summary, the pathogenesis of hygroma remains unclear.

7.6 Histology and Microscopic Dating of EDH and SDH

Microscopically the dura hematomas are characterized by a clot on the outside (EDH – see Fig. 7.18a) or inner side of the dura mater (SDH – see Fig. 7.18b–d), often associated with an accompanying discrete (Fig. 7.18c) or distinct subarachnoid hemorrhage (Fig. 7.18d). In most cases an associated intradural hemorrhage will be observed (Fig. 7.19a, b) as well as red blood cells (and hemosiderophages) within the Pacchionian bodies (Fig. 7.19c, d).

The time course of SDHs is characterized by a blood cell reaction and a scarring process by fibroblast proliferation and collagen fiber synthesis. According to our own investigations the very first reactive process will be the emigration of neutrophilic leukocytes as demonstrated by means of histochemistry (naphthol-AS-D chloracetate esterase – Fig. 7.20a) followed by a macrophage reaction (Fig. 7.20b, c); the macrophages phagocytose red blood cells and – as mentioned above – digest them. Intracytoplasmic siderin will be the final residue of this type of scavenger function (Fig. 7.20d).

The subsequent mesenchymal reaction is characterized by proliferating fibroblasts and their synthesis of an extracellular matrix, i.e., collagen fibers, as demonstrated in Fig. 7.21. In particular, Fig. 7.21c demonstrates the increasing vasculature of the hematoma with thin-walled giant vessels which may explain the rebleeding phenomenon in SDHs.

In 1988, a detailed time-dependent morphological pattern for dating SDH was presented by Leestma (1988). A modified version of the table is reproduced here (Table 7.2). The time-dependent changes exhibit three phases:

- *1st phase* (<2 days): the blood coagulates. The blood stays fairly well preserved and a layer of fibrin forms on the surface of the clot.
- *2nd phase* (2–10 days): the number of fibroblasts in the dura increases and a fibroblast layer appears between the dura and the clot. By the 7th day, a well-formed membrane is evident between the dura and the clot as well as between the clot and the arachnoid. Mesothelial cells, endothelial cells, and fibroblasts proliferate and the clot is invaded by capillaries, venules, and fibroblasts.
- *3rd phase* (>10 days): beginning on about the 15th day, a definite membrane composed of mesothelial cells is visible on the inner surface of the clot (inner membrane); fibroblastic strands extend into the clot.

Krauland (1982) points out that since recurrent bleeding is more the rule than the exception, examination of the dural hematoma alone can lead to a false impression. According to this author, survival time is best determined by additional microscopic examination of the vein or artery constituting the potential source of the bleeding supplemented by examination of the contiguous brain tissue.

During the first two phases the brain itself is commonly characterized by intense edema and by additional (facultative) mechanically induced parenchymal hemorrhages. The cytological reaction to these hemorrhages as well as cytological reactions in the associated subarachnoid hemorrhages and cutaneous hemorrhages, lacerations or bruises will give additional evidence of the time course. Moreover,

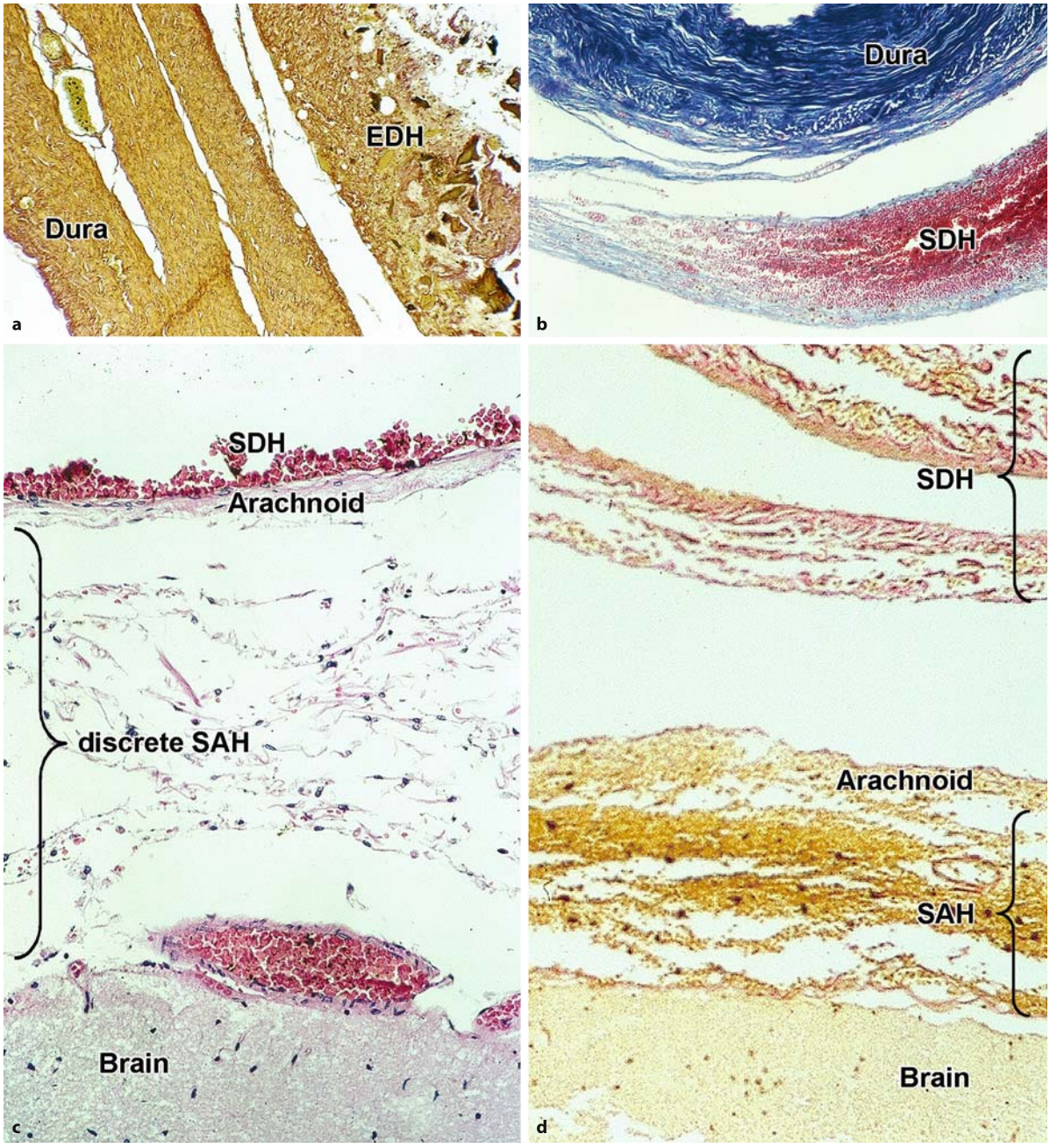

Fig. 7.18a–d. Histologic distribution of extravasated blood in epidural and subdural spaces. **a** Epidural hemorrhage associated with bone fragments within the extradural clot (van Gieson, magnification ×200); **b** initial organization of the clot within the subdural space demonstrating (blue colored) membrane-like structures (Azan, magnification ×100) and associated with a discrete (**c**) or massive (**d**) subarachnoid hemorrhage (*SAH*) (van Gieson, magnification ×300)

signs of axonal injury are nearly always demonstrable (Fig. 7.22) in cases with survival times of at least 105–180 min, which will give additional evidence of the timetable of survival interval.

Estimation of the age of an SDH can be based not only on cytological and histological criteria, but also on its water content (Klöppel and Weiler 1977) and a comparison of alcohol or drug levels in the hematoma versus those in blood (see Fig. 7.9). If, for example, the hematoma blood has a higher alcohol concentration than the peripheral blood, this can sometimes be used to estimate the minimum interval between onset of bleeding and death. In the same way, pharmacokinetic analyses can compare drug levels in hematoma blood versus those in peripheral blood.

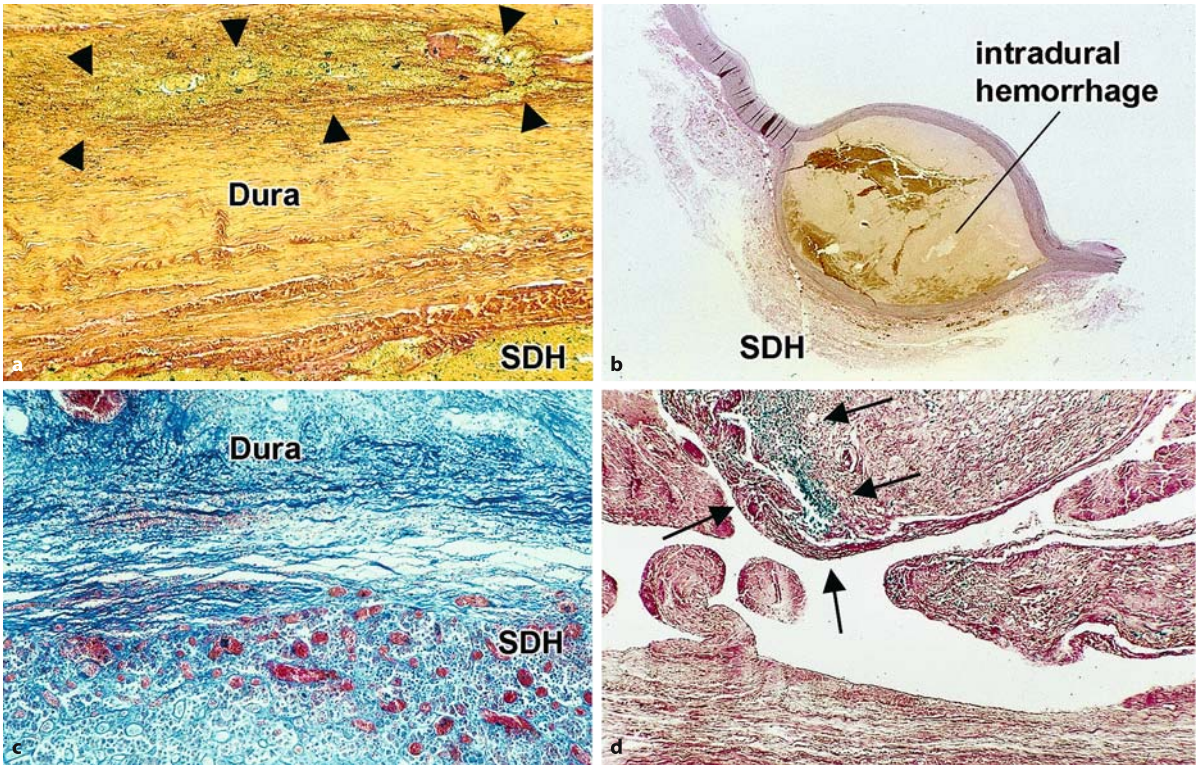

Fig. 7.19a–d. Intradural hemorrhage. **a** Extravasated red blood cells (van Gieson, magnification ×300); **b** transverse intradural rupture and hemorrhage (H&E, magnification ×20); **c** red blood cells within the network of the Pacchionian bodies (Azan, magnification ×200); **d** hemosiderin-containing macrophages within the Pacchionian bodies (van Gieson, magnification ×100)

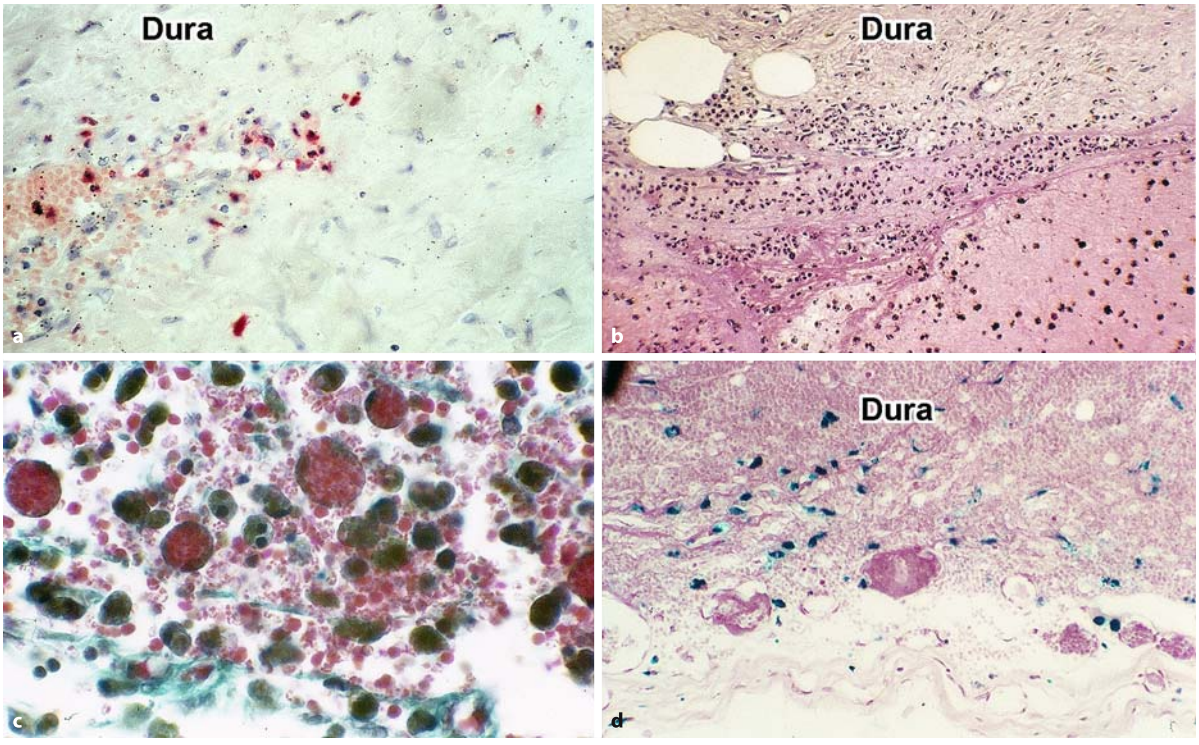

Fig. 7.20a–d. Blood cell reaction in dura hematomas. **a** Leukocyte emigration (N-AS-DCIAE, magnification ×500); **b** combined leukocyte-macrophage reaction (H&E, magnification ×300); **c** phagocytosis of red blood cells = erythrophagocytosis (Azan, magnification ×1,000); **d** hemosiderin-containing macrophages = siderophages (Prussian blue-reaction, magnification ×500)

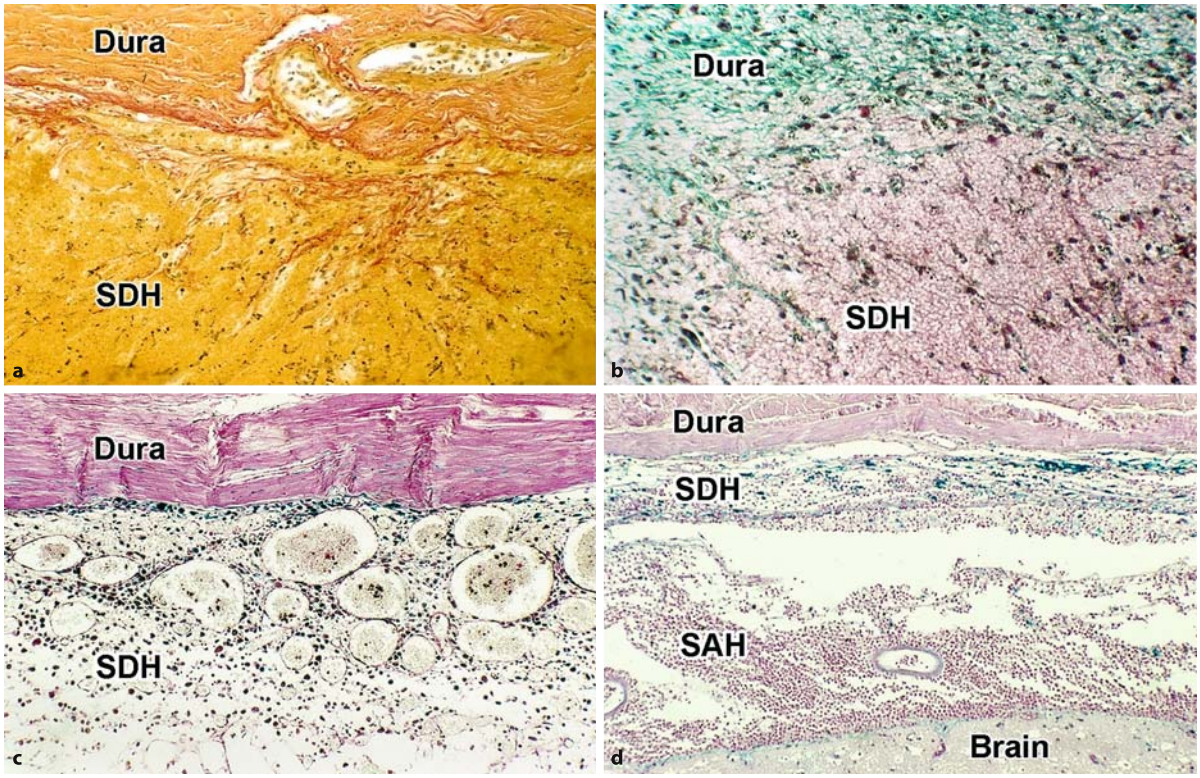

Fig. 7.21a–d. Mesenchymal reaction. **a** Star-like invasion (*red colored*) of collagen fibers (van Gieson, magnification ×100); **b** diffuse collagenous infiltration of the hematoma associated with macrophages (Gomori, magnification ×500); **c** increasing thin-walled giant vessels associated with multiple hemosiderin-containing macrophages within the organizing hematoma (Gomori, magnification ×200); **d** rebleeding phenomenon as demonstrated by a layer of hemosiderin-containing macrophages beneath the dura (*SDH*) and a Prussian blue-negative hemorrhage within the associated subarachnoid space (*SAH*) (Prussian blue-reaction, magnification ×100)

Moreover, a timetable of MRI changes of hematomas is still being published. According to Mori (1991) the morphological alterations, i.e., the signal intensity, are time-dependent (Table 7.3).

7.7 Injuries of Intracranial Vessels

Mechanical loading can cause injury of intracranial or extracranial vessels. Only injury of intracranial vessels will be discussed here (for extracranial vessels, see below, pp 146 f). Moreover, a distinction must be made with regard to extracerebral intracranially located vessels. The extracerebral vessels include the subarachnoid arteries, especially the large basal arterial vessels, internal carotids, and the intracranial portions of the vertebral arteries. They also include the (venous) vessels of the arachnoidea, dura mater, and the venous sinus at the base of the skull. The biomechanics of injuries of intracranial vessels were expertly reviewed by Unterharnscheidt (1993). The following types of injury are distinguished:

- Longitudinal rupture of vessel walls can be caused by positive or negative pressures resulting from differences in the pressures within and outside the vessel walls.
- Longitudinal traction of vessel walls causes transverse rupture.
- Direct complete or partial penetration of the vessel wall results in complete or incomplete rupture (with resultant loss of blood) or injury of the intima and secondary thrombosis.
- Penetrating or non-penetrating impact can injure the tunica media of the vascular wall and lead to a (dissecting) aneurysm.
- Blunt mechanical traumatization of a vessel may result in an intimal tear, with subsequent thrombosis and vascular stenosis or occlusion.
- Vessel injury, stenosis or occlusion can occur if the vein becomes strangled or constricted in a fracture.
- Simultaneous injury of arteries and veins can lead to a communicating arterio-venous anastomosis.

Table 7.2. Cytological and histological changes of subdural hemorrhages (SDHs) dependent on the survival times of the victims (*RBC* = Red blood cells). Source: Leestma 1988, modified

Survival interval	Clot	Dura side	Arachnoidal side
<24 h	Spherical RBCs	Thin fibrin layer, leukocytes emigrate	Thin fibrin layer, single leukocytes
24–48 h		Single macrophages and fibroblasts	Single macrophages
3–4 days	Hemoglobin loss of RBCs, granulocytes, single macrophages	2–4 layers of fibroblasts, periversal macrophages and RBC-ingesting macrophages	Macrophages increase, RBC-ingesting macrophages
5 days		Single hemosiderin-containing macrophages	
6–10 days	Laked RBCs, clot liquefies, fibroblasts enter the clot	12–14 layers of fibroblasts, neomembrane visible grossly	
10–15 days	Proliferation of capillaries		Hemosiderin-containing macrophages
15–20 days		Membrane to 1/2 dural thickness	Membrane up to 1/2 dural thickness, hemosiderin-containing macrophages in the membrane
21–25 days	Clot completely liquefied	Dura-like membrane, hemosiderin-containing macrophages in the membrane	Dura – like membrane
26–30 days	Large capillaries (secondary bleeding)	Well-formed membrane	Well-formed membrane
1–3 months		Hyalinization of the membranes: fewer cells, more collagen	Hyalinization of the membranes: fewer cells, more collagen

7.7.1 Mechanically Induced Subarachnoid Hemorrhage and Intraventricular Hemorrhage

7.7.1.1 Biomechanical Aspects

Mechanically induced SAH results when the strain produced by angular acceleration is sufficient to damage the superficial vessels in the subarachnoid space. Ommaya and Gennarelli (1974) theorized that lesion depth correlates with the intensity of impact, suggesting that SDH associated with SAH reflect relatively severe injury of the brain from high angular acceleration of long duration. Though each EDH and SDH may be accompanied by an SAH, an impact can also lead to an isolated SAH as seen in Fig. 7.23, the sequelae of a blow.

Ruptures of superficial vessels in the leptomeninges, especially veins, are common in mechanical brain injury. Their occurrence is sometimes isolated, and sometimes in association with dural hematomas and/or cortical hemorrhages. The literature describes only a few cases of rupture of the intact large arteries at the base of the brain. The biomechanical factors in such cases are described by Ommaya and Gennarelli (1974).

Krauland (1982) has reviewed and analyzed a number of cases involving *mechanically induced basal arterial rupture* without preexisting vessel damage: in rare cases, *rotation- and/or acceleration*-induced changes in tissue pressure, tension or shearing forces in association with an increase in

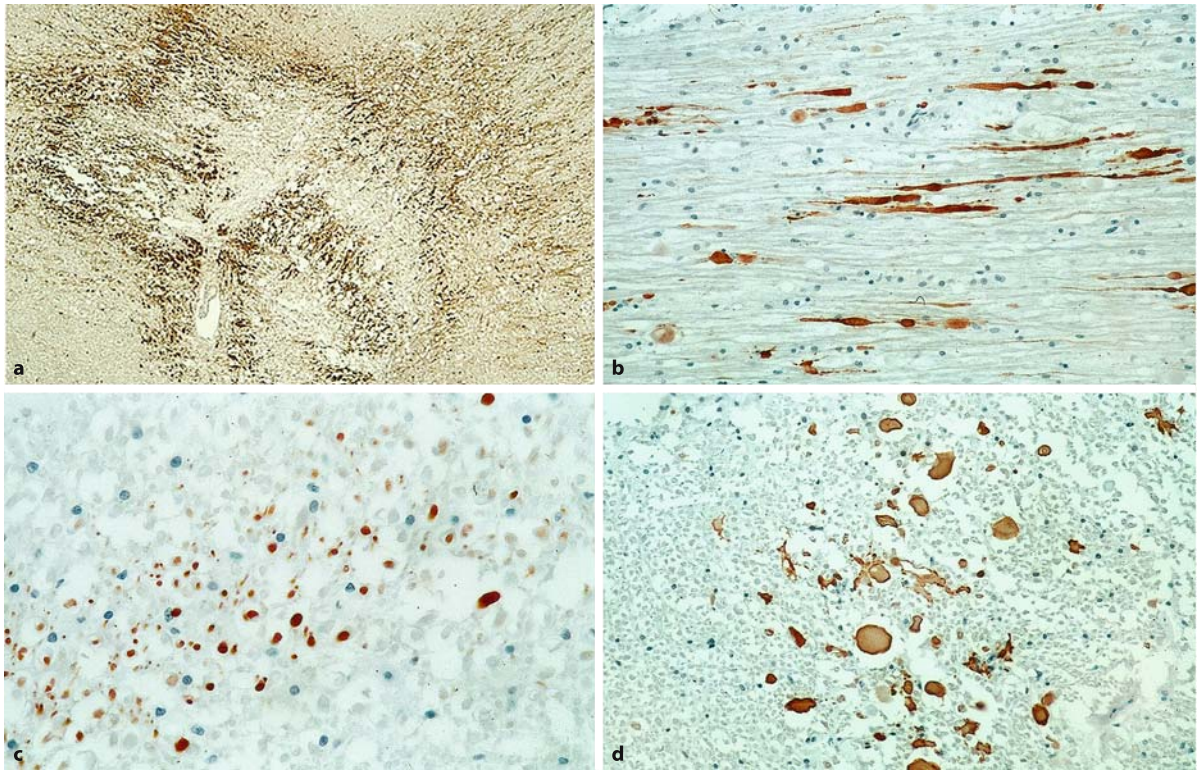

Fig. 7.22a–d. Axonal injury indicating acceleration damage associated with SDH as demonstrated by means of immunohistochemistry using an antibody against β-amyloid precursor protein (β-*APP*). **a** Central parts of the pons (magnification ×100); **b** corpus callosum (magnification ×1,000); **c, d** cervical spinal cord (magnification ×1,000)

Table 7.3. MRI changes of SDHs dependent on the survival times of the victims. Source: Mori 1991

Survival time	Biochemical and cytological composition	Signal intensity	
		T1	T2
Acute (1–4 days)	Deoxyhemoglobin	Low	Low
Subacute (5–12 days)	Intracellular methemoglobin	High	Low
Chronic (2 weeks to 1.5 years)	Extracellular methemoglobin	High	High
Old (6 months to 5 years)	Residual methemoglobin, CSF, gliosis	Low	High
Old (5 days to several years)	Hemosiderin	Void	Void

intravascular arterial pressure can cause tearing of intact vessels within the arterial circle of Willis (see also Koszyca et al. 2003). The inertia-induced displacement of the brain relative to the skull appears to cause tearing of the vascular wall. In at least some cases, the location of the vascular tear may depend in part on an additional rise in intravascular pressure. To establish a forensically relevant causal link between an impact and the bleeding, it is particularly important to demonstrate the temporal coincidence of the traumatic event, acute loss of consciousness, and the basal bleeding (see Fig. 7.24). Even if no vessel tear can be found in cases of basal SAH, the time coincidence of impact and symptoms will establish the causality.

In rare cases an isolated pial hemorrhage may be observed lacking an accompanying SAH (Fig. 7.25) as a consequence of an impact. In certain kinds of

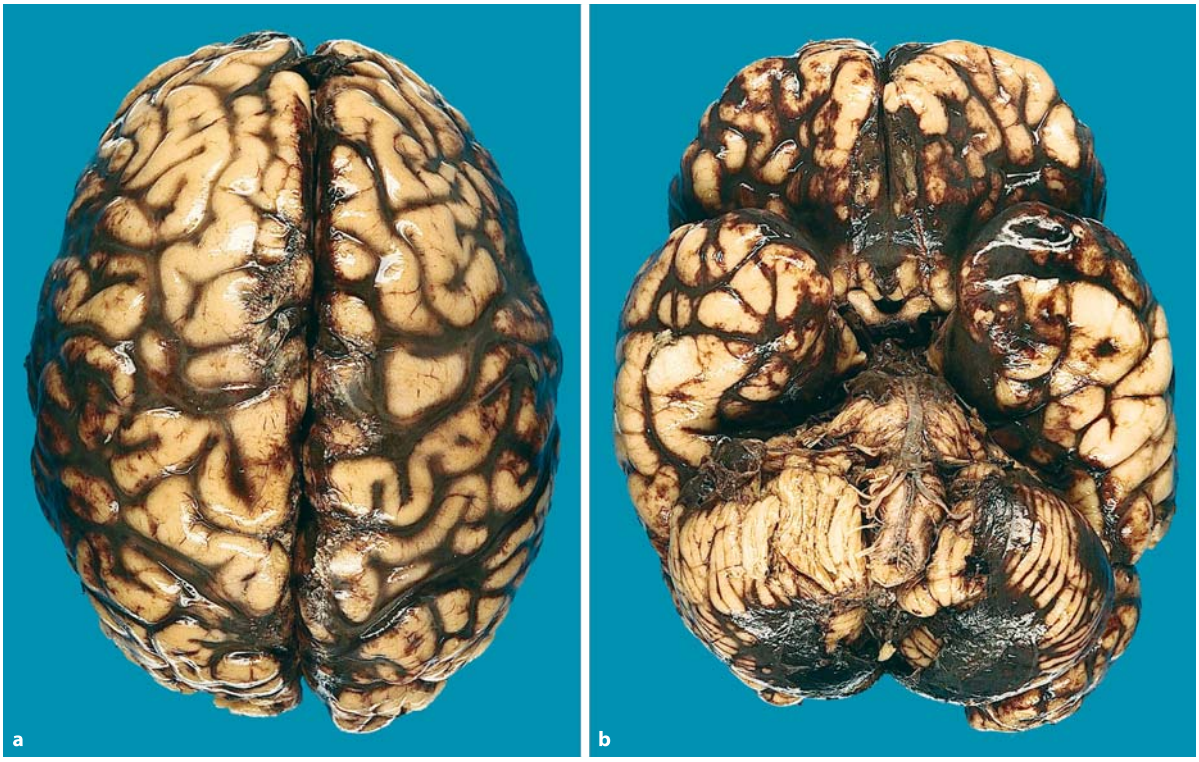

Fig. 7.23a, b. Isolated, mechanically caused bilaterobasal subarachnoid hemorrhage as a result of a blow (slap in the face) – associated with massive brain swelling

traumatic events, shear and rotational forces may give rise to massive IVH extension to the subarachnoid space. In such cases, the possible sources of bleeding include ruptures of the choroid plexus, the fornix or of the septum pellucidum. Moreover a retrograde flux of blood through the medial (Magendie) or lateral apertures of the IVth ventricle (Luschka), or a disruptive hemorrhage of the white matter may be possible. Minutes after the impact, SAH and IVH often lead to an irreversible cardiac arrest; in these cases the causal link between the traumatic event and death is evident.

From the forensic point of view the question may arise as to whether a perpetrator could have foreseen that the violent assault could result in rupture of an intact artery at the base of the brain or within the brain. Since even massive forces seldom induce injury of these basal arteries, the question must be answered in most cases with a definitive "no" and the fatality classified as an "accidental" death.

7.7.1.2 Clinical Features

Mechanically induced SAH often produces symptoms that overlap those of accompanying injuries of brain parenchyma and/or of space-occupying processes associated with SDH or EDH. Clinically, isolated SAH is characterized by xanthochromic CSF and complaints of intense headache by victims.

The causative events and symptoms of basal SAH are highly characteristic: the victim is usually *under the influence of alcohol* at the time of the traumatic event, stumbles or falls, becomes *acutely unconscious*, and remains lying on the ground. Although it may be easy to establish an impact to the face or head as the cause of the vessel tear, it can be extremely difficult to determine in retrospect whether it resulted from a blow or the fall. Chronic alcoholics often have low muscle tone, which can contribute indirectly to the severity of the brain trauma. Even if attempts at resuscitation begin immediately, most victims suffer a centrally induced cardiac and/or respiratory arrest. Should the victim survive the immediate crisis, there is stiff neck, nausea or vomiting and intense headache. One possible late sequela may be an obstructive hydrocephalus. Hemosiderin-containing macrophages can be demonstrated in the xanthochromic CSF (Oehmichen 1976). Courville (1962) thought that every traumatic event involving a loss of consciousness of more than 3 h duration is associated with a SAH.

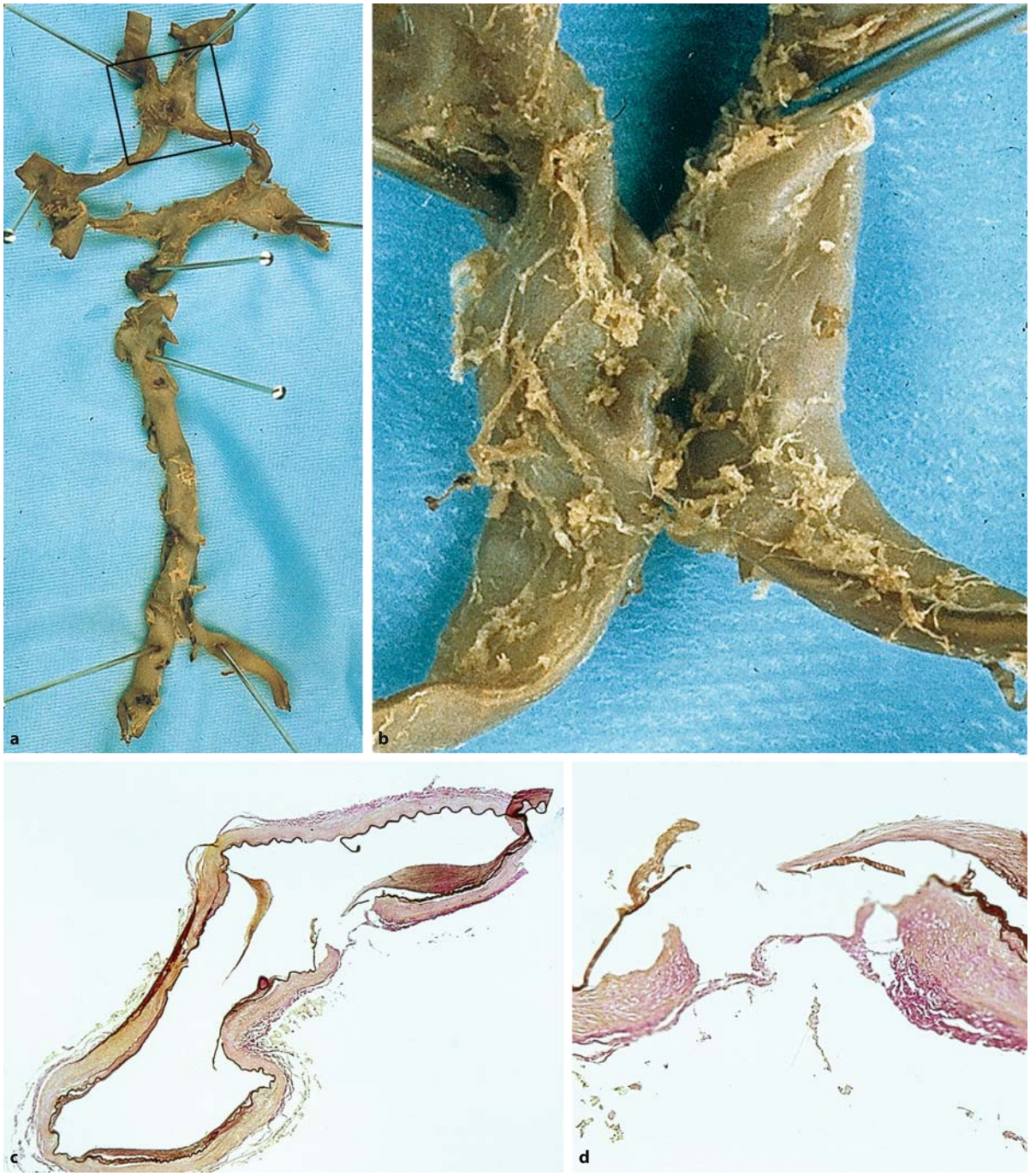

Fig. 7.24a–d. Mechanically caused rupture of a large basal artery of the brain as a sequel of a blow with immediate loss of consciousness and death within 30 min. **a, b** Rupture of the anterior communicating artery, as also demonstrated by histology (**c, d** elastica – van Gieson; magnification **c** ×100; **d** ×300)

7.7.1.3 Pathology and Differential Diagnosis

SAH have three main localizations (Courville 1962):

1. Diffuse basilar SAH
2. Diffuse dorsolateral SAH
3. Focal (localized anywhere) SAH

Although dorsolateral and localized SAH are usually a supplementary finding, they can provide information on the biomechanics of the traumatic event(s) that can be valuable in its reconstruction. Basilar SAH with massive bleeding in the large basal cisterns, and possibly spilling over into the ventricular system (also retrograde), are usually fatal.

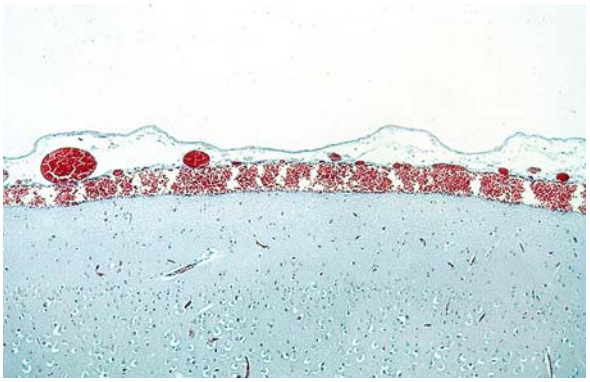

Fig. 7.25. Isolated pial hemorrhage after fall caused by seizure (Azan, magnification ×200)

The morphology of basilar SAH is said to be crucial for distinguishing between a mechanically induced hemorrhage and a spontaneous aneurysmal hemorrhage (Avdeef 1974; Krauland 1982). The morphology holds the key to whether an intact artery or an altered vessel, i.e., a preexisting aneurysm, could have ruptured as a result of impact. In cases of presumed mechanical loading, the large basal arteries should be carefully prepared. To ensure disclosure of vessel tears, the arterial vessels must be dissected using a microscope or magnifying glass at autopsy (and not on the formalin-fixed brain). In 8–27% of cases of spontaneous rupture an aneurysm cannot be demonstrated (Lange-Cosack 1966; Krauland 1982), making accurate reconstruction of the traumatic event indispensable for determination of the cause.

As already stated, a preexisting aneurysm has to be excluded even in apparent cases of mechanical loading. Other types of preexisting vessel disease or damage to the vessel should also be ruled out. Thus, for example, a hyalinosis, amyloidosis, arteritis and an idiopathic cystic medial necrosis need to be excluded before any inferences can be made regarding the external event. By demonstrating hemosiderophages (Fe-containing macrophages), microscopic examination can confirm the occurrence of repeated hemorrhages. It must also be ascertained whether the mechanical impact was of sufficient violence to cause the SAH.

In an investigation of 31 cases of mechanically induced SAH of the large basal arteries not involving aneurysms, 27 from the literature (for a more recent review see Bunai et al. 2000), Krauland (1982) found the large majority to be located in the area of the basilar artery and the vertebral arteries. Of the 250 cases of ruptured aneurysm examined by Freytag (1966), a traumatic event was associated with the acute hemorrhage and was considered to have caused the rupture in 16 cases (6.4%). But cortical hemorrhages were discovered in none of the cases. Richardson and Hyland (1941) found a mechanical loading to be the cause of the rupture in only 2 of 108 cases they investigated.

The following relationships between mechanical injury and aneurysms were described by Newbarr and Courville (1958) for their own material:

1. A preexisting aneurysm that did not rupture despite severe impact (n=1)
2. A preexisting aneurysm that ruptured immediately upon impact(n=6)
3. A preexisting aneurysm that ruptured some time after impact (n=9)

In contrast several recent investigations give no evidence of a causal relationship between mechanical loading and rupture of an aneurysm (Asari and Ohmoto 1993; Rinkel et al. 1998; Cummings et al. 2000; Juvela et al. 2000). These authors suggest that the hemorrhage of the ruptured aneurysm will cause an impact, e.g., by spontaneous breakdown.

The cytological response to SAH is comparable with the morphology mentioned in association with dural hemorrhages (p. 135), but the timetable is different (see Oehmichen 1976, 1990): leukocytes in the subarachnoid space will increase within 1 h, macrophages will be seen within 7–15 h, erythrocyte-containing macrophages are observed after 17 h, and siderin-containing macrophages are not described before 72 h. The time dependence of a mesenchymal reaction is not evaluated.

7.7.1.4 Delayed Mechanically Induced Apoplexy

According to the literature a delayed mechanically induced "apoplexy" associated with the name of "Bollinger" is characterized by massive intracerebral bleeding occurring days, weeks or months after the traumatic event. The bleeding is accompanied by sudden loss of consciousness and neurological deficits. But there is good reason to doubt that delayed traumatic apoplexy represents a discrete entity. Criteria for excluding the diagnosis of this phenomenon were published by Singer (1922), and later supplemented by Zülch (1969). Because application of these criteria almost invariably produces a different diagnosis, the existence of this syndrome can be regarded as improvable (see Unterharnscheidt 1993).

7.7.2 Mechanically Induced Aneurysm

7.7.2.1 "False" Aneurysm

Non-dissecting intracranial aneurysms of potentially mechanical origin must be distinguished from spontaneous aneurysms (congenital malformations –

Busse 1921; the result of a rudimentary weakness in the blood vessel walls – Forbus 1930 – for details see pp. 549 ff), which have been the subject of numerous studies. Only a comparatively small number of cases of mechanically induced aneurysms have been incontrovertibly confirmed (Krauland 1982).

Most mechanically induced aneurysms have the following *pathogenesis*: a traumatic event leads to an injury extending throughout the vessel wall, but extravasation of blood is limited by the fascia or dura. The hematoma soon becomes encapsulated. After an interval of days or weeks, the clot eventually dissolves, leaving a sac communicating with the artery, a so-called false aneurysm. *Clinically*, an interval of days or weeks can separate the original wounding event and rupture of such a sac. It is much more difficult to establish a causal connection between wounding event and sequelae in such instances than is the case with acute mechanical SAH.

Pathology. If macroscopic or microscopic examination discloses a tear in the vascular wall, and the wall of the "false aneurysm" consists of precipitated fibrin and thrombi, a mechanical etiology can be regarded as certain. Histology can demonstrate the break in the vessel wall: the intimal, medial, and adventitial layers are all interrupted at the rupture site. After prolonged periods of survival, secondary changes (scarring, recurrent ruptures) are consistently found. It is extremely difficult to prove a mechanical origin for chronic aneurysms.

There remains the elusive question as to whether the spontaneous rupture of an idiopathic, congenital aneurysm could also lead to formation of a so-called false aneurysm. Unterharnscheidt (1993) has speculated that such a process could underlie the formation of so-called giant aneurysms.

7.7.2.2 Dissecting Aneurysm

Dissecting aneurysm refers to a condition in which blood enters the wall of the artery, dissecting between its layers and creating a cavity within the vessel wall. The morphological picture is characterized by the formation of intramural hematomas. Nedwich et al. (1963) surveyed the literature up to 1962 and found that intracranial dissecting aneurysms are rare. Mechanically induced dissecting aneurysms represent only a small fraction of all dissecting aneurysms. Sato et al. (1971) reviewed 31 cases from the literature (see also Stehbens 1972): trauma was implicated in the rupture in one-third of all cases, and idiopathic cystic medial necrosis in one-tenth. In a more recent study, Desfontaines and Despland (1995) found mechanically induced dissecting aneurysms of the internal carotid artery in only 10 of 60 patients, the remaining 50 patients had spontaneous aneurysms. Although aneurysms of the mechanical type most frequently occur in the intracranial carotid artery (Ohkuma et al. 2002), they are also occasionally seen in the vertebrobasilar artery (Caplan et al. 1988; Mizutani et al. 1995) and middle cerebral artery (Shaw and Foltz 1968; Sharif et al. 1995).

Mechanically induced dissecting aneurysms cannot be distinguished from spontaneous aneurysms based on clinical symptoms alone. The most common symptoms for either type of aneurysm are unilateral headache or neck pain associated with symptoms of cerebral ischemia or oculosympathetic palsy (Desfontaines and Despland 1995). In two-thirds of patients, the first symptom is the SAH (Ohkuma et al. 2002); if the aneurysm is not treated, recurrent SAH can occur (Mizutani et al. 1995) which may be fatal.

Biomechanically their pathogenesis resembles that of false mechanical aneurysms, although the vessel wall is not entirely interrupted, just the intima and media. Such aneurysms can also be caused by chiropractic manipulation of the neck in patients with preexisting idiopathic medial necrosis (Peters et al. 1995).

A mechanical pathogenesis may be suspected if a primary vascular disease such as idiopathic medial necrosis can be excluded and a temporal relation with a MBI is confirmed. A mechanically induced aneurysm entails the risk of a secondary rupture of the entire vessel wall; i.e., of SAH or thrombosis.

The difficulty of distinguishing between a spontaneous and a mechanically induced dissecting aneurysm has been pointed out by Krauland (1982): the first impression at autopsy is that the lesion represents a primary thrombosis or embolism. An idiopathic medial necrosis can be excluded after microscopic examination while the mechanical pathogenesis of a dissecting aneurysm is strongly suspected in the absence of signs of medial necrosis and in the presence of additional signs of mechanical loading.

7.7.3 Mechanically Induced Arterial Thrombosis

Mechanical loading to the head sometimes induces stenosis or occlusion of the large arteries at the base of the brain, most commonly the extracranial carotid arteries (80–85%; Reisner and Reisner 1976 – see also below: pp. 146 f), but occasionally the intracranial arteries (35 of 123 cases; Födisch 1970). Injury of the vertebral arteries is a known complication of chiropractic manipulation of the neck (see Green and Joynt 1959; Schmitt 1978).

The *clinical* symptoms of mechanically induced arterial thrombosis depend on the vessel involved, the area it supplies and on whether the consequence of the vessel injury is stenosis or occlusion. It is not

uncommon for victims to experience a lucid interval, which can last 3–5 min or even months. This can lead to the mistaken diagnosis of an SDH (see Födisch and Kloss 1966).

Morphological examination (for review see Perry 1981) requires exposure of the vessels for examination of the internal elastic membrane, which has often ruptured. The thrombus adheres to the site of the lesion. Further changes in morphology are dependent upon the extent of possible collateral circulation. In a small number of cases, a brain stem infarct occurs which is invariably fatal. A causal connection between the two events can only be established if mechanically induced vessel injury is found and/or other explanations are excluded by the course of the disease. Here again, very careful dissection of the basal arteries is essential.

7.7.4 Injury of the Veins

7.7.4.1 Injury of the Sinuses (Sinus Thrombosis)

Thrombosis of dural venous sinuses may occur due to a variety of etiological factors including pregnancy, sepsis, dehydration, hypercoagulability, inflammation, arteriosclerosis, or tumors – especially metastasizing tumors (for review Crawford et al. 1995; Daif et al. 1995 – see also Chap. 28, pp. 558 ff). Mechanical violence is the third leading cause (see Huhn 1965; Krücke 1971). Dural sinus thrombosis occurs both in adults (Daif et al. 1995) and children (Lee et al. 1995). Due to impairment of blood flow in affected areas, the clinical presentation and the morphological appearance both depend upon which of the sinuses is involved.

Injuries of the dural sinuses can lead to massive uncontrollable bleeding, with consequent hemorrhagic shock and possible death; a fracture at the base of skull in particular can cause thrombosis (Sedzimir 1955) due to compression or injury of the vessel. In cases of open MBI, any or all of the sinuses may be affected. The most commonly observed sinus thrombosis involves the sagittal sinus secondary to an impression fracture of the calvarium. Thromboses are also associated with closed MBI (Hesselbrock et al. 1985). These rather rare events can have a variety of causes (see above), but their sequelae resemble those of open MBI. Finally, fracture can also create openings between the basal venous sinus and the paranasal respiratory sinuses, thus inducing a CSF fistula and possibly lead to cerebrospinal rhinorrhea, meningitis or fatal air embolism (Patscheider 1962). Blood flowing into the trachea and its aspiration into the respiratory tract can result in death by suffocation.

The *clinical symptoms* associated with thrombosis usually appear only after a delay. Whereas intracranial hemorrhage leads to a space-occupying lesion (for a comparison with SDH – see Scholtz 1965), and air embolism causes systemic hemodynamic effects, sinus thrombosis is a particular consequence of MBI. The symptoms are usually non-specific and characterized by intracranial hypertension and normal initial computed tomography (Leker and Steiner 1999). Diagnosis can be confirmed by angiography or magnetic resonance imaging.

Pathology. Dependent upon the localization of the thrombus and the course of the affected veins, a hemorrhagic infarction develops in the area drained by the veins. A confluence of hemorrhages can occur, creating a picture of massive bleeding. The end stage in adults is rarely observed; in children, there is porencephaly of the white matter and/or lobular ulegyria. The thrombus itself undergoes a series of changes depending upon the period of survival: in the early phase it appears reddish-brown and loosely structured; later it takes on a grayish-red hue and becomes more solid until it organizes and adheres to the sinus wall.

7.7.4.2 Carotid Artery – Cavernous Sinus Fistula (Carotid-Cavernous Fistula, CCF)

A fracture at the base of the skull can cause the formation of a fistula between the large basal artery (internal carotid artery) and large basal sinus which is difficult to demonstrate at autopsy. Fistulas are most often caused by mechanically induced (less often spontaneous) tears in the carotid artery (see Lewis et al. 1995: 76 of 100 cases). Injury often results from stretching or tearing of the basilar vessels, though such fistulas are found in only about 5% of frontobasal fractures (Schima 1961; Isfort 1965). A large Korean study (Chung et al. 2002) found the cavernous sinus to be the most common location. Other causes included craniotomy, sinus thrombosis, acupuncture, or cerebral infarction (Chung et al. 2002).

Clinical Features. Patients report hearing intracranial noises. The classic objective symptom is a pulsating exophthalmos, regarded to be a firm criterion of an abnormal connection between the internal carotid artery and the cavernous sinus (Friedmann et al. 1970). At times, protrusion of both ocular globes (Kupersmith et al. 1986) and/or an orbital bruit (80%), proptosis (72%), chemosis (55%), etc. (Lewis et al. 1995) have also been reported.

Morphology. The fistula can be easily visualized using angiography. For autopsy the technique described by Krauland (1982) is recommended: the

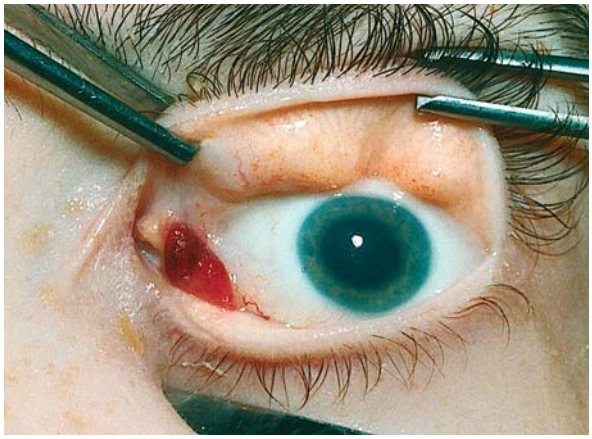

Fig. 7.26. Mechanically induced carotid-cavernous fistula, i.e., a single hole communication between the carotid artery and the cavernous venous sinus. At autopsy a characteristic marker will be the orbital chemosis caused by a conjunctival vascular enlargement and exposure ophthalmitis

roof of the cavernous sinus is split to allow outward opening of both the side wall and the anterior clinoid process. Any signs of hemorrhage in the adventitia of the vessel are to be regarded as indicating damage to the vessel wall. Moreover, in single cases, orbital chemosis is visible, also at autopsy, secondary to the conjunctival vascular enlargement and exposure ophthalmitis (Fig. 7.26). Splitting of the vessel wall will expose any tears in the intima. Death can result from loss of blood through the nose, mouth and/or ears, or from aspiration of blood.

7.8 Injuries of the Extracranial Arteries

Penetrating and blunt impacts to the throat can cause injury of vessel walls, which can lead to changes in the brain despite their extracranial and extracerebral localization. These injuries will be discussed briefly in the following.

It is easy to understand how damage can result from penetrating injury. Blunt vascular injury can lead to compression, edema, and bleeding in the surrounding soft tissues or tears in the intima, in each instance with consequent thrombosis and/or vessel stenosis. Such injury can be caused, for example, by safety belts in traffic accidents (Mattes et al. 1983) associated with injury of the external carotid artery and the extracranial part of the internal carotid or vertebral arteries. Indirect injury of vessel walls can also be the result of hyperextension or strangulation. Miller et al. (2001) recently published data on the incidence of blunt cerebrovascular injuries (n=139). A 0.5% incidence was noted for carotid artery injury, with 13% stroke-related mortality, and of 0.4% for vertebral artery injury, with a stroke-related mortality of 4%. In rare cases a mechanically caused rupture of the extracranial vertebral artery occurs resulting in a (intracranial) subarachnoid hemorrhage (Koszyca et al. 2003).

7.8.1 Injury of the Carotid Artery

Blunt carotid injuries appear to be underdiagnosed and may well be more common than once thought. The mortality rate has been calculated at 31% (Fabian et al. 1996) or 11% (Ramadan et al. 1995). Because carotid injury is rarely suspected in patients with neurologic deficits, the diagnostic work-up usually includes only CT of the head. If observed neurological deficits are incompatible with CT findings, angiography should be performed (Sanzone et al. 1995).

A blunt injury can interrupt carotid arterial perfusion, reducing or stopping altogether the supply of blood to one hemisphere of the brain. The severity of subsequent effects depends upon the status of the collateral arterial circulation at the base of the brain. They can include necrosis of an entire hemisphere or, optimally, the complete absence of neurological deficits. While the carotid artery mainly supplies the cerebral hemispheres, the vertebral arteries supply the basal parts of the cerebrum, the brain stem, and the cerebellum. According to the systematic analysis of Rubio et al. (1974), the following types of injury of the carotids can be differentiated (see also Unterharnscheidt 1993):

- Complete transection, rupture or mechanical disconnection of a carotid artery: this results either in exsanguination or, after involution of the intima, disturbance of cerebral perfusion to one cerebral hemisphere.
- Incomplete dissection or tear of the wall of a carotid artery: depending on the severity of the tear, there is blood loss or impaired perfusion due to compression of the vessel by the hematoma.
- A blow to, strangulation or hyperextension of the neck can cause isolated injury of the carotid intima or media. The sequelae include secondary stenosis or occlusion by thrombosis of the vessel.
- Mechanically induced aneurysm, i.e., a false aneurysm (pseudoaneurysm, aneurisma spurium), caused by complete mechanically induced rupture of the arterial wall (El-Sabrout and Cooley 2000). The cause of such an aneurysm is described above (pp. 143 f).
- Dissecting aneurysm: tearing of the intima and or the media followed by intramural bleeding. Such injuries can also be caused in the vertebral artery by hyperextension of the cervical spine (Simeone and Goldberg 1968; New and Momose

1969). The pathogenesis of both types of aneurysm is described above (p. 144).

- Arterio-venous fistula with simultaneous injury to a carotid artery and accompanying veins.

7.8.2 Injury of the Vertebral Artery

Because the vertebral arteries are located within the cervical spine, they are better protected than the carotid arteries, but are also at greater risk from direct or indirect loading to the cervical spine. Moreover, the vertebral arteries vary widely in their anatomic courses and diameters, so that the consequences of injury depend on the particulars of the individual case: narrow or wide-lumen vessels, typical or atypical course within the extra- or intracranial compartments.

Mechanically induced injuries of the vertebral artery must be differentiated according to penetrating (direct) or closed (indirect) injuries. Penetrating injuries are caused by gunshot or stabbing (Gage 1942). Indirect injuries result from injuries of the cervical spine, such as fractures of the vertebral bodies or their transverse processes, luxations, hyperextension (e.g., from whiplash), chiropractic manipulation, and injury at birth (e.g., traction injury).

Different types of vascular injury are distinguished: complete or partial transection or rupture, intimal or combined intimal and medial lesions, compression and stenosis or injury related to fracture of the transverse processes. These can result in blood loss or impaired perfusion with consequent necrosis and/or thrombosis. A bilateral rupture of the vertebral artery can be fatal, rapidly leading to death.

It should be pointed out, however, that injury of the vertebral artery can result from other types of violence (see Saternus and Burtscheidt 1985): at autopsy, 52% of 27 victims of traffic-accident-induced acceleration loading were found to have tears in the intima, a finding also described in 25% of victims of hanging. Detection of even discrete injuries like these always requires careful exposure and dissection of the vertebral arteries.

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Open Brain Injuries

8

8.1 Basic Principles

8.1.1 Classification

A fracture or penetrating wound of the skull associated with *rupture or incision of the dura mater exposing the brain* is termed an "open brain injury" or – if there is injury of skull and brain at the same time – "open craniocerebral injury." Open brain injuries can be caused by depressed fractures or by fractures piercing the dura mater, and – in extreme cases – by stabbing or gunshot. The associated risk of bacterial invasion and development of meningitis or abscess requires the clinician and the pathologist to differentiate between closed and open craniocerebral injury.

The clinical and morphological features of open brain injuries depend on the localization and intensity of the mechanical violence. Open brain injuries can result from an *accident*, e.g., *a traffic accident*, *a fall from a height*, or from *acts of violence* committed with different types of weapons. It is seen in victims of *suicide* and *homicide* involving violence to the head by means of a *hammer*, *bottle*, *knife*, *axe*, *hatchet*, *or firearm*, etc.

8.1.2 Biomechanical Aspects

The clinical symptoms and morphological changes associated with open – and closed – craniocerebral trauma depend on the mass (m) and velocity (v) of the object affecting the head; i.e., – with some reservations – on its kinetic energy (E=1/2 mv^2). Analogously, the same is true of the mass and velocity of the head itself, if it is the moving object, if for example the head strikes a hard surface during a fall (pp. 179 ff). The effects also depend on where and how the energy is transferred: the energy E expended by a hammer blow, for example, can be locally confined if the skull is depressed without giving rise to significant primary neurological deficits in some cases. In contrast, E released when a high-velocity missile of small mass penetrates the cranial cavity can cause the skull to burst and lead to acute circulatory arrest.

The clinical symptoms and morphological changes also depend on the localization of the injury of the brain parenchyma: local injury of the frontal lobe without involvement of the ventricles and/or basal ganglia can be accompanied – at least in the short term – by retention of the ability to act, whereas destruction of the brain stem and/or bleeding into the ventricular system can lead to immediate respiratory and circulatory arrest.

8.1.3 Pathology

The morphology of an open brain injury depends largely on the localization and dimensions of the

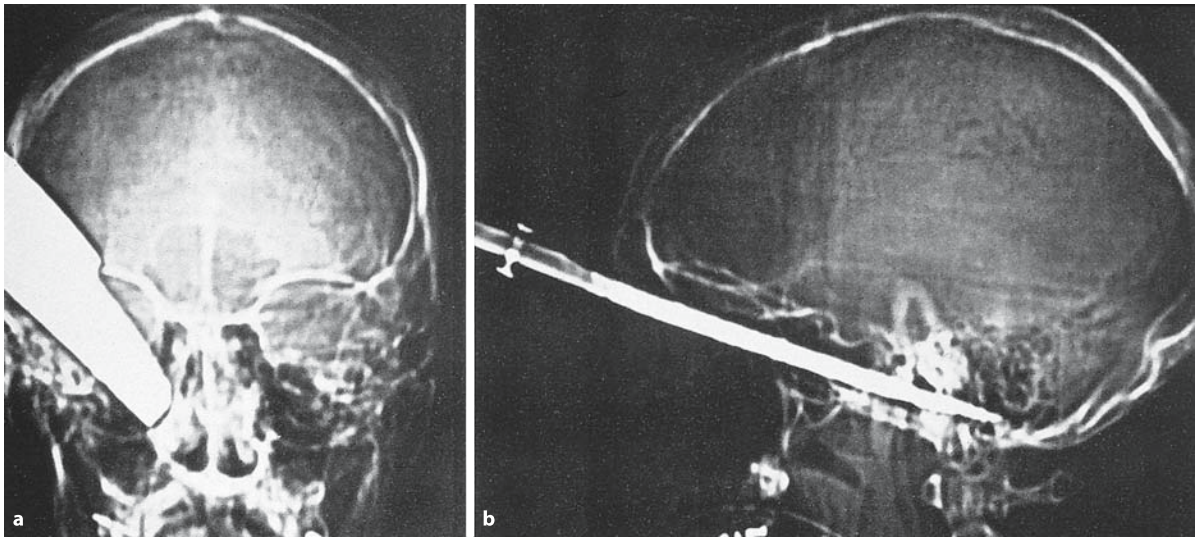


Fig. 8.1a, b. Roentgenogram of a stabbing with a knife penetrating the skull through the orbit and wounding of the large basal vessels of the brain

skull fracture or the extent of the opening and the size, severity, and type of the *craniocerebral brain injury*, especially of the attendant bleeding. The primary disturbances may be negligible, but the secondary effects are sometimes fatal.

8.2 Stabbing and Incision Wounds

Cases involving stabbing of the brain by knives or similar weapons (screwdriver, ice pick, chisel, knitting needle, pencil, etc.) are rarely encountered in civilian life (for survey see Unterharnscheidt 1993, p 641 ff). Unlike bullets, such objects strike the head at low velocity. The possibility of complete penetration of the skull depends on the thickness of the bone at the impact site and the magnitude of the locally applied force. Penetration is common in areas of relatively thin bone [e.g., orbit (Fig. 8.1), temporal bone (Fig. 8.2), transnasal drain of the frontobasal bones and, in infants, the fontanel]. A sharp object striking thick bone is more likely to break itself than to penetrate the skull (Fig. 8.3). Although it can be extremely difficult to identify the penetrating object based solely on the hole in the skin, the morphometry of a hole in the skull usually provides exact information regarding both its shape and diameter.

Objects penetrating the brain at low velocity do not create "temporary" cavitation (see below): the brain tissue injury is limited to the damage along the "permanent" cavity. The penetrating object can cause intracranial and/or intracerebral bleeding, however, if it injures a major artery or vein. The risk of this happening persists during neurosurgical removal of foreign bodies. If blind removal of a knife blade is attempted, it must be determined in advance that the blade is not in the close vicinity of major arteries or veins. Moreover, a typical – but sterile – stab wound is the cavity resulting from such therapeutic interventions as ventricular puncture or ventricular drainage (shunt) in neurosurgical practice. As this surgical intervention occurs "blind," hemorrhage and ventricular tamponade may not always be avoided in individual cases.

Other types of open brain injury may be caused by half-sharp or blunt forces, i.e., by a chisel (Fig. 8.4), by a cut with an axe (Fig. 8.5), by a hammer (Fig. 7.4e; 8.6), by a fall from height (Fig. 8.7a, b) or by a blow caused by the fall of an iron rod wounding the head (Fig. 8.7c, d).

In cases of accidental injury, one (or several) circumscribed depressed fracture(s) are *clinically-radiologically* conspicuous. Any stab wound of the brain may be complicated by mechanically induced pneumoencephalos and infection (meningitis, encephalitis, abscess) and/or by intracerebral bleeding. Adult victims usually suffer additional injuries, stab wounds for example on the victim's hands or forearms incurred in an attempt to ward off the attack.

Factors significantly predictive of *outcome* in patients with transcranial stabbing injuries are the Glasgow Coma Scale, the occurrence of intraventricular hemorrhage, the type of associated lesions, i.e., intracranial bleeding, vascular abnormalities, or brain abscess, and the number of operations (Nathoo et al. 2000). Nathoo et al. (2000) evaluated the clinical data and outcome of 17 cases of transcranial brain stem stab injuries in a cohort of 597 patients with transcranial stab injuries (=2.9%). Knives were the most common instruments of penetration. Cere-

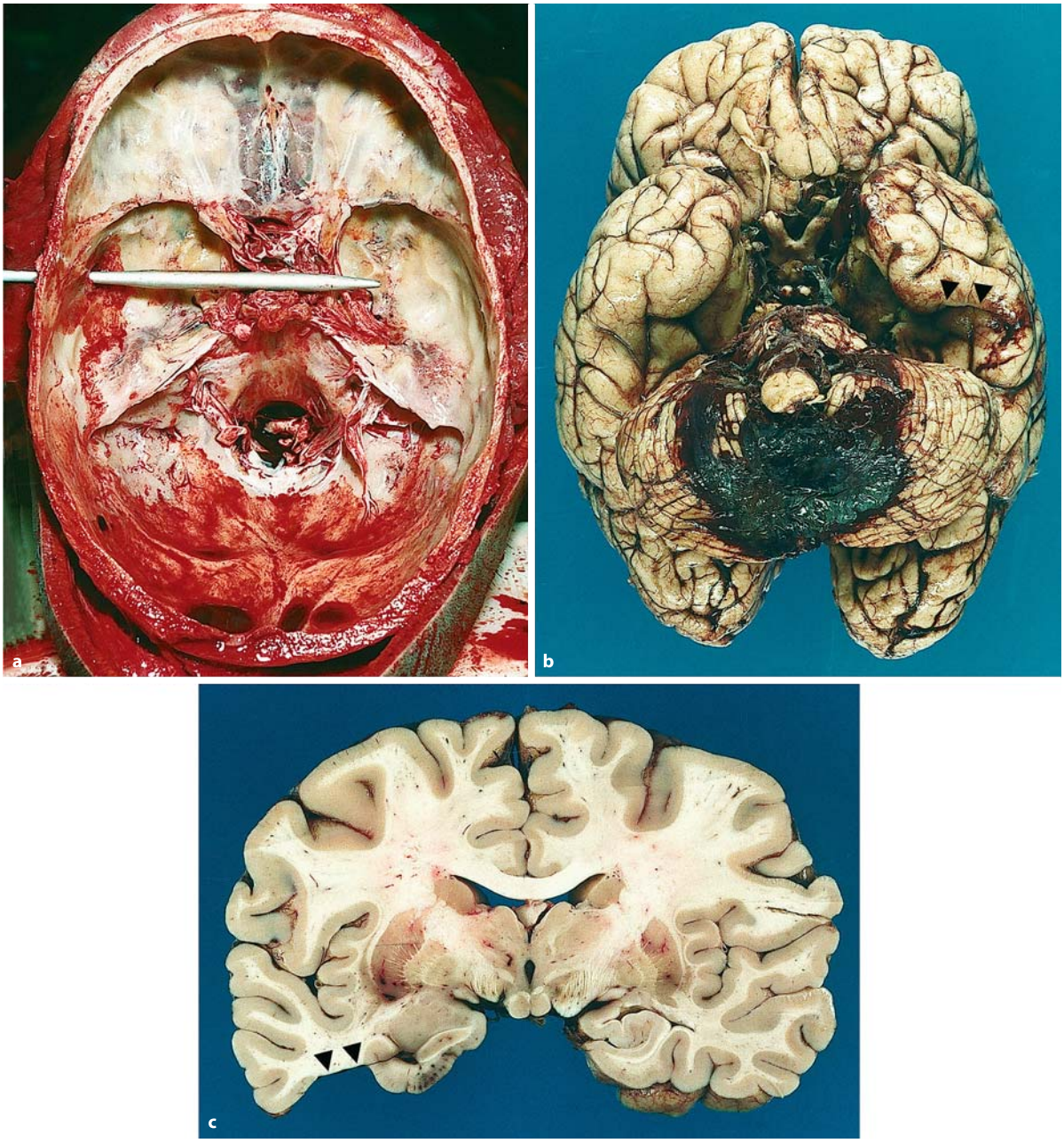


Fig. 8.2a–c. Stabbing with a knife at the left temporal bone (**a**) which injured the basilar artery (**b**) after laceration of the left temporal lobe (**c**)

bral angiography identified 4 patients with vascular injury and 10 patients with obstructive hydrocephalus. Thirteen of the 17 patients died of their injuries (=76.5% mortality).

An earlier survey of stab wounds of the brain was made by de Villier (1975). He found a 17% mortality rate, most of the deaths attributable to intracerebral bleeding. The scalp wound in many cases was small, so small in some cases, as to be overlooked. Most cases involved attempted murder or other type of physical attack. In rare cases, the injury was accidental or – even more exceptionally –was associated with attempted suicide.

In addition to typical stab wounds, a *particular type of injury* is that caused by *a hatchet, axe blade or sword*, i.e., by any sharp-edged but not pointed weapon. Such injuries are characterized by a straight, smooth-bordered wound in the scalp, and a straight sharp perforating defect of the skull along the course of the gash, on the outer table often combined with a narrow depressed fracture on one side or both sides of the sharp defect, bursting fractures starting

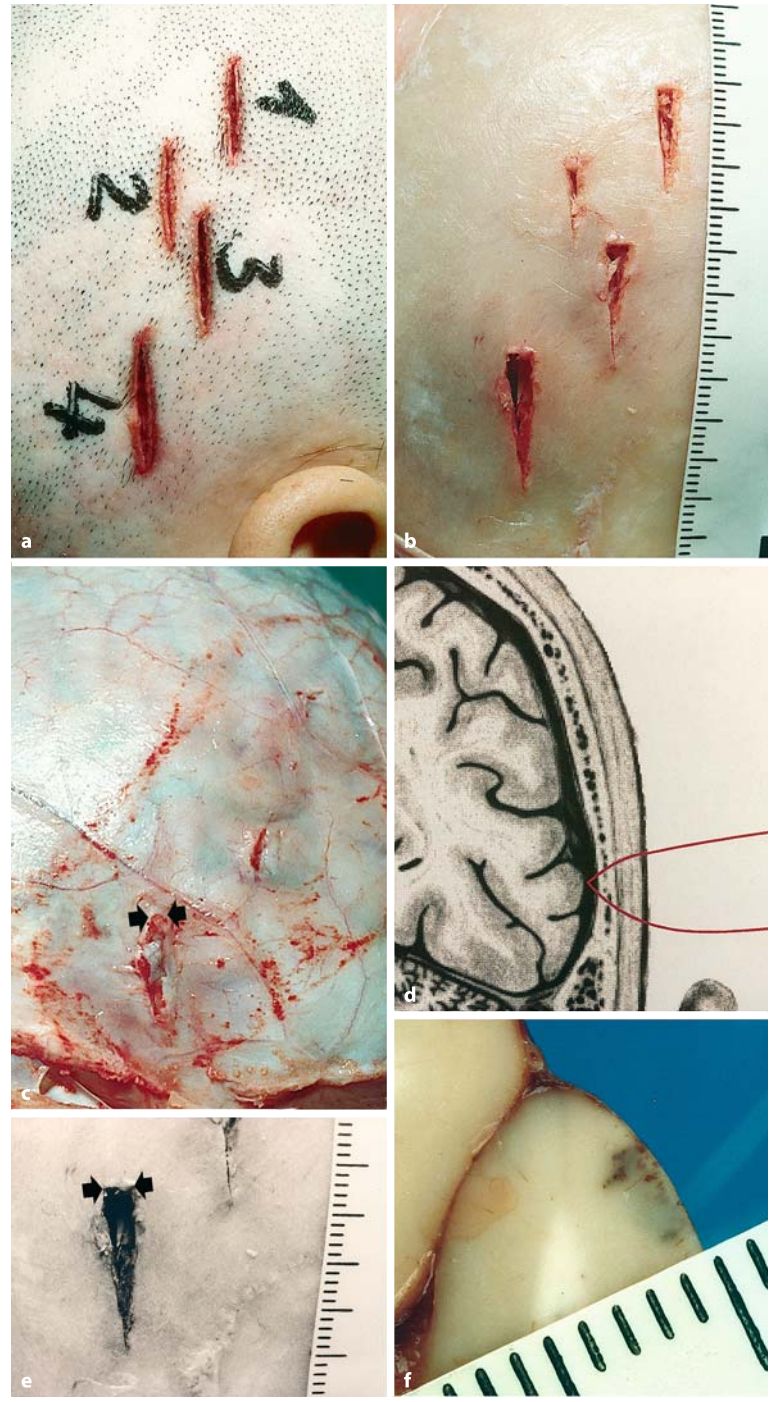


Fig. 8.3a–f. Wounding of the head, especially: **a** the scalp; **b** the skull; **c** the dura; and **d, f** the brain by incision with a knife. **e** The biometrically important characteristic cross section of the knife blade is seen in the skull wound

from its ends and by fine superficial internal beveling. Again, such injuries are usually inflicted during a physical alteration and are thus accompanied by other injuries of the body or limbs. Similar injuries can result from an accident involving, for example, the propeller of a plane or a ship. They can even occur postmortem, e.g., in drowning victims located within a harbor area with heavy boat or ship traffic.

8.3 Gunshot Wounds

A number of questions must be addressed at autopsy of gunshot victims:

1. Gunshot wound – yes or no?
2. Entry wound or exit wound?

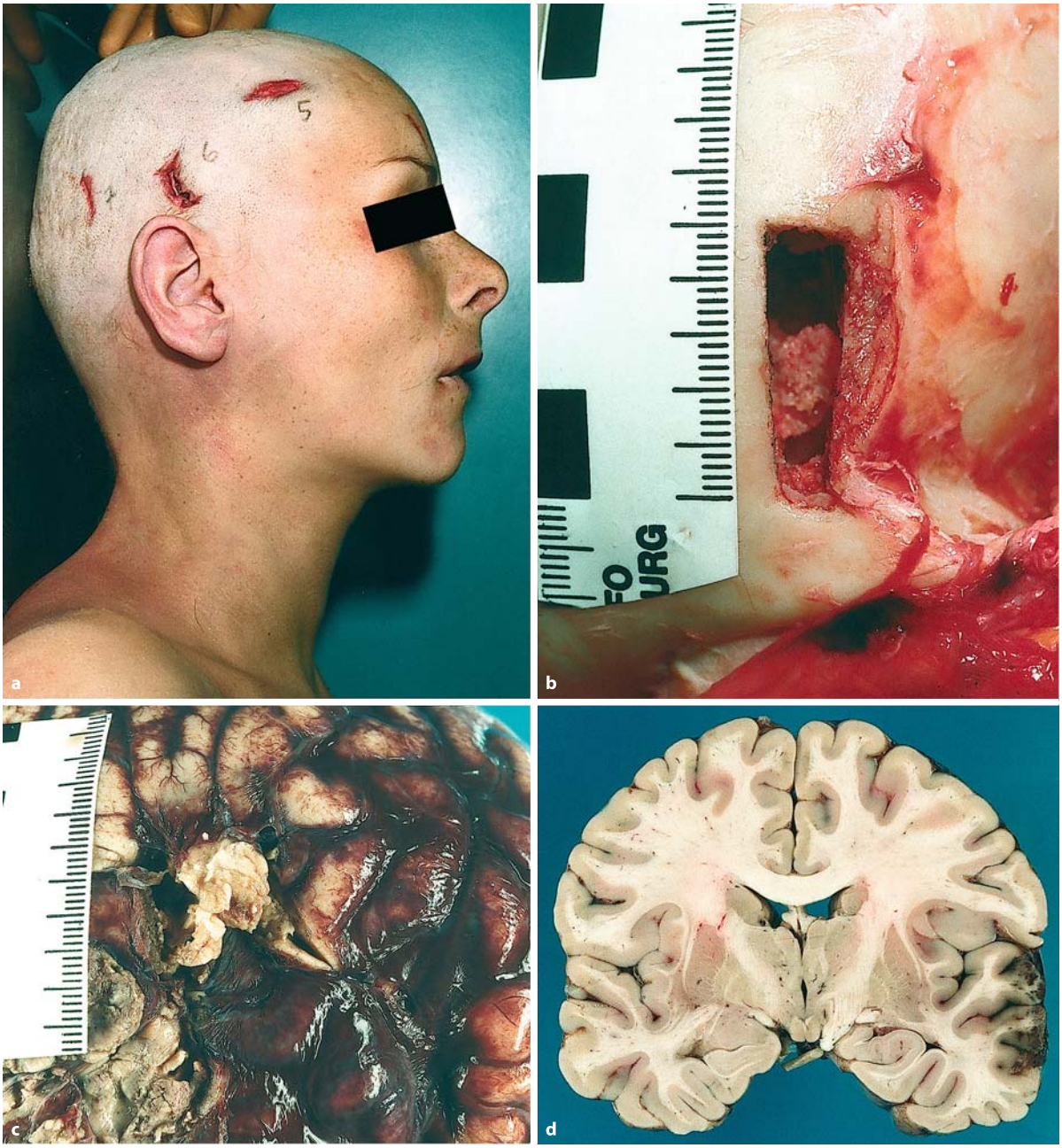


Fig. 8.4a–d. Open brain injury by stabbing with a chisel: **a** the scalp; **b** the skull; **c** the brain surface; and **d** the cortex of the brain

3. What is the course of the missile track (wound ballistics)?
4. What was the distance between the weapon and the victim?
5. Was the death an act of suicide or homicide, or was it accidental?
6. What types of weapon and ammunition were used?
7. How many shots have hit the victim?
8. What was the precise cause of the victim's death?
9. How long did the victim survive the fatal injury/ies?
10. Was the victim incapacitated by the wound?

8.3.1 Clinical Features and Capability to Act

Gunshot wounding to the brain is usually followed by immediate *muscle relaxation* and *loss of consciousness*. Only in rare cases is clarity of consciousness

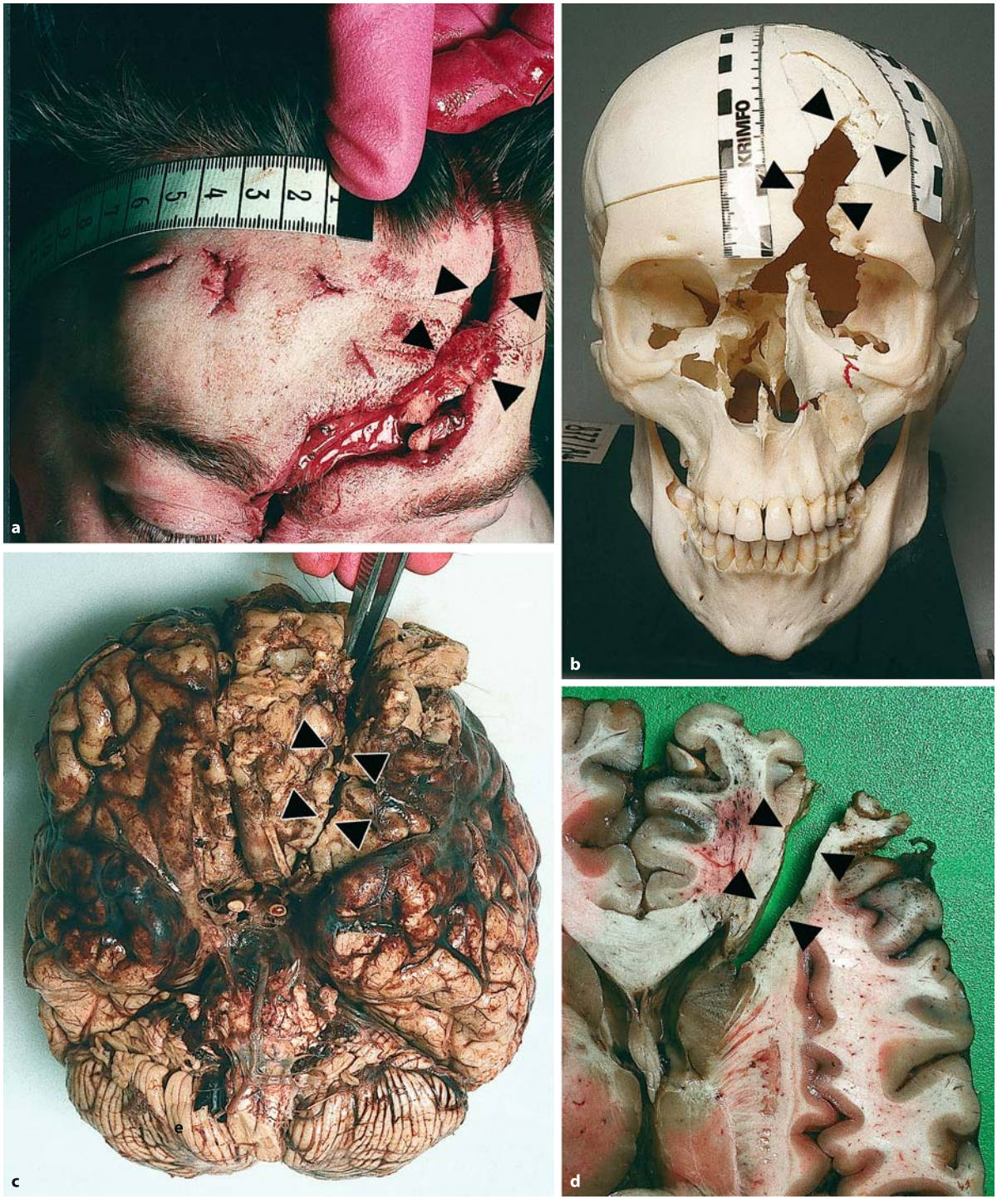


Fig. 8.5a–d. Open brain injury by cut with an axe (*arrowheads*) demonstrates the wound edges

maintained for a short time (cf. Spatz 1941). Animal experiments as well as clinical experience have demonstrated acute *respiratory failure* following head injuries and gunshot wounding to the brain (Brown et al. 1979), as well as *cardiovascular disturbances* such as bradycardia, conduction abnormalities, and ST-segment depression within seconds after wounding (Maynard et al. 1997). It can be assumed that these symptoms are caused by diffuse axonal injury (DAI), which is also seen at sites distant from the permanent missile track, in particular in the brain stem and pons (see below).

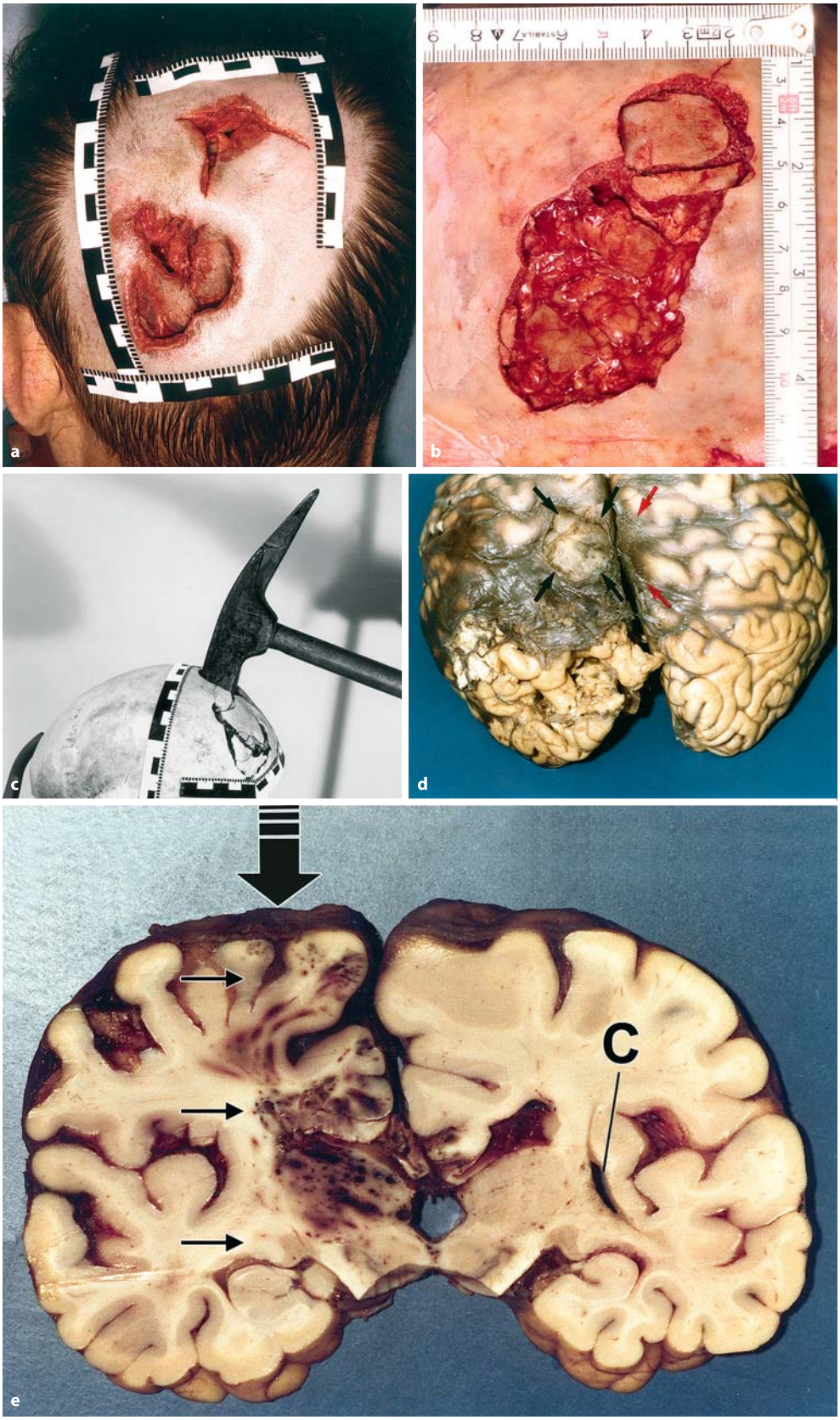


Fig. 8.6a–e. Open brain injury by blow with a hammer. **a** Scalp lesions; **b** skull lesions; **c** the hammer is adapted to the impression fracture of the skull; **d** impression mark of the hammer on the brain surface (*arrows*); **e** hemorrhages along the compression caused by the blow with the hammer. (*C* marks an old cystic necrosis)

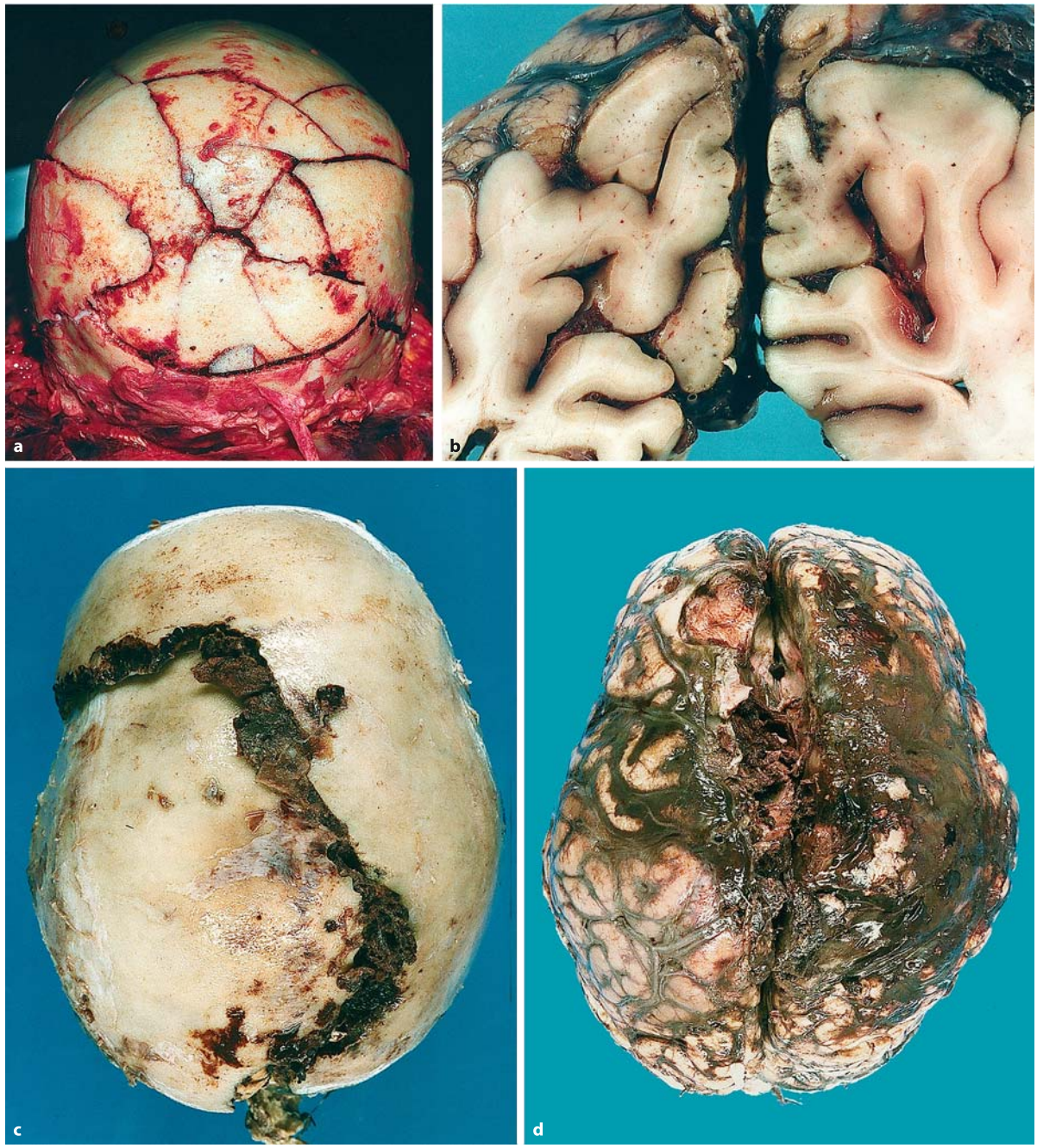


Fig. 8.7a–d. Open brain injury **a, b** by fall from height and **c, d** by the falling of an iron rod onto the head

The *prognosis* of gunshot wounds of the brain is generally poor. The prospect is grave for gunshot injury of the basal ganglia or ventricular system (ventricular wound). In surviving victims, prognosis depends in part on the extent of edema and on the risk of infection.

The *ability to act* in a conscious and purposeful manner (capacitation), such as attacking or escaping, is among the four grades of physical activity after gunshot wounding of the head as differentiated by Petersohn (1967) and Staak and König (1977):

1. Reflexes, which are part of agony
2. Automatism, such as continuing movements, which began before unconsciousness ensued
3. Instinctive reactions as meaningful reactions
4. Conscious, purposeful activity

Depending on the course and topography of the missile track as well as the velocity of the missile, the victim‘s movement can be abruptly disrupted, sometimes accompanied by acute respiratory and circulatory arrest. Such an event requires the direct

or indirect destruction of brain tissue of vital importance, such as the brain stem or medulla oblongata. Massive bleeding, especially in the ventricular system, can also lead to acute death. High energy transfer (Sturdivan 1969) or high energy deposit (Di Maio 1999) can also cause sudden incapacitation and death. Among the other causes of gunshot-wound-induced incapacitation are motor paralysis, hypovolemic shock, and/or spinal shock, all of which depend on the localization of the missile track, the primary or secondary tissue destruction, and the energy released by the projectile. Injury of the brain stem for example is followed by immediate loss of consciousness. A shot to the base of the skull can separate the spinal cord from the medulla oblongata, leading to acute incapacitation as well as acute cardiorespiratory arrest.

Only a few systematic studies have been published on the physical activity of victims after gunshot wounding to the brain. Karger (1995) provides a survey of the entire literature, with special reference to the investigations of Spitz et al. (1961), Levy and Rao (1988), and Newgard (1992). Our own systematic investigation of 41 cases of handgun wounds of the brain (Oehmichen 1992) disclosed only 2 cases in which the capacity to act remained intact. In these two cases, the missile passed through the frontal lobe without affecting the corpus callosum, the ventricular system or the basal ganglia.

8.3.2 Biomechanical Aspects

Handheld firearms (Besant-Matthews 1993; Sellier and Kneubuehl 2001) can be classified into three groups according to the barrel length, the mass of the projectile (m), the muzzle velocity (v_0), and the muzzle energy (E_0), each of which contributes to a firearm's penetration power and capacity to wound:

1. Short firearms (handguns), i.e., revolvers, pistols, and submachine guns: bullet mass m=1.8–16.2 g, velocity v_0=170–615 m/s, energy E_0=26–1,560 J. Bullets of the caliber 6.35 mm Browning or .22 L.R. usually do not pass through the head (retained missile), while projectiles of caliber 9 mm Luger or .38 special almost always cause through and through wounding.
2. Long firearms with rifled barrel (rifles), i.e., hunting rifles, sporting rifles, and military rifles: bullet mass m=3.0–32 g, velocity v_0=650–1,150 m/s, energy E_0=800–11,000 J. A release of energy of this magnitude almost invariably produces massive bursting fractures of the skull together with lacerations of the scalp. The brain suffers massive damage or is thrown outward to rest next to the victim (so-called Krönlein shot – with a muzzle velocity of >800 m/s; cf. Sellier 1982).
3. Shotguns (shoulder weapons with smooth barrel for firing shot): shot pellet diameter 1–4.5 mm (buckshot 4.5–10 mm), pellet mass m=0.006–5.8 g, shot charge mass 12–53 g, shot pellet velocity v_5=300–400 m/s, shot pellet energy E_5=1–300 J.

The type and extent of damage caused by a bullet entering the brain depend on characteristics of the bullet, its behavior in flight, and its trajectory within the tissue. Assessment of a bullet's wounding potential requires the following data:

1. The distance between the muzzle of the weapon and the victim
2. The angle at which the bullet enters the body
3. The type of weapon and ammunition (design, velocity, and mass; see above), the bullet's stability in flight, and whether any objects were interposed between the gun and the victim

Wound ballistics are determined by the kinetic energy E transferred to tissue damage, i.e., wounding. The amount of energy released depends mainly on the bullet's velocity which is greatest upon expulsion from the barrel (v_0). The high velocity creates three physical phenomena, which determine the extent of tissue destruction:

1. *Shock waves*: moving at the speed of sound ahead of the missile, their amplitude can be sufficient to cause reversible functional disturbances or irreversible changes in the tissue structure (Suneson et al. 1990a, b).
2. *Permanent cavity*: for low-velocity missiles, the diameter of the permanent track corresponds roughly to that of the missile.
3. *Temporary cavity*: depending on the amount of energy released, intracranial pressure is created that causes radial displacement of the brain parenchyma. The temporary cavity arising in the wake of the missile is several times larger than the diameter of the missile. This cavity pulsates, the temporary cavity collapsing in less than 20 ms, followed immediately by formation of another cavity of lesser magnitude. The very high local pressures created by the missile as it passes through the tissue lead to high temperatures that (vaporize the tissue and) fill the temporary cavity with steam.

   Low-velocity missiles leave a cavity, the maximum diameter of which is about three times that of the missile (Oehmichen et al. 2000, 2001 – see Fig. 8.12), whereas high-velocity missiles create a cavity 10–14 times as large (Fackler and Malinowski 1985). The temporary cavity produces a sudden dramatic increase in intracranial pressure that is thought to bring an apnea and bradycardia (Selden 1987).

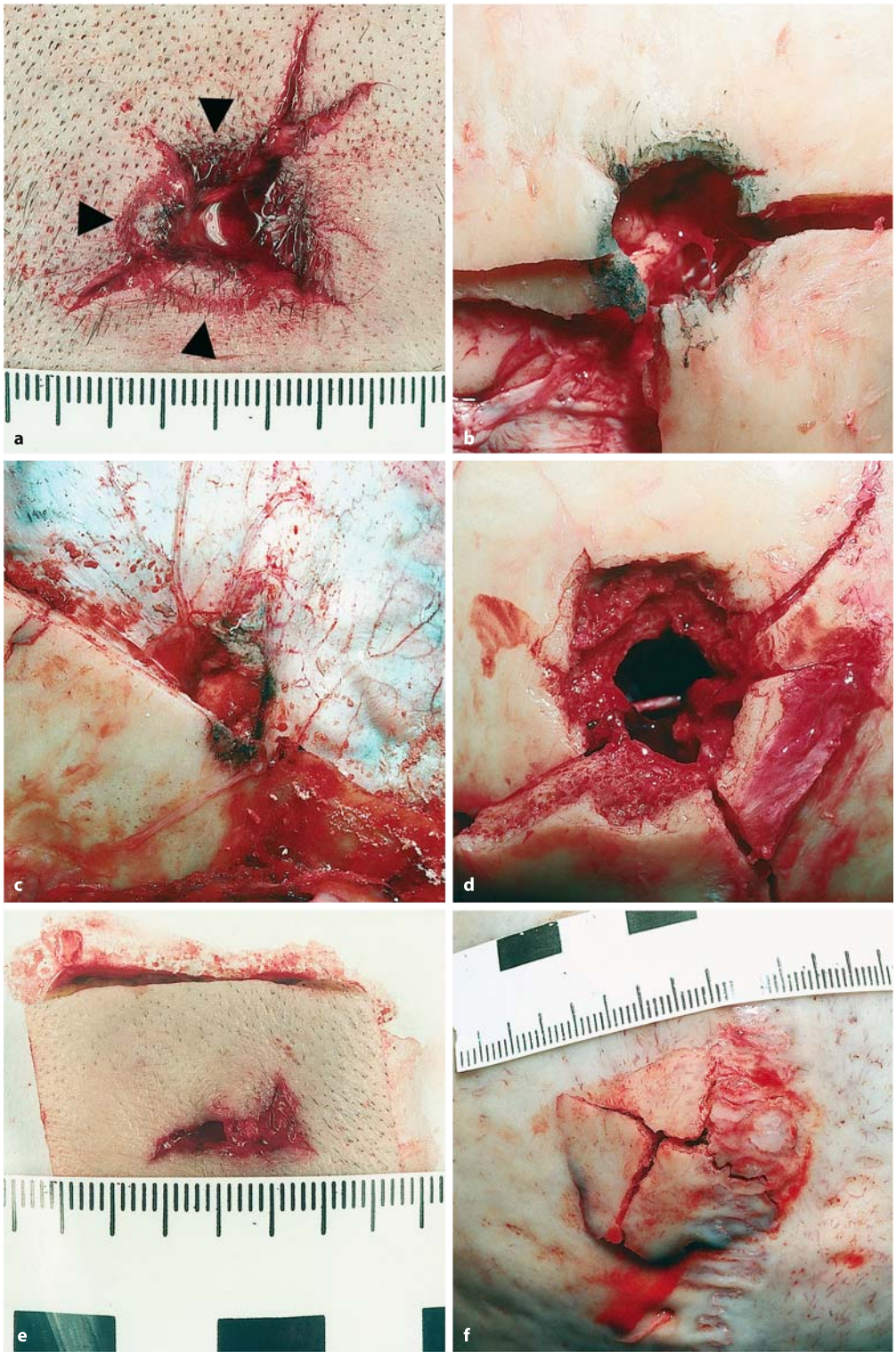


Fig. 8.8a–f. Gunshot injury. Typical shape of the skin, skull and dura wound at the site of entry (**a–c**) and exit (**d, e**), of the projectile. The impression mark is demonstrated by *arrowheads* (**a**). If the missile has insufficient residual energy to leave the cranium (**f**), the bone may only be fractured instead of totally opened (**d, e**). Soot blackening of bone (**b**) and dura (**c**) may be visible in cases of shots with contact

4. *Hemorrhages*, cortical hemorrhages in particular, are possible in areas distant from the missile track. In appearance and location, they resemble those resulting from blunt head trauma. They are caused by brain displacement and/or pressure changes secondary to the sudden intracranial pressure wave created by the missile and are usually situated in the cortex and subcortical white matter.
5. *Diffuse axonal injury*: like acceleration loading, gunshot to the brain causes DAI, usually at sites remote from the permanent cavity (cf. Koszyca et al. 1998; Oehmichen et al. 2000), the midbrain and pons being particularly prone to this type of injury. One possible explanation of the DAI is the widespread mechanical deformation by the complex of forces created by the missile's passage through the brain. The widespread axonal injury can also result from ischemia, intracranial pressure, vasospasm, and/or acidosis (Koszyca et al. 1998). The DAI phenomenon may explain the acute respiratory and circulatory arrest seen in some cases in which the missile passes tangentially through the cerebral white matter of the frontal or temporal lobes without direct involvement of the basal ganglia or ventricular system.
6. *Edema* was reported to have appeared minutes after fatal wounding in an autopsy series (Kirkpatrick and Di Majo 1978). It has also been noted within 30 min of experimental missile wounding of monkeys (Allen et al. 1982), with extensive swelling of perivascular astrocytes (Allen et al. 1983).

In addition to handguns and rifles, other types of firearms are capable of causing injury: shotguns, which can inflict extensive damage of scalp, skull, and brain at close range (Sellier 1977, 1982; Di Maio 1999), and air weapons, tear-gas weapons, and blank cartridge weapons can inflict wounds which may be fatal under special circumstances (Sellier 1977; Di Maio 1999; Rothschild 1999).

Several studies have examined how the shape of firearm projectiles affects both their stability in flight and in passing through organic tissues (Moss 1997). The phenomenon of the tumbling bullet within the brain tissue may be of additional importance in the origin and form of the secondary cavity (Sellier and Kneubuehl 1994, Janzon 1997).

8.3.3 Pathology

8.3.3.1 Scalp

When a gun is fired, the missile is expelled from the muzzle together with propellant that begins to disperse immediately upon exit and continues to disperse with increasing distance. The propellant is hot upon leaving the muzzle, often accompanied by a small flame. The gas consists of carbon dioxide, nitrogen oxides, hot air, and carbon monoxide. The expelled soot contains traces of a number of elements, including antimony, barium, and lead.

The *entry wound* of the skin (and the scalp) can exhibit one or more of the following characteristics (Fig. 8.8a):

1. Blanked out wound, lacking adaptable wound edges, exhibiting a circular (Fig. 8.8a) or elliptical (Fig. 8.9a) wound defect (punch wound).
2. Shelved wound zone (zone of contusion and/or abrasion) (Fig. 8.8a).
3. Zone of debris, carbon and oil deposition (grease ring).
4. Soot-smoke zone associated with burnt and unburnt propellant particles (smoke blackening).
5. Burning of the skin and/or hair (flame effects).

The following additional criteria/factors may be of interest in a given case:

6. Muzzle impression mark (= contact wound) (Fig. 8.8a). The temporal pressure contact between muzzle and skin may leave a visible imprint on the skin surface. If the muzzle is held tightly against the skin of the scalp, soot gas expands subcutaneously, forming a cavity between the scalp and skull which results in a contusion of skin towards the muzzle demonstrating a seal-like mark of the muzzle on the skin surface.
7. Secondary, ragged wound. Tight muzzle contact with the scalp can also result in the gas being reflected back, raising a dome of the skin which may split to produce a stellate or ragged entrance wound with skin flaps (stellate bursting wound).
8. The shape of the entry wound will be circular if the bullet enters perpendicularly the skin, and elliptical if it enters at an angle, with undercut edges on one side and extensive shelved wound edges on the other.

The skin's ability to resist penetration by projectiles was the subject of a review of the literature by Sellier and Kneubuehl (2001): for usual handgun ammunition the minimal velocity at which a projectile can penetrate into the skin is about 40–50 m/s.

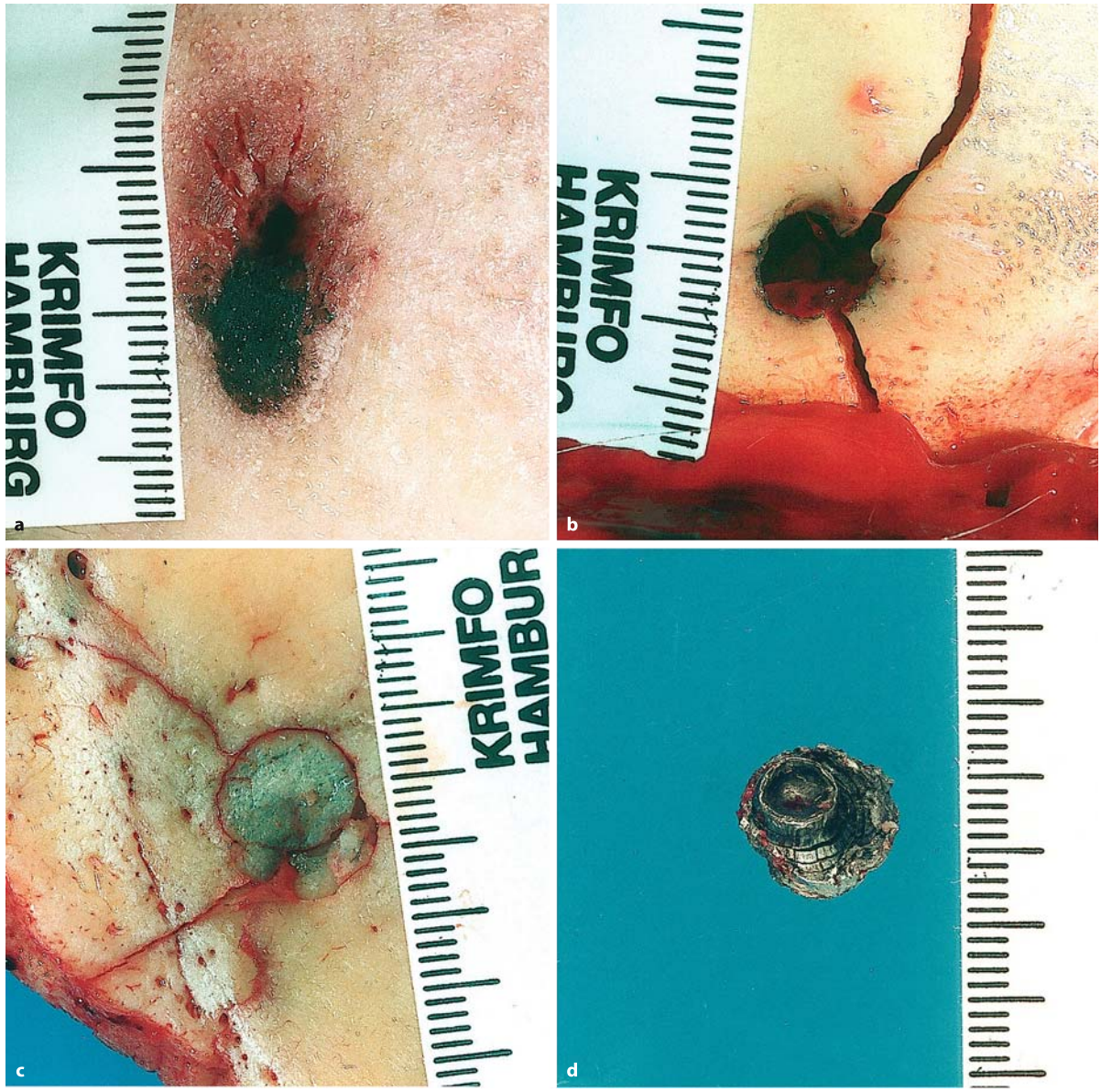


Fig. 8.9a–d. Retained missile. After entry of the missile passing skin (**a**) and bone (**b**) the missile returns into the brain after having contact with the inner table of the contralateral skull (**c**); the contact is visible by a gray staining pattern and a circular fracture, which correlates with the diameter of the deformed missile (**d**)

8.3.3.2 Skull

The minimal velocity of a projectile to enter a bone is 60 m/s (Sellier and Kneubuehl 2001). Injury of bone may result from a direct hit at high velocity or occur indirectly by the temporary cavitation that fractures the bone (Amato et al. 1989).

The passage of a bullet through a flat skull bone produces the phenomenon known as "cratering." The entering missile's initial contact punches a clean sharp-edged hole through the outer table of the skull (clean-cut outer aspect – Fig. 8.8b). When the bullet perforates the bone it bevels out the bone fragments in the direction of movement, forming a crater noticeably larger than the external hole (cone-like appearance – Fig. 8.8c). In contact wounds, the external surface of the bone can also exhibit soot, which is sometimes seen on the external surface of skull and the dura mater (Fig. 8.8b, d).

If the bullet penetrates the cranium on the opposite side, an analogous pattern occurs: a small hole on the inner table, a crater on the outside (Fig. 8.8c). The direction of the bullet's path can be determined on the skull itself by the orientation of the craters, which always point in the direction in which the

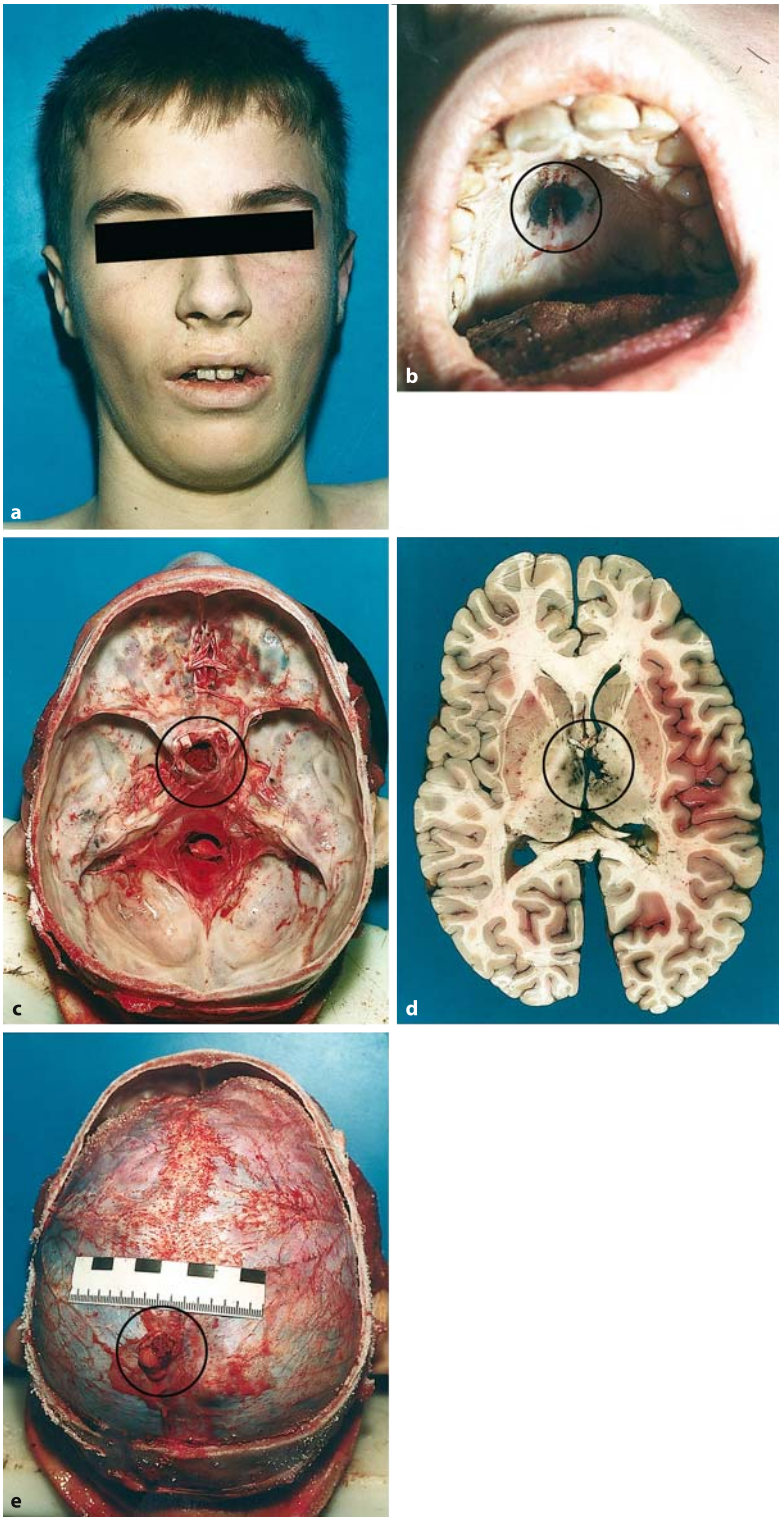


Fig. 8.10a–e. Gunshot through the mouth. **a** A hidden entry wound in the closed mouth; **b** soot is seen around the entry wound in the oral cavity. **c** A shot through the oral cavity here associated with a missile track penetrating the base of the skull, **d** passing through the brain along its the midline structures and **e** leaving the brain at the left hemisphere

missile was traveling. These defects penetrating the skull are sometimes accompanied by fissures and fractures running away from the central hole, especially from the entry hole.

As the projectile decelerates in the brain, it releases energy, displacing tissue outwards to form the temporary cavity. With high-velocity projectiles this expansion generates extremely high pressures within the skull and can cause bursting of the cranium sometimes associated with a laceration of the skin. There are a number of exceptions to these typi-

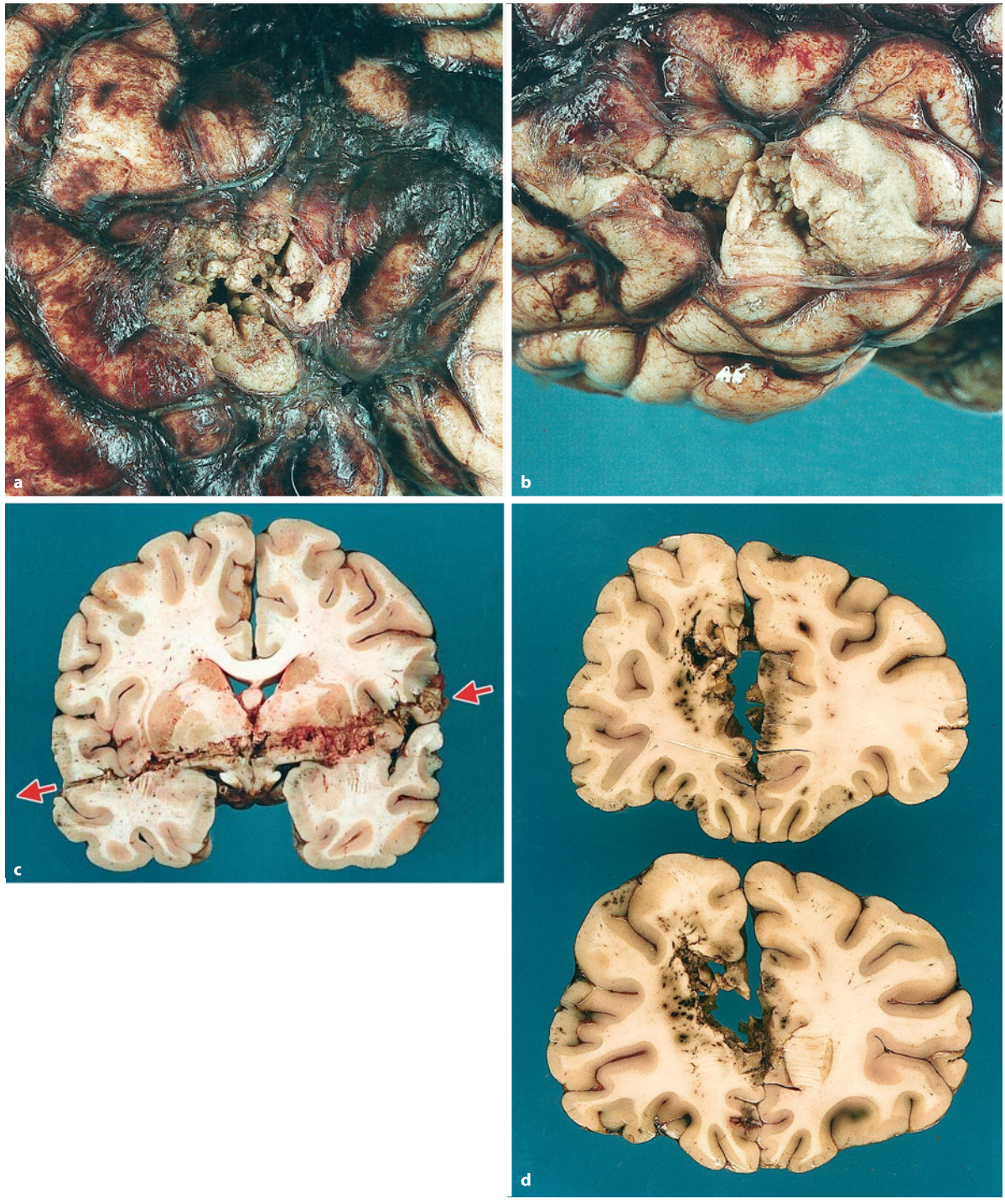
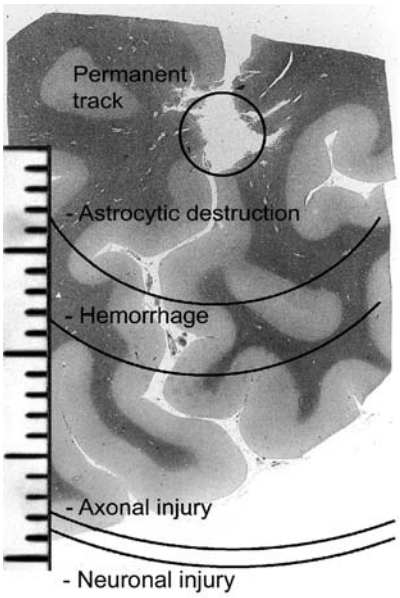


Fig. 8.11a–d. Gunshot injury – the morphology within the brain. The entry wound of the brain is characterized by a circular laceration of the leptomeninges (**a**) while a more irregular laceration is seen in the exit wound (**b**). The brain itself is characterized by the straight permanent missile track cavity (**c**) which is surrounded by a zone of hemorrhage (**d**)

cal changes produced in the skull and brain by gunshot.

Bone fragments have too little energy to create separate tracks outside the temporary cavity (Sellier and Kneubuehl 2001). Within the brain, bullet fragments may diverge from the course of the missile itself, creating an irregular cavity. Because the kinetic energy of the penetrating bone fragments is always lower than that of the bullet and its fragments, bone



Type of cytologic injury	Radial distance (mm)
Astrocytic destruction	3.2 ± 1.2
Hemorrhage	8.2 ± 5.0
Axonal injury	17.7 ± 4.7
Neuronal injury	18.4 ± 5.2

Fig. 8.12. Gunshot wound. Zones of injury around the permanent missile track indicating tissue damage secondary to the temporary cavity (see Oehmichen et al. 2000, 2001)

fragments tend to be located nearer entry wounds than are missile fragments.

If, after penetrating the brain tissue, the missile has insufficient residual energy to enter the opposite inner table, it may ricochet back into the brain (Fig. 8.9), producing a second missile track (Lindenberg 1971; Cooper 1987), or it may fracture the skull with or without leaving the cranial cavity (Figs. 8.8f, 8.9c). This is more likely to happen if the bullet strikes the head or the opposite inner table at a smaller angle than if it strikes perpendicularly to the bone surface (Spitz 1993).

An entry wound may be hidden by a closed mouth (Fig. 8.10a) as demonstrated by soot within the oral cavity (Fig. 8.10b). The gunshot wound may be associated with a sagittal missile track penetrating the base of the skull (Fig. 8.10c), passing through the brain along the midline structures (Fig. 8.10d) and leaving the brain at the left parietal lobe (Fig. 8.10e).

8.3.3.3 Brain

The clinical sequelae are largely determined by the course of the projectile through the anatomy, and the energy is released along this course (Sellier and Kneubuehl 1994). A direct consequence of the passage of the projectile is the *destruction of brain tissue* along the permanent missile track cavity (Fig. 8.11). Around the zone of destruction, a *bleeding zone* is created (Fig. 8.11d), whose irregular shape will be explained by differences in blood supply of the local brain tissue. The zone of hemorrhage is overlapped and surrounded by a zone of necrosis, chiefly of neuronal elements (neurons and axons – Oehmichen et al. 2000), secondary to the temporary cavitation (Fackler 1988; Janzon 1997; Janzon et al. 1997; for review: Oehmichen et al. 2004). In an isolated formalin-fixed brain the direction in which the missile traveled can only be determined by the distribution of bone and missile fragments within the parenchyma: as mentioned above, their number being greater near the entry hole than near the exit hole. X-ray examination is adequate for answering this question (Schumacher et al. 1985).

Light microscopic examination can distinguish four zones of injury (Oehmichen et al. 1985, 2001, 2003):

1. Defect zone (permanent channel)
2. Destruction zone (destruction of astrocytes, myelin and axons)
3. Zone of hemorrhage
4. Zone of neuronal destruction, i.e., axonal and neuronal injury

The following additional remarks are in order here (see also Fig. 8.12):

1. Although the permanent channel usually collapses or is compromised by the surrounding edematous neuropil, it can easily be followed by both CT and MRT as well as in the formalin-fixed brain (Oehmichen et al. 2003). If the weapon is fired at close range, the missile track may be contaminated by gunshot residues and other foreign material (soot, propellant, oil, metal fragments, bone fragments, etc.).
2. The destruction zone (Fig. 8.12) is characterized by a total loss of detectable GFAP-reactive astrocytes or β-APP-reactive injured axons or dendrites. This zone is demarcated by macrophages and limited by β-APP-reactive axons which are injured but obviously in further connection with

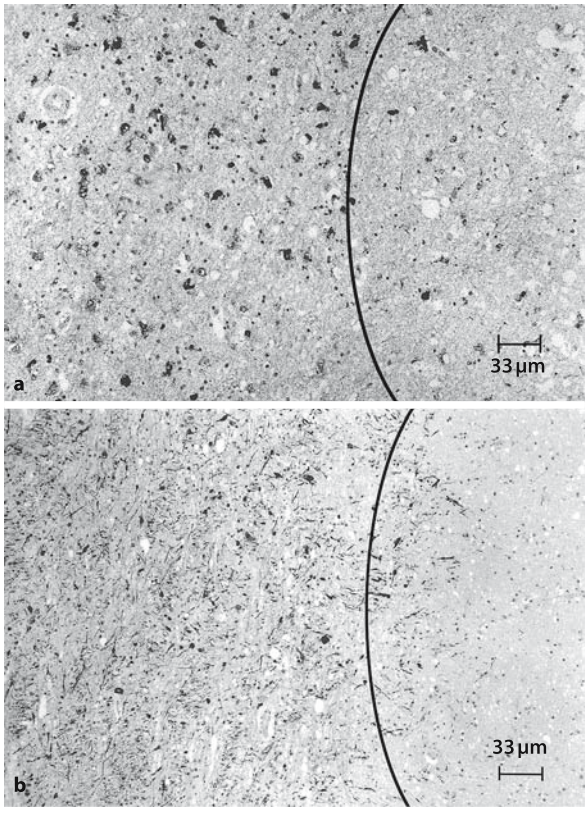


Fig. 8.13a, b. Gunshot wound. Border lines of the demarcating macrophages (**a**) and the demonstrated injured axons (**b**) as an indication of the end of the mean destruction zone which is seen on the *right part* of the figure [immunoreactivity to CD68 (**a**) and β-APP (**b**); magnification **a, b** ×500]

the neuronal perikaryon (Fig. 8.13) while within this disturbed central area leukocytes may be visible.

3. The extent of the surrounding hemorrhages depends on the blood supply of the region – as mentioned above. Thus, the gray matter of the brain, especially of the basal ganglia and the cortex, is well supplied with blood and provided with numerous capillaries, which tear under the force of the released energy; the associated cerebral white matter is less well supplied with blood, so that at most a narrow zone of hemorrhages will be seen (Oehmichen et al. 1985).
4. Neurons are deformed and axons are torn and injured as demonstrated by means of silver staining as well as by β-APP immunoreactivity.

In addition to direct mechanical injury, foci of *contusional bleeding* (Fig. 8.14b) in the cortex of the gyral crests may occur in regions of the brain surface distant from the missile track (Henn 1989). Primary *hemorrhages in the pons* (Fig. 8.14c) may be caused by forces which are also responsible for *axonal injury* at a distance from the permanent missile track. These morphological alterations are a further indication of the energy release by the passing missile, responsible for the temporal cavity.

In most cases with unknown survival time (suicide, homicide) a neutrophilic reaction is commonly demonstrable as an indication of an intact circulation during wounding. In cases involving long survival times local reactive mononuclear inflammation develops, followed by astrocytic proliferation and formation of connective tissue composed of a dense network of collagen and glial fibers (inflammatory granulation tissue – see also Spatz 1941) that meshes closely with the overlying tissues (dura, bone, skin). *Foreign bodies* such as soot, missile fragments or bone fragments may become encapsulated within the scar tissue and may lead to granulomas (Fig. 8.15).

The inflammatory process may smolder within the brain wound for a long period of time and then flare up (Lund 1955; Peters 1970). Years after the traumatic event the wound area exhibits coagulation necrosis, macrophages – i.e., lipid-, siderin- or hematoidin-containing macrophages – activated astrocytes and vessel proliferation, sometimes accompanied by aggregations of lymphocytes. This must be interpreted as a "progressive necrosis." Some victims may suffer a renewed flare-up of an infection or local circulatory disturbance (Peters 1970) and/or formation of a delayed brain abscess.

If the bullet or bullet fragments embedded in the brain cannot be removed surgically, they usually become encapsulated. Migration will occur only if the foreign body has a smooth surface or if there is a simultaneous ambient suppurative infectious reaction. "Migration" can also occur if the bullet or a bullet fragment lies in a pre-existing cavity. The metal of the foreign body can also have a toxic effect: lead poisoning is a common consequence of bullets embedded in any tissue including the brain.

A special type of wounding is caused by shotguns (Sellier 1982; Di Maio 1999). The common ammunition is a shotgun shell containing (according to its diameter and length) up to several hundreds of shot pellets of pure or hardened lead or softened steel. After firing, the shot sheaf suffers a certain extension in length and width. Because of the relatively low gas pressure (65–75 MPa) a high muzzle velocity cannot be expected. Therefore, single shot pellets which strike the body usually produce penetrating not perforating wounds, independent of their size. Since the pellets rarely exit the body the full kinetic energy of all striking pellets is absorbed by the body and transformed to wounding, according to their number, mass, and velocity. Depending on the caliber and length of the shotgun shell and the range from muzzle to target, the entry wounds will be very large (at close range) as a result of the action of the whole undissolved shot charge or will be characterized by multiple, small circular injuries (at distant range).

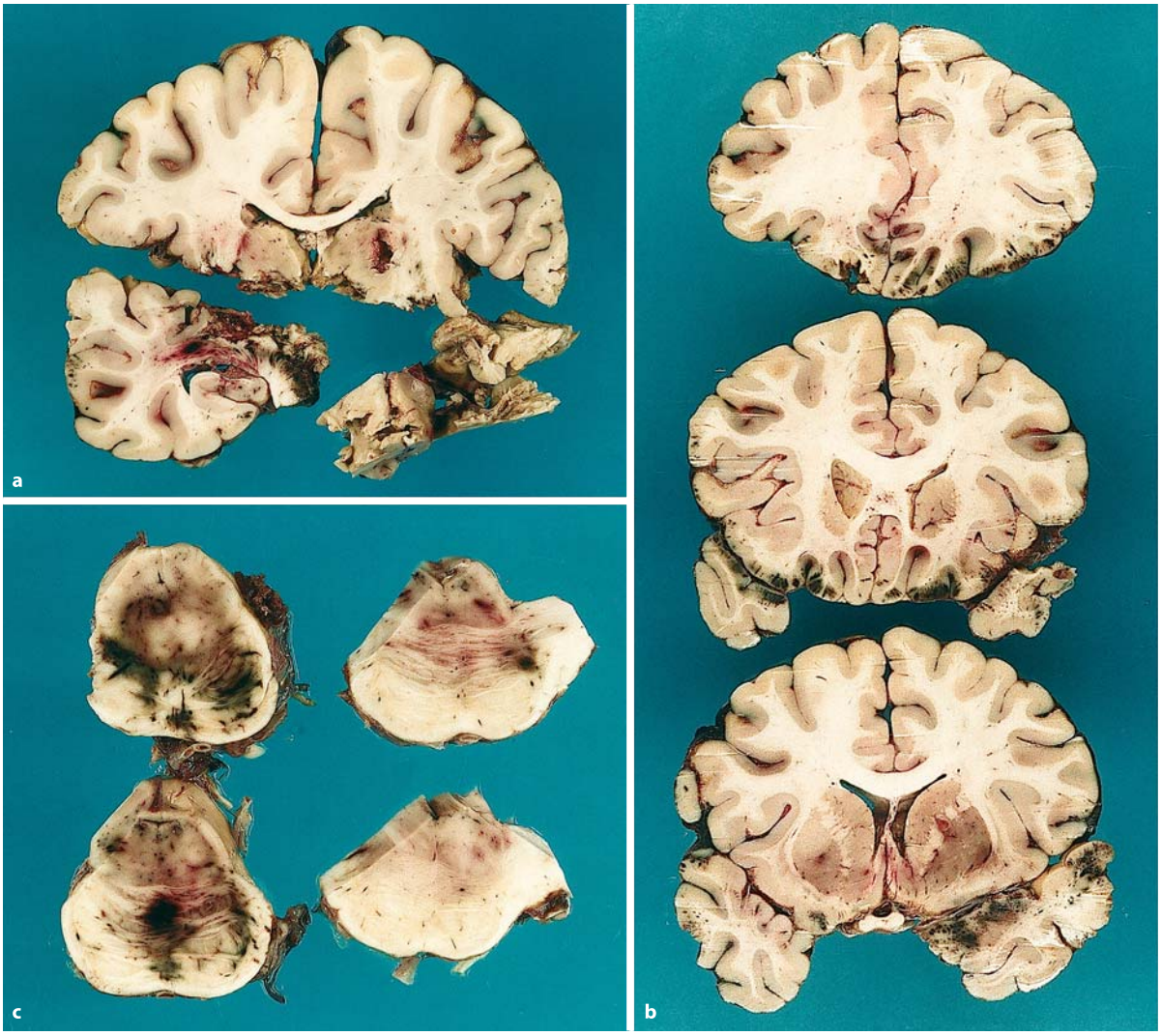


Fig. 8.14a–c. Gunshot wound. Cortical hemorrhages (contusional-like hemorrhages) and pons hemorrhages may be seen at larger distances from the permanent missile track as a further indication of the temporal cavity which leads to tears of the capillaries. **a** Permanent missile track and **b** corresponding cortical hemorrhages as well as **c** pontine hemorrhage

At close range shotguns are the most destructive of all small arms. Contact and near-contact wounds of the head belong to the severest wounds produced by shooting. Usually the head is bursting, the skull may be fragmented and the brain ejected or totally destroyed and blown out as a result of the entering of the whole shot charge and the pressure of the injected propellant gas. Figure 8.16a shows a contact wound by a shotgun and a broad distribution of the multiple shot pellets within the cranium (Fig. 8.16b) as well as the pellets within the formalin-fixed brain (Fig. 8.16c, d). The cranial bones and the brain were totally destroyed.

Other possible ammunitions of shotguns are cartridges with single projectiles of lead or copper. According to the caliber of the shotgun these shotgun barrel projectiles (slugs) have a mass of 20–32 g. As slugs usually stay in the body, they produce very massive injuries comparable in severity to those produced by high-velocity rifle bullets.

8.3.4 Postmortem Imaging

As already mentioned in Chapter 4, postmortem imaging has proved to be a particular success in cases of gunshot injury. The technical improvement allows more information to be gathered than ever before, regarding the reconstruction of the scene. Seventeen cases of gunshot injury of the head/brain (Oehmichen et al. 2003) studied with imaging techniques revealed the following:

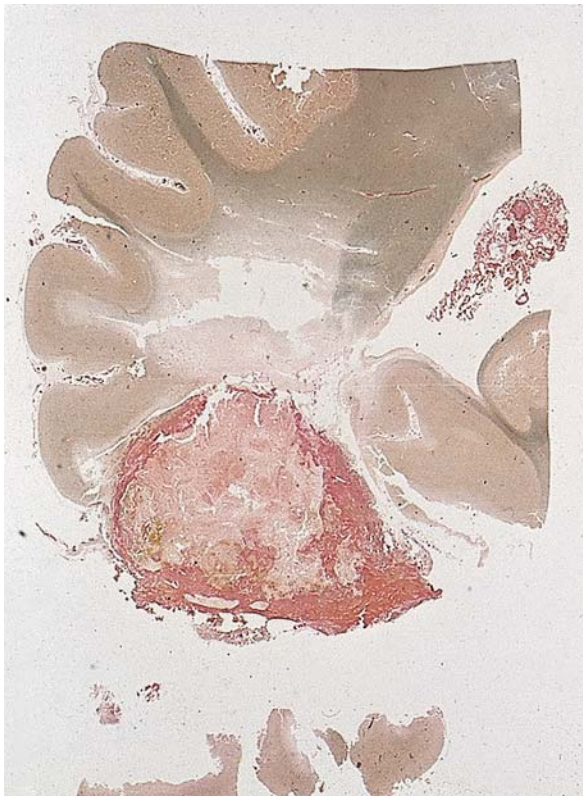


Fig. 8.15. Foreign body granuloma by soot. Granulation tissue characterized by intense collagenous fibers (van Gieson stain; magnification ×50)

1. Entrance (Fig. 8.17a) and exit wound (Fig. 8.17c) in the skull could be differentiated in nearly all cases by imaging methods alone, by for example 3D reconstruction (Fig. 8.17b, d, e) of the internal and/or external surfaces of the skull. Involvement of the base of the skull, which happens for example if the gun is fired with the muzzle in the victim's mouth, was found.
2. Change in density of the trail of opaque bone and projectile fragments marks the direction of the missile track in CCT scans, or in 3D reconstructions of the skull's interior.
3. The patterning of skull fracture lines provides clues regarding bullet velocity or the muzzle-to-head distance.
4. The missile track itself can be traced along the distance from the entrance wound to the exit wound in axial/coronal CCT scans (Figs. 8.18, 8.20d), in 3D reconstructions, or by demonstrating the path of destruction through the parenchyma, both in situ prior to autopsy and in the isolated, formalin-fixed brain (Figs. 8.20d, 8.19). Special changes in the brain parenchyma are also important:
   - Entry of air into the skull and the (secondary) collapse of the brain ventricles or the missile track and (possible) displacement of the brain depending on the position of the head at the time of wounding (Fig. 8.20a–d).
   - Deformation of the brain as an artifact of formalin fixation.
5. Secondary changes, such as bleeding, air bubbles, edema (cf. Carey et al. 1990) and/or hypoxia or tissue destruction (Fig. 8.19d) can be demonstrated both in situ and in the isolated, formalin-fixed brain by MRI.

8.3.5 Homicide, Suicide, Accident

Reconstruction of the circumstances surrounding a fatal event requires detailed examination of the scene. The expert witness must establish the location of the weapon, the projectiles, expended cartridge cases, the distribution of blood traces, the type of entry hole (contact wound, near-contact wound, intermediate wound, long-distance wound), localization of the entry and exit hole, all alterations in the victim's clothing, etc. as well as the position of the victim and the probable perpetrator.

In Western Europe, gunshot wounds of the head are most commonly seen in cases of *suicide*. The entry hole in the majority of cases is located in the right temple, the left temple, or in the mouth (Möllhoff and Müller 1975). Most of the wounds are therefore contact or near-contact wounds. The weapon is invariably found near the victim, sometimes gripped tightly in the victim's hand (Krauland 1984).

Suicide cannot be ruled out even if the entry hole is in a location usually not associated with suicide, for example on the top of the skull, or in the occipital region. Suicide is also not ruled out in the event of multiple gunshot wounds of the head, since wounding with small caliber weapons of low energy does not always produce immediate incapacitation (for a survey see Missliwetz 1983; Unterharnscheidt 1993).

In cases involving intermediate or long-distance wounding, or if no weapon is found at the scene, *homicide* is likely. If the localization of the entry hole is incompatible with accident or suicide, or if there are multiple entry wounds, *homicide* is of course to be suspected. Suspicion is also in order if reconstruction of the scene fails to explain the victim's movements and localization of the gunshot wounds.

Accidental gunshot injury is a possible explanation in cases with atypical trajectory. Only in extremely few cases does it prove impossible to establish whether the death was due to suicide, homicide, or accidental wounding with certainty.

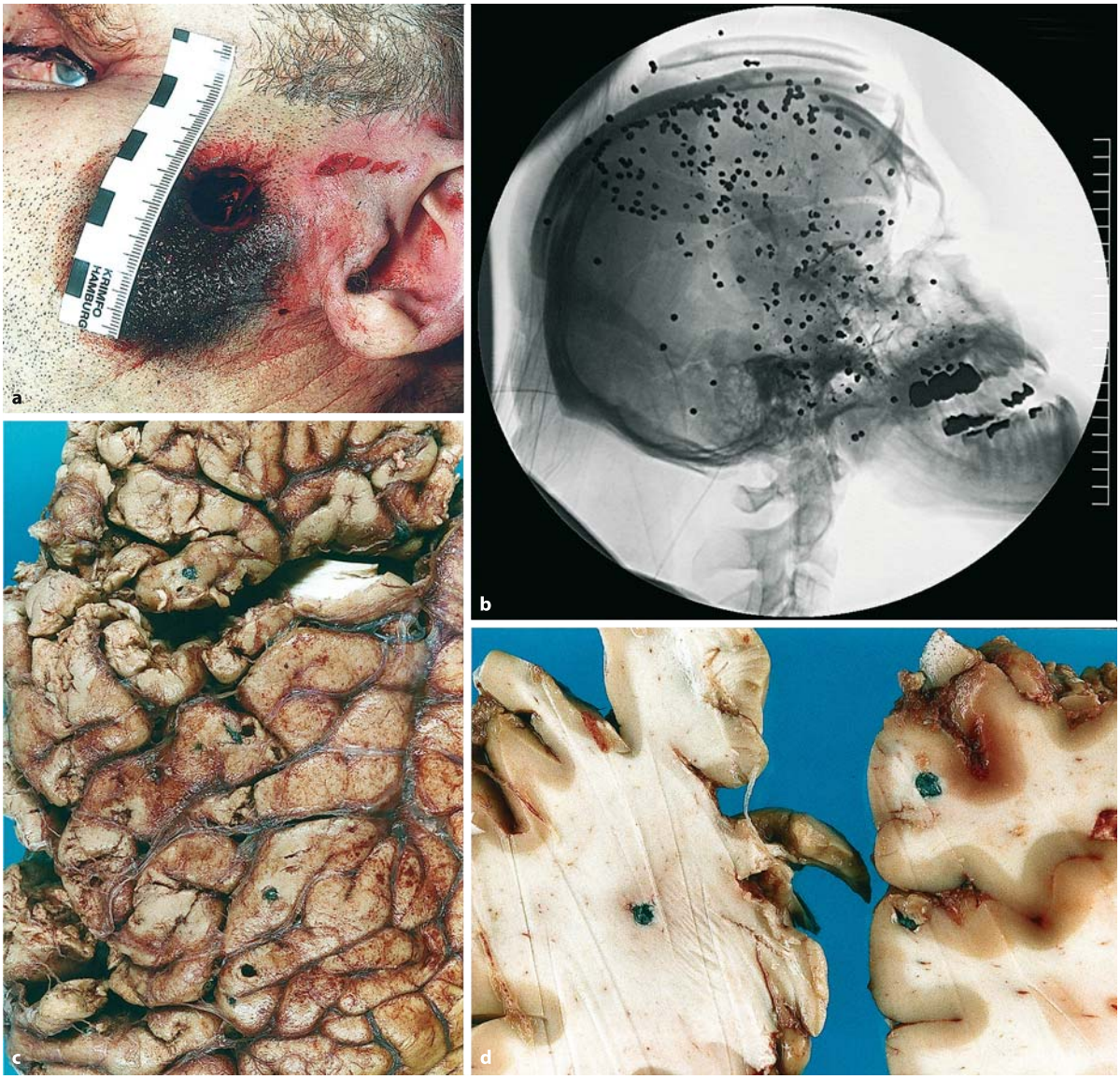


Fig. 8.16a–d. Shotgun wound. **a** Entry wound as a contact wound; **b** distribution of multiple shot pellets within the cranium and demonstration of multiple fractures of the cranial bone; multiple pellets on **c** the brain surface and **d** the brain section

8.3.6 Dating of Gunshot Wounds

Injuries in living victims must be distinguished from postmortem injuries (vital versus postmortem injuries). If an injury occurs shortly after cardiac arrest, it can be extraordinarily difficult to make a differentiation: the hallmark can be the lack of significant bleeding. If bleeding has occurred and/or if there is a zone of hemorrhage and/or edema around the permanent missile track, postmortem injury is unlikely (Oehmichen 1992).

Reliable criteria for the vitality of a wound are the reactive changes associated with life (cf. Oehmichen et al. 1985, 2001). The emigration of leukocytes can be noted after survival times <70 min (maybe >10 min – see below, pp. 190 ff), and expression of β-amyloid precursor protein after survival times >105 min (Blumbergs et al. 1995). Further criteria of vitality are the development of a perifocal edema, i.e., perineuronal and perivascular vacuolization. The temporal sequence of these edematous changes cannot be reliably established since they depend on a number of variables such as blood pressure, the extent of primary and secondary hypoxic changes, whether intoxication has occurred, etc. The first signs of edema may appear after survival times >20–30 min.

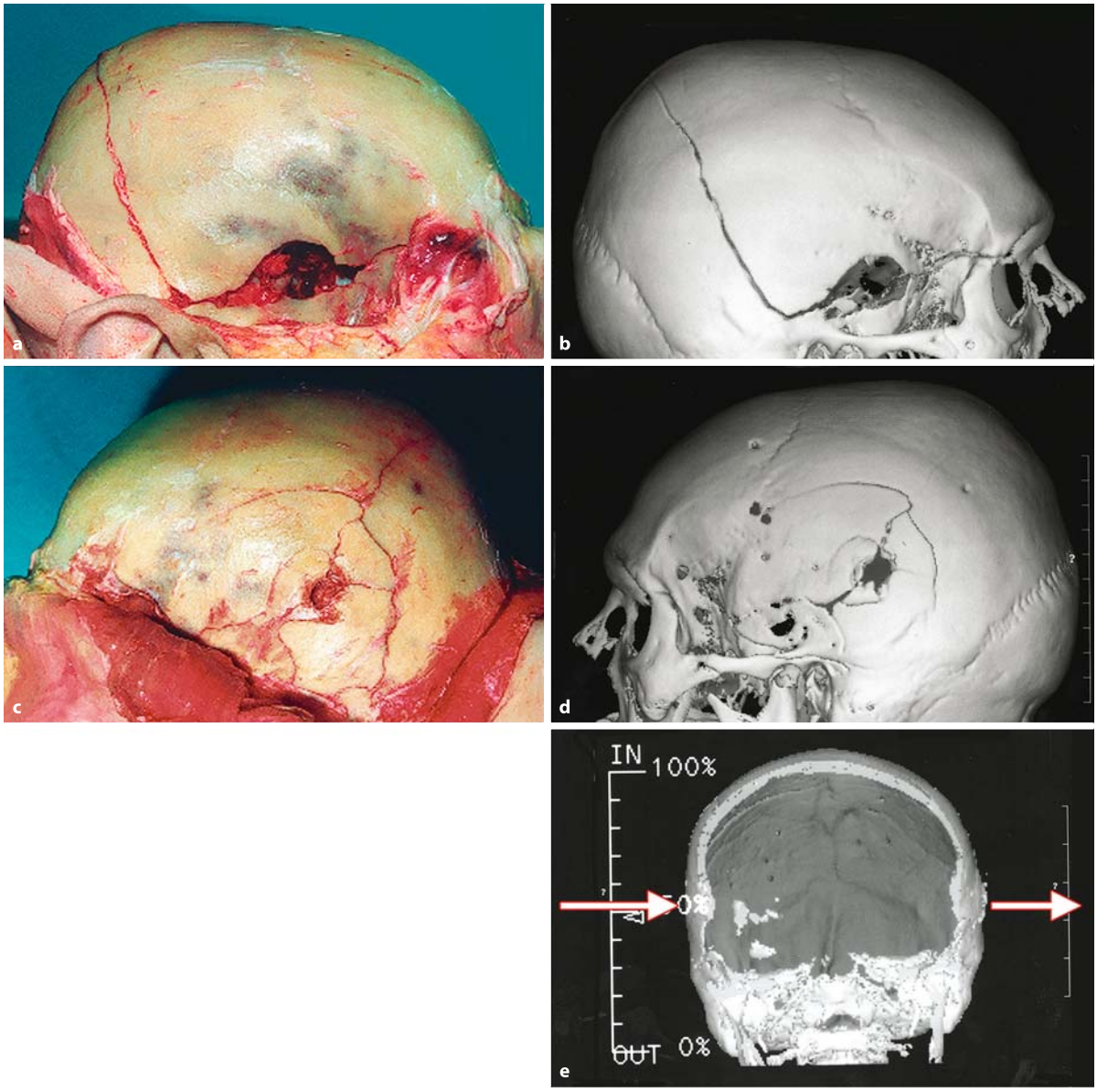


Fig. 8.17a–e. Differentiation of entrance and exit wound based on the bony structures found at autopsy (**a, c**) and on CT 3D reconstruction of cranial surfaces (**b, d**). A smooth-surfaced, bony defect appears to have been punched out of the interior of the skull at the entrance wound (**a, b**); bone fragments have broken off to form a funnel-shaped bone defect on the outside of the skull at the exit wound (**c, d**). Bone fragments in the interior of the skull are more densely grouped the nearer they are to the entrance wound (**e**). (*CT* Computed tomography.) (*cf.* Oehmichen et al. 2003)

The following histomorphological criteria have been determined for different lengths of posttraumatic survival intervals (Oehmichen 1992): (1) nerve cell shrinkage (30 min–62 h), (2) nerve cell vacuolization (30 min–62 h), (3) perineuronal vacuolization (30 min–62 h), (4) white matter edema (50 min–62 h), (5) oligodendroglial swelling (90 min–62 h), (6) leukocyte emigration (70 min–62 h), (7) macrophage reaction (17–62 h), (8) erythrocyte-containing macrophages (19–62 h), (9) neuronophagia (19–62 h).

These observations are based on a relatively small number of cases (n=17), since gunshot injuries of the brain under non-war conditions are only rarely survived and the exact time of death – especially in cases of suicide – is usually impossible to determine. The above observations however are in accordance with the findings of other authors (cf. Rand and Courville 1934; Campbell and Kuhlenbeck 1950; Campbell et al. 1958).

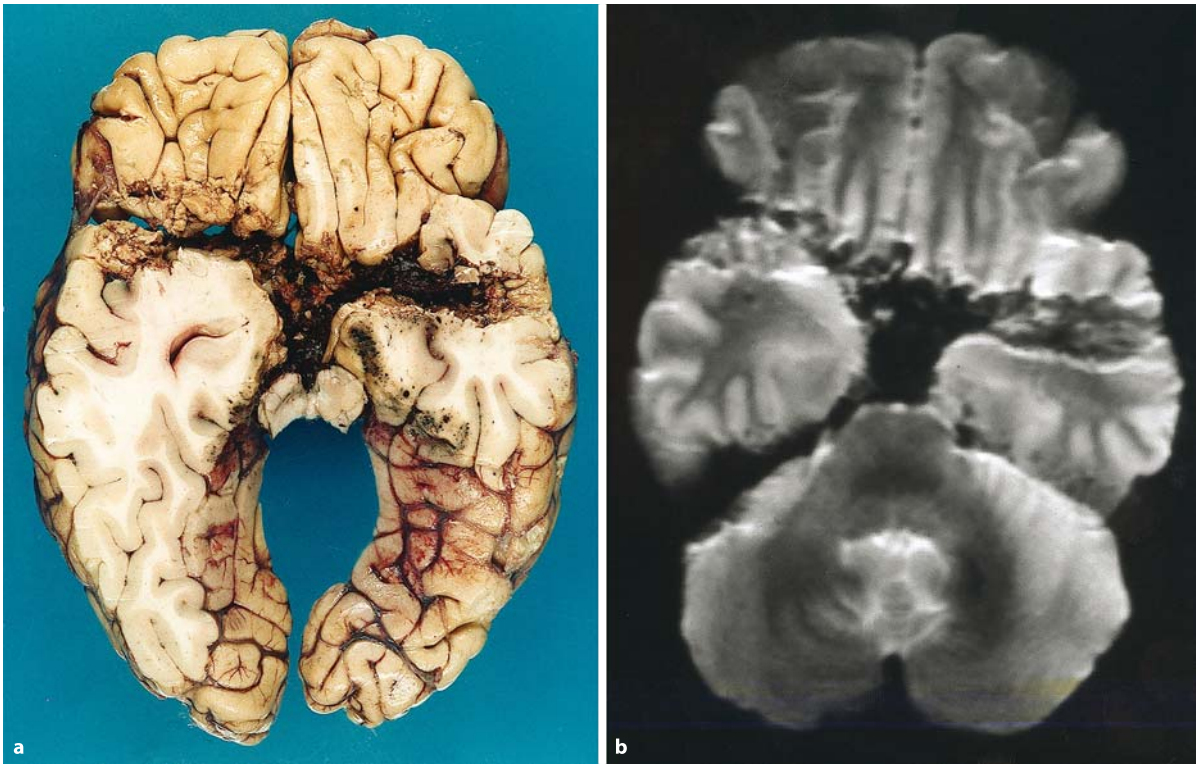


Fig. 8.18a, b. Demonstration of the missile track within the brain parenchyma by macroscopic inspection of the sectioned, formalin-fixed brain (**a**) and after CT imaging of the whole formalin-fixed brain (**b**)

8.4 Secondary Lesions

The most common complication in open (as well as closed) head injury is *brain edema*. In gunshot wounds not resulting in immediate death, edema leads to an intracerebral space-occupying situation, which can cause *herniation* as well as *brain stem hemorrhage*.

The shot-induced opening of the skull and dura also allows atmospheric air to enter the cranium, giving rise to a mechanically induced *pneumoencephalos*. Roentgenography can demonstrate the air in an epidural, subdural, subarachnoid, intraventricular or intracerebral location. In severe head injuries, especially if the missile penetrates the basal area, the large veins may be opened, leading to *air embolism* with consequent cardiorespiratory disturbances (air sinus wound – see Adams and Hirsch 1989). Embolized air may be detected in the right ventricle of the heart. The air can enter the body through the entrance or exit wound or, more often, through fracture systems involving the dural sinuses and the air spaces of the base of the skull. Fractures of the cranial base may lead to venous aspiration of necrotic brain tissue, resulting in a brain tissue embolism or in tracheal/bronchial aspiration of blood or, in rare cases, in brain tissue – each phenomenon indicative of a vital reaction.

Brain-tissue embolism of the lungs following gunshot wounding to the head, which is commonly associated with disruption of a major dural sinus, has been described by several authors (Ogilvy et al. 1988; Miyaishi et al. 1994; Levy et al. 1999). They concluded that a dramatic increase in intracranial pressure resulted in herniation of brain tissue into the simultaneously ruptured superior sagittal sinus, forcing brain tissue into the blood stream.

Every open brain injury bears the risk of *bacterial contamination* caused by primary or secondary bacterial infection (Sellier and Kneubuehl 2001) transported by the bullet into the tissue: a wound infection can lead to a suppurative *meningitis*, *cerebral phlegmon* or *cerebral abscess*. The prognosis of all of these forms of inflammation is extremely poor. As mentioned, even years after healing and scarring of an open brain injury a *flare-up* of infection can occur in an encapsulated focus, or a so-called delayed abscess may develop (see above).

An open communication between the CSF-containing spaces and the paranasal sinus may result in a *cerebrospinal fluid rhinorrhea*. Finally, mechanical sinusoidal injury may result in the formation of a *bullet embolus* within the vascular system. *Move-*

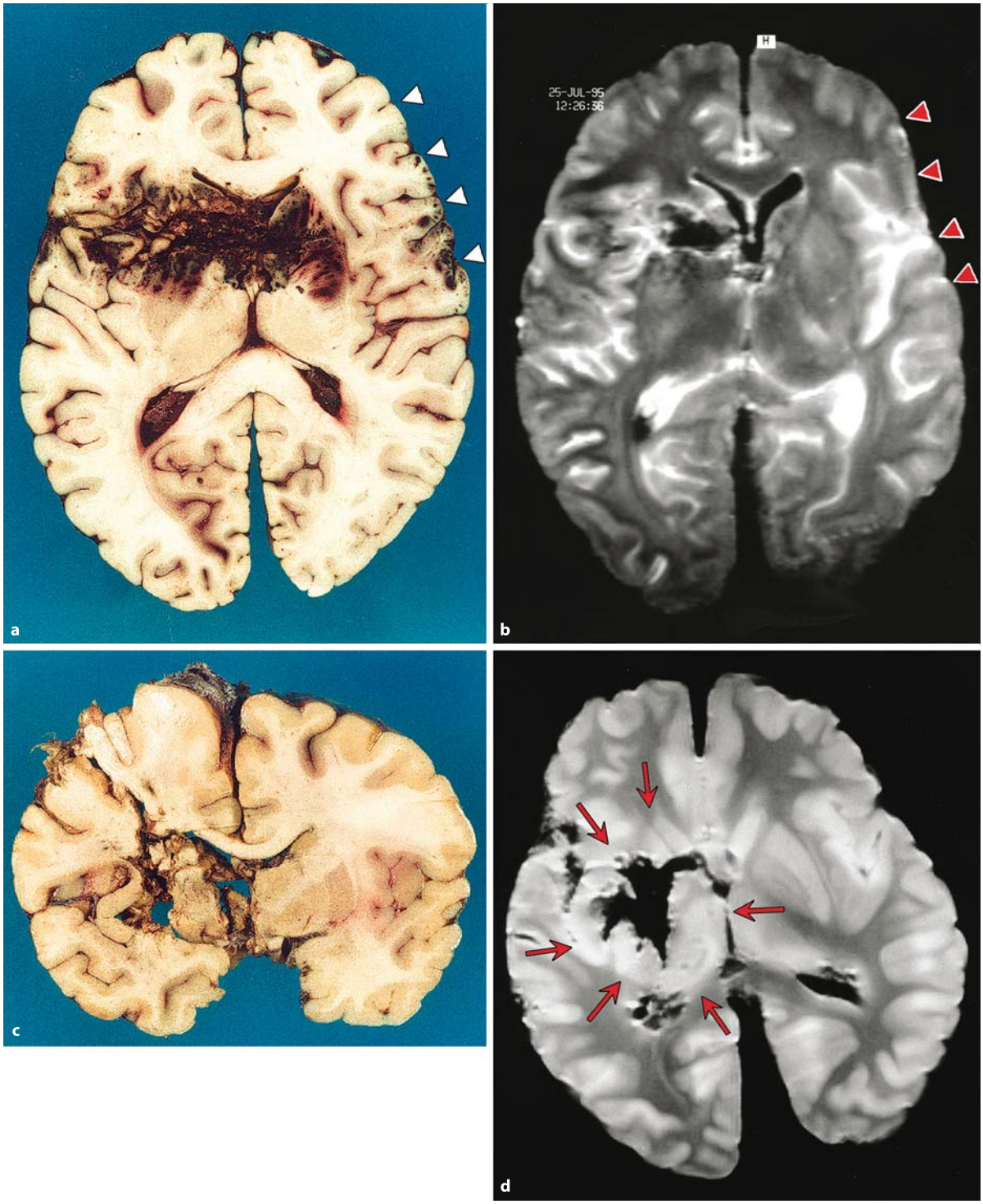


Fig. 8.19a–d. Imaging of secondary changes in isolated formalin-fixed brains. Photo documentation (**a**, **c**) versus MRI (**b, d**). **a, b** The missile track with surrounding bleeding as well as bleeding in the cerebral cortex (*arrowheads*, **a, b**) and in the ventricular system. Variations in the degree of translucence in cortical areas, the translucence being especially pronounced in the grooves between the gyri, possibly indicating hypoxic damage. **c, d** Axial T2-weighted MRI image of the incised missile track through the left basal ganglia, with a zone of hyperintense signal (*arrows*, **d**) possibly indicating tissue destruction secondary to the temporary cavitation (cf. Oehmichen et al. 2003)

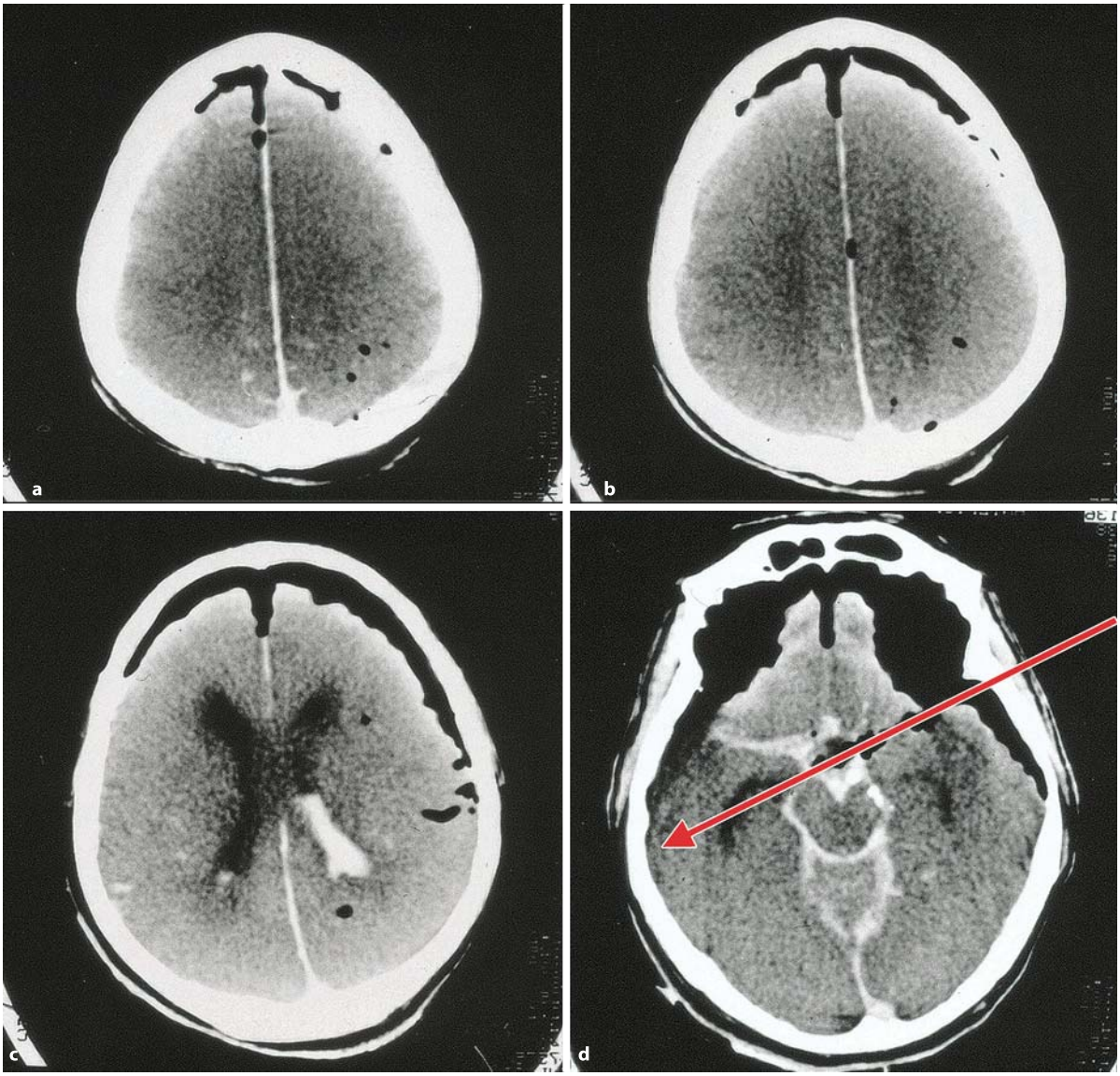


Fig. 8.20a–d. In situ demonstration of human brain injured by gunshot to the head by postmortem CCT. **a–d** Entry of air into the skull and collapse of the missile track

ment or wandering of the missile may occur in some cases, especially along the spinal cord cavity.

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Closed Brain Injuries 9

9.1 Classification

This chapter discusses the differentiating aspects of closed brain injury in adults. Concussion injury (mild brain injury) is distinguished both clinically and morphologically from contusion injury (moderate to severe brain injury). Due to significant differences in their presentation and prognosis, closed brain injuries in infants and children are discussed elsewhere (Chap. 24, pp. 471 ff).

Cerebral concussion injury refers to a sudden brief impairment of consciousness, paralysis of reflex activity, and loss of memory but in the absence of focal neurological signs and morphological alterations (for review see Shaw 2002). Consciousness returns within 1 h. It typically occurs after blunt impact or deceleration of the frontal or occipital areas that creates tissue strains within the deep white matter of the brain associated with local brain displacements. The sequelae include seizures, transient headache, nausea, and vomiting (Stein 1995). Victims experience retrograde and posttraumatic amnesia. The duration of the retrograde amnesia is dependent on the severity of the injury. In some patients, memory disturbances, dizziness, nausea, anosmia, and depression are long-term. Because concussion leaves no visible morphologic changes, the entire syndrome appears to be functional in nature.

Cerebral contusion injury is clinically characterized by long-term loss of consciousness (>1 h) and other neurological disturbances, the morphological correlates of which can be demonstrated by CT or MRT. The neurological deficits, e.g., paralyses, speech disturbances, seizures, etc., can be temporary or of long duration. The *temporal courses* of the sequelae of brain injury as well as *prognosis* can be assessed by appraisal of the clinical symptoms according to the *Glasgow Coma Scale* (Jennett et al. 1980; Gennarelli et al. 1982 – see pp. 104 f) and/or the morphological findings according to the *Glasgow Contusion Index* (Adams et al. 1985):

- The *clinical* (Glasgow Coma Scale) *score* is arrived at by adding the results of three tests, including eye opening, best motor response and best

Table 9.1. Contusion index grading the depth and the extension of hemorrhages in the human brain after loading. Source: Adams et al. 1985

Depth of mechanically induced hemorrhages (D)	
Not present	0
Partial thickness of the cortex	1
Full thickness of the cortex	2
Extending into digitate white matter	3
Extending into deep white matter	4
Extension of hemorrhages (E)	
Not present	0
Localized (one gyrus or two adjacent gyri)	1
Moderately extensive (involvement of the greater part of the surface of one lobe)	2
Extensive (more than the surface of the lobe involved)	3

CI = D × E (for each anatomical locator).
TCI is the total contusion index for a given brain:
Addition of **CI of all locators**

verbal response (Table 6.2). The Glasgow Coma Scale score and duration of unconsciousness are then used to differentiate five degrees of severity (Table 6.3), ranging from temporary confusion without amnesia or loss of consciousness (category 1) to long-term loss of consciousness with complete amnesia and focal neurological deficits (categories 3–4) or respirator brain (brain death) syndrome (category 5).

- *Morphological changes* are quantified using the contusion index, which assesses both the depth and severity of cortical hemorrhages (Table 9.1), and the principle site(s) of injury, namely the frontal, temporal, parietal, and occipital lobes, or the Sylvian fissures and cerebellum. These two indices are multiplied to produce a "contusion index."

Adams et al. (1980, 1985) applied these instruments to show that: (1) cortical hemorrhages are more severe in patients with skull fracture than in patients without fracture, but are (2) less severe in patients with diffuse axonal injury (DAI) than in patients without; (3) mechanically induced hemorrhages are most common and most massive in the frontal and temporal lobes; (4) brain damage is worst directly opposite the site of impact; but cortical hemorrhages are not more severe in the hemisphere contralateral to a fracture, or in the occipital lobes in patients with predominantly frontal fractures; (5) the duration of posttraumatic amnesia has a direct bearing on prognosis.

The *prognosis* of cortical hemorrhages does not depend on the effective forces or the type or extent of the injury of the brain alone, but is also a function of the severity and type(s) of *simultaneous injuries of other organs*. A contusio cordis or hemorrhagic shock resulting from multiple impact mechanisms with attendant respiratory and circulatory disturbances can aggravate the effect of brain injury-induced hypoxic injury via secondary disruption, for example, of the blood–brain barrier (brain edema). Particularly in children, but also in adults, the subsequent course and sequelae of a traumatic event are greatly dependent upon whether an edema develops or not (Adams et al. 1980).

We have to differentiate between cortical hemorrhages and *intracerebral hemorrhages*. There are principal differences in the biomechanical background and the morphological alterations as well as the clinical sequelae. Closed brain injuries can be further classified according to whether the lesion is *focal or diffuse* (Graham et al. 1995; cf. Table 9.2) as determined by morphological criteria and biomechanical principles. Contact-induced closed head injury is distinguished from injury caused by acceleration forces (non-contact injury, Gennarelli and Thibault 1982; Gennarelli 1993). *Contact injury* is caused by an object striking the head or vice versa and is commonly associated with focal injury of the scalp, skull, and/or brain (dura hemorrhages, surface contusion injuries or lacerations). In contrast, *acceleration injury* results from shear/tensile and

Table 9.2. Classification and relative frequency of the different types of lesion associated with fatal non-missile head injury. Source: Graham et al. 1995

	Relative frequency (%)
Focal lesions	
Fracture of the skull	75
Cortical hemorrhage and laceration	95
Intracranial hemorrhage	60
Damage secondary to raised intracranial pressure	75
Diffuse lesions	
Axonal injury (DAI)	90
Ischemic brain damage	55
Brain swelling	53

compressive strains or cavitation; the morphological picture is dominated by subdural hemorrhage (SDH) and DAI. In addition to these primary mechanically caused brain injuries, *secondary diffuse injuries* may also occur, including edema, ischemia, and vascular injuries (see below).

In the scientific literature the term "deceleration" means negative "acceleration." The biomechanical effect is the same except that the force is acting in the opposite direction. In the following text only one term will be used for both events, the term "acceleration."

9.2 Concussion Injury and Cortical Hemorrhage

9.2.1 Biomechanical Aspects

The following common biomechanical finding has become the basis of many theoretical and experimental considerations: a blow (i.e., a moving object strikes the resting head) is likely to cause injuries (contusion injuries or cortical hemorrhages) (Fig. 9.1) of the brain directly beneath the impact site (homolateral = "coup" hemorrhages), whereas a fall (i.e., the moving head strikes a firm or unyielding surface or an object) tends to induce cortical hemorrhages at a location directly opposite the point of impact (contralateral = formerly known as "contrecoup" cortical hemorrhages) (Figs. 9.2, 9.3). Such lesions occur with greater frequency at the frontal and temporal poles and on the inferior surfaces of the frontal and temporal lobes than they do elsewhere in the brain; cortical hemorrhages are rare at the occipital poles. Biomechanical considerations must be based on the following phenomena (Dawson et al. 1980; Leestma 1988; Gennarelli and Meaney 1996):

1. Biomechanically, it makes no difference whether the moving head strikes a big stationary object (deceleration) or a moving big and massy object strikes the stationary head (acceleration). Impact is the dynamic interaction of two bodies colliding.
2. As a deformable (non-rigid) object, the skull is capable of significant local and global deformation during impact.
3. The brain is a glycerin-like, non-homogeneous body that consists of different types of tissue; for example, the dura mater with its falx and tentorium, the connecting structures of the interhemispheric commissures, i.e., the corpus callosum, or the brain stem. The brain parenchyma is differentiated according to the white and gray matter and the course of the axons. By impact or impulsive loading to the head, the brain is set under local and global strains and displacements, and there may be considerable pressure swings (especially negative) acting on the tissue, leading to vascular, axonal, and brain tissue damage.
4. Blunt impact to the occiput is likely to induce cortical hemorrhage at sites opposite the application of force. In addition, contralateral hemorrhages tend to be fewer and less severe when the skull fractures than if it remains intact.

The published data on the biomechanics of impact to the head are based on head models in which the skull does not fracture on impact. This results in *focal in-*

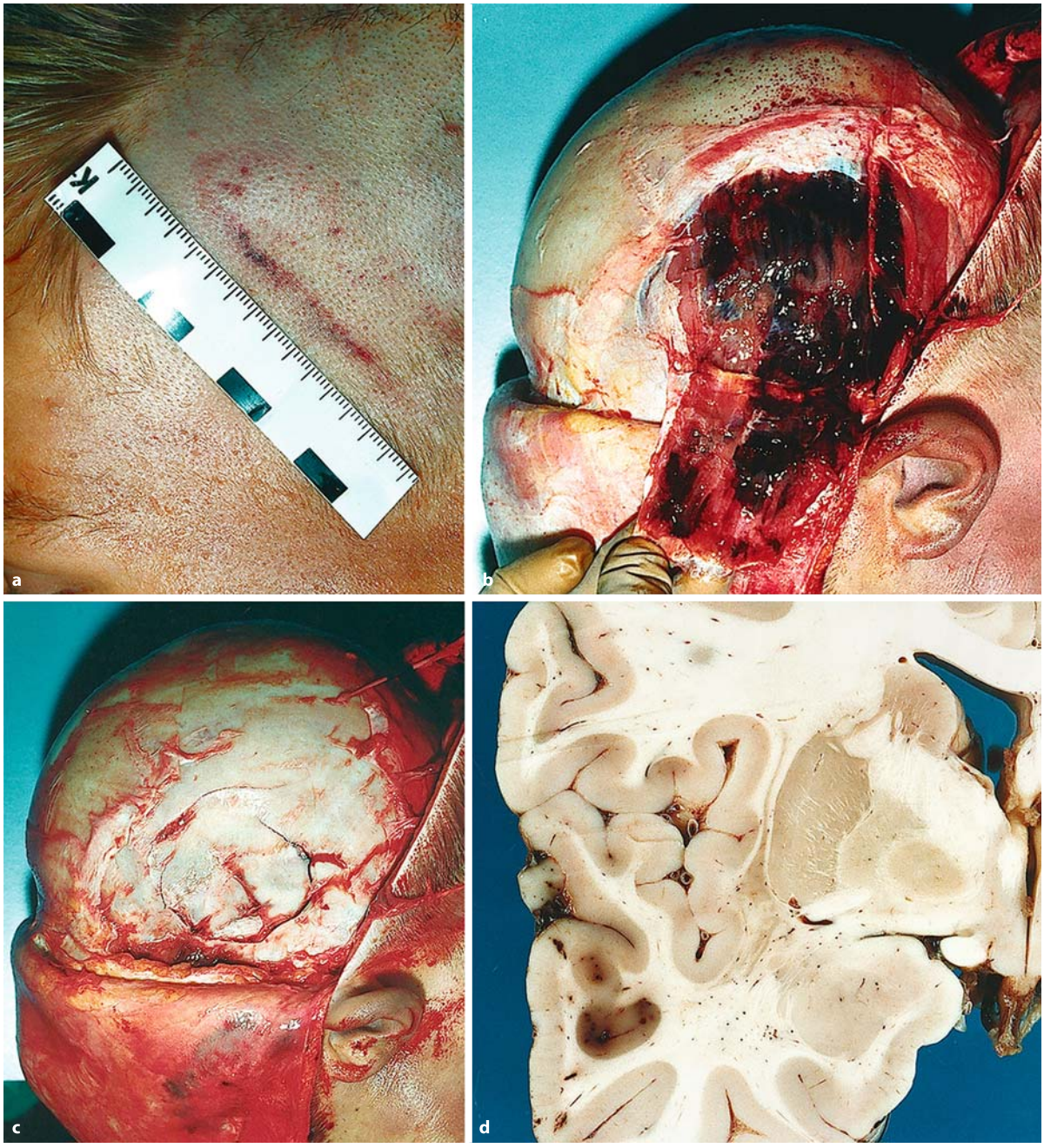

Fig. 9.1a–d. Ipsilateral hemorrhages caused by blow. **a** Contusion injury in the scalp; **b** hemorrhages in the temporal muscle beneath the skin wound; **c** skull fracture beneath the skin wound; **d** focal cortical and subarachnoid hemorrhages

juries at the contralateral site of impact. These are usually visible macroscopically due to cortical hemorrhaging. The biomechanics of *diffuse injuries* are in part assessed using a brain deformation model in which the impact is delivered to the brain parenchyma and exposed dura in a form simulating impulsive loading (see Sect. 9.4).

The severity of focal injury depends on the *magnitude of energy delivered*, the skull's *resistance to deformation*, and the *direction of deformation*. At the same time, acceleration and rotational forces may create shearing which results in *tearing* of *axons and myelin sheaths*, sometimes also of *vessels* in the depths of the white matter with consequent immediate loss of consciousness (Voigt et al. 1977) and simultaneous diffuse axonal injury.

The forces transferred to the brain from the outside, the period of impact, and the acceleration of the skull upon blunt impact depend upon the kinematics and size of the striking object, but also on properties

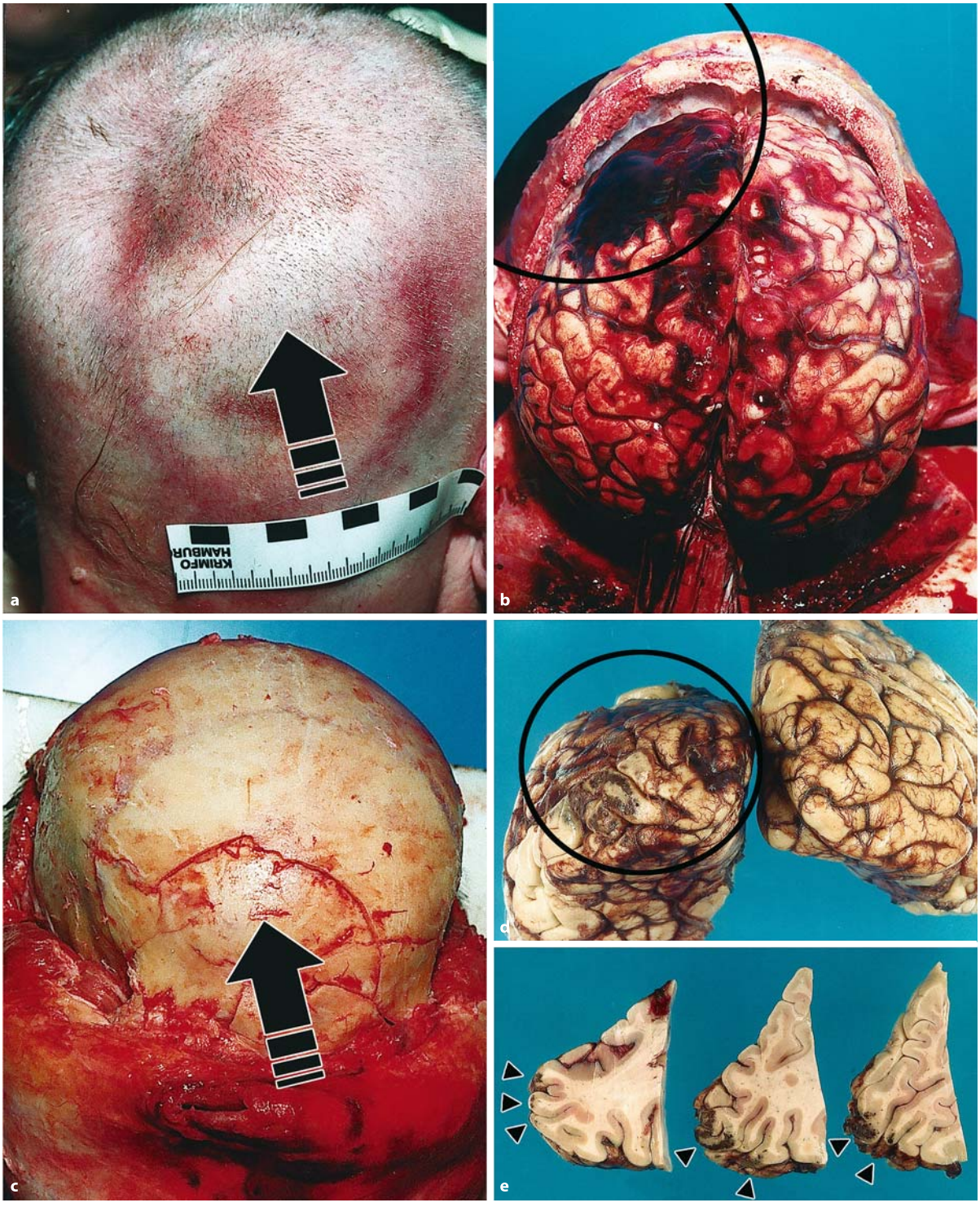

Fig. 9.2a–e. Contralateral wounding of the brain caused by fall (two cases). **a** Galeal hematoma in the right parietal region and **b** corresponding, i.e., contralateral subarachnoid hemorrhage on the left frontal pole. **c** Blunt impact on the right frontal bone by fall associated with circular and radial fracture lines; **d, e** associated with cortical hemorrhages at the gyral crests of the left occipital pole

of the tissues of the face, the scalp, and the skull covering the brain and, to an extent, on the anatomical site of contact. The cushioning effect of the facial soft tissues is greater than that of the back of the head; the skull's elasticity and resistance to fracture are different in the temporal region than in the parietal or

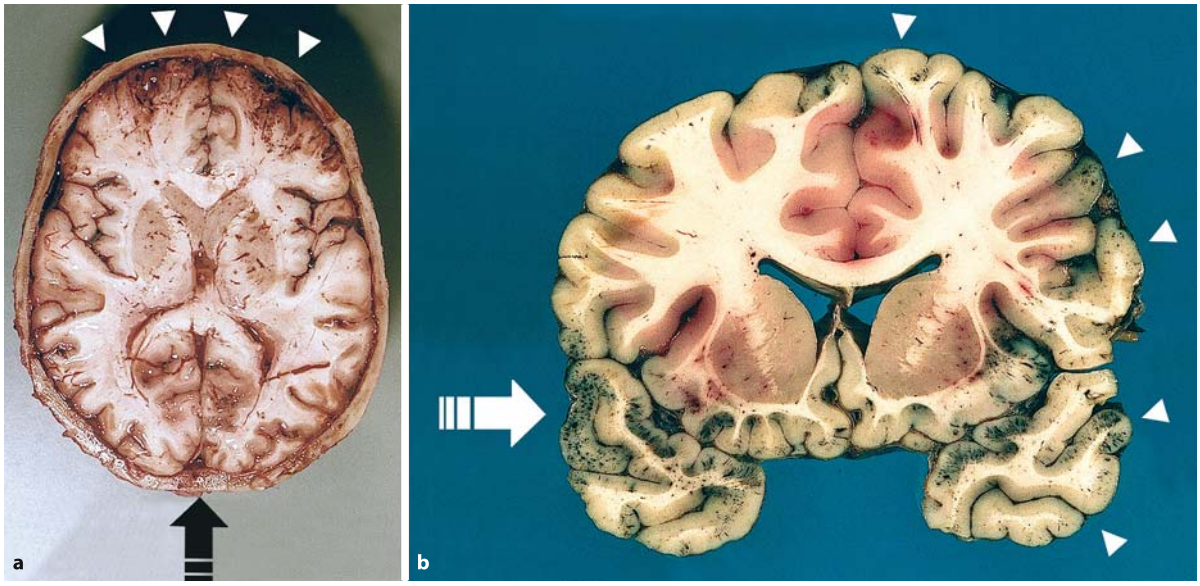

Fig. 9.3a, b. Cortical hemorrhages of the gyral crests of the cerebral surface – associated with subarachnoid hemorrhage (two cases). **a** Frontal hemorrhages caused by a fall associated with an occipital impact as seen on a horizontal section at autopsy; **b** nearly the whole surface of the right hemisphere and the cortex of the left temporal lobe are marked by stripe-like hemorrhages on a frontal section after formalin fixation. The *arrowheads* mark the secondary cortical hemorrhages while the *thick arrow* mark the areas of the impact and the primary contusion injuries

occipital regions. The mechanical load on the brain depends not only on the cushioning and elastic properties of the coverings, but also on the direct effects of the impact, e.g., whether the covering remains intact or is destroyed, whether the scalp is contused or lacerated, whether bending or compression fracturing of the skull occurs on the side of impact and/or secondary bursting fractures take place.

As mentioned above, closed brain injuries are characterized – depending on the intensity and type of inner loads generated – by bleeding in the area of impact and/or focal hemorrhages in the gyral crests of the contralateral cortex. Extensive, confluent or focal hemorrhaging can occur at the site of impact or may be totally absent. If the skull remains intact, bleeding often occurs only at a site opposite the site of impact; this agrees with clinical observations that cortical foci of bleeding are far more common at the contralateral pole. Hemorrhages can also occur in deep brain areas distant from the site of impact; this bleeding can be interpreted as being due to shearing or tensile forces or as a result of localized motions within the brain.

The dynamic load exerted on the brain by a hard blunt impact to the head is generated by positive and negative pressures and shearing forces. Numerous hypotheses exist as to which of these loads are responsible for which types and localizations of brain injury (for review see Leestma 1988). One hypothesis that has found general acceptance is the cavitation theory. According to Sellier and Unterharnscheidt (1963; cf. also Bandak 1997), the foci of cortical bleeding at the contralateral pole are not due to compression (contusion) as a result of an impact on the contralateral site ("contrecoup"), but to the cavitations created by negative pressure. According to these authors, the cortical hemorrhages result from an external hard blunt impact with short impact time and sufficient force accelerating the skull, creating transient positive pressure at the impact site and – depending on the degree of skull deformation – a temporary zone of lowered pressure at the contralateral pole. If the vapor pressure remains below normal levels (negative pressure), gases dissolved in fluids such as CSF and blood are released as bubbles (cavitations), with consequent rupture of small vessels as a result of the following collapse of these bubbles.

The cavitation hypothesis was first put forth by Goggio (1941 – cf. also Gross 1958), who experimentally demonstrated the formation of gas bubbles in fluids during brief periods of lowered pressure. The hypothesis has been subsequently confirmed by high-speed cinematographic documentation (Gurdjian 1975) and by experimental studies on cadavers (Nahum et al. 1977; Table 9.3), on which the finite element models of direct head impact created by Ruan et al. (1993) were based. According to the latter, hard blunt impact to the central occiput lasting several milliseconds generates sufficient force (a lower limit of 125 *g* head acceleration is given) only fractions of milliseconds later at the contralateral pole to create maximum temporary negative pressures of ca.

Table 9.3. Differences in brain pressures and shearing forces in the brain parenchyma induced by impact to the head at various anatomical sites, with consequent hemorrhages in the homolateral and/or contralateral cortex. Source: Nahum et al. 1977

Impact localization	Head acceleration (*g*)	Force (kN)	Brain pressure		Shear force (kPa)
			Impact point (kPa)	Contralateral site (kPa)	
Frontal	233	8.1	275	–92	75
Occipital	199	6.9	252	–118	199
Temporal	220	7.6	270	–86	47
Parietal	174	6.4	205	–15	29

100 kPa (approximately 1 atm), which is sufficient to induce cavitation.

Young and Morfey (1998) used simple finite element modeling to study the formation of cavitation following blunt impacts lasting from 0.05 ms to 10 ms. For such brief impact times, the primary pressures were higher at the impact site, the negative pressures higher at the contralateral pole. Since the further temporal course was characterized by a reversal of the pressure distribution, negative pressures occurring at the impact pole, positive pressures at the contralateral pole, they concluded that formation of cavitation at the impact pole may also account for the foci of cortical bleeding observed there.

Lubock and Goldsmith (1980) were able to experimentally demonstrate that the collapse of gas bubbles at the end of the period of temporary negative pressure creates transient pressure spikes of at least 400–500 MPa, which they thought was sufficient to cause the observed vessel injury. The greatest structural injury therefore results from the collapse of the cavitation bubbles. Spikes created in this manner have been calculated to be capable of attaining up to 1–10 GPa.

Other forces, however, also have an (additional) effect (Gennarelli and Thibault 1982), particularly rotational shearing forces. Shear strains are especially common in the frontal/temporal regions, regardless of the impact site, and in locations where the surface of the overlying skull is relatively uneven. Shear strains can cause tearing of cerebral blood vessels and thus induce cortical hemorrhages.

The term "contrecoup" is misleading for two reasons: first, contralateral cortical hemorrhage is not the result of an "inner impact" of the brain parenchyma against the inner table of the skull, but results from negative pressure. Second, cortical hemorrhages are caused by inertial forces and not by contact forces. Cortical hemorrhages in the sense of "contrecoup," therefore, do not necessarily occur contralateral to the site of impact, but rather at the opposite temporal and frontal poles (Ommaya 1995). If the mechanism of injury is a lateral impact to the head, ipsilateral (40%) or contralateral cortical hemorrhages (50%) are almost equally likely, the remaining 10% occurring bilaterally (Sano et al. 1967).

A fundamental question in forensic neuropathology is the differentiation of wounds (their topography and the associated injuries) caused by fall and by blow, as mentioned above (p. 114, see Fig. 7.3). Further criteria in cases with closed brain injury are summed up below.

9.2.1.1 Injury by Fall

Falls on a level plane are often used in traumatology in establishing standardized control cases for estimation of the forces generated when the head strikes a hard, immovable object. Forensic medical experience shows, for example, that if an adult slips while walking and falls on his back without reacting to cushion the force of the fall and strikes the back of the head on a hard level surface, the force of the impact is just sufficient to cause a bursting skull fracture. The force of such a fall can be estimated as follows:

While walking, the average adult bears his head at a height (h) of about 1.6 m and thus at a potential energy level relative to the ground of $E_{pot}=m\,g\,h \approx 70$ J (with a head mass $m=4.5$ kg, and gravitational acceleration $g=10$ m/s^2). If there is a complete conversion of energy, this value corresponds to the experimentally measured threshold load for inducement of skull fractures.

The injuries caused by falls resulting in hard blunt impact of the head are classified as acceleration traumas. There is always a relevant accelerated mass (the head) and the sudden deceleration over a few milliseconds from speeds of 5–6 m/s in 1–2 cm generates head accelerations of more than 200 *g* (see

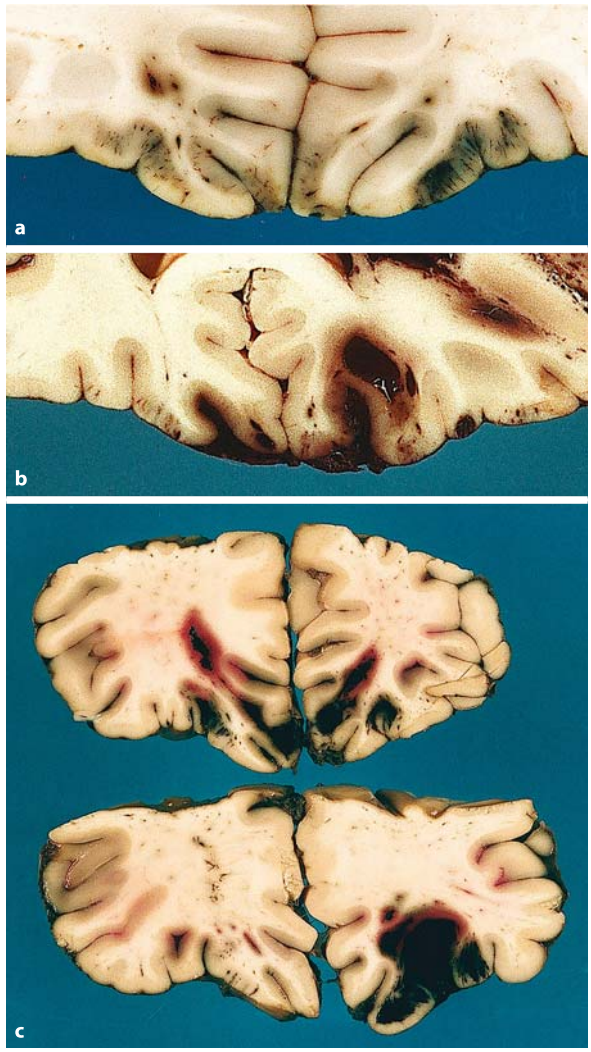

Fig. 9.4a–c. Contralateral cortical hemorrhages at the base of the frontal lobe, the most frequent phenomenon after occipital impact caused by fall (three cases). The different extensions of the hemorrhages are correlated with the increasing intensity of impact – see text. **a** Discrete stripe-like hemorrhages in the rectal and pararectal gyri; **b** more distinct hemorrhages combined with bleeding in the white matter; **c** extensive, space-occupying hemorrhages of gray and white matter

also pp. 99 ff). This exceeds the critical threshold for the formation of cavitation at the contralateral pole.

Fall-induced cortical hemorrhages tend to occur at sites opposite the site of impact (Figs. 9.2, 9.3a, 9.4). Since, in falls, the most common impact site is the occipital area, cortical bleeding is encountered mainly in the frontobasal area. Forward falls on a level plane are frequently accompanied by reflexive actions to break the fall, whereas falls to the side are often cushioned by the intervening shoulder. Those arguments may explain why contralateral cortical hemorrhages in the occipital lobe are very rare (Fig. 9.2c–e).

Falls constitute the classic model of deceleration in which, in addition to cortical hemorrhages opposite the impact site, subdural hematomas (SDH) and DAI are observed. This means that falls generate not only pressure, but shearing forces as well (see Sect. 9.4, pp. 201 ff).

The presence of foci of cortical bleeding at a single site in the brain is sometimes useful in reconstructing the impact site and direction of the blunt impact. If there are cortical hemorrhages in the brain, the impact site will be located diametrically opposite to them (with one exception: frontal blunt impacts are rarely associated with contralateral, i.e., occipital cortical hemorrhages). The direction of impact generally runs from the pole of impact toward the focus of cortical bleeding (contralateral pole).

9.2.1.2 Injury by Blow

A *blow* inflicts brain injuries (Figs. 9.1, 9.5) mainly at the impact side (impact pole). If the skull remains intact, injury of the brain is due to local deformation (depression and recoil) of the bone. In very violent blows, the energy is transformed and delivered by deformation and fracture along a relatively long pathway. Acceleration is lower at the contralateral pole and the resulting injuries – mainly caused by negative pressure – are minimal or absent altogether. In contrast to falls, under these conditions, *massive hemorrhages* develop at the impact site and are limited not merely to the gyral crests, but can extend deep into the white matter.

Manually induced forceful impact of blunt instruments with small surface areas, but relatively low accelerated masses, generally do not create the critical negative pressure at the contralateral pole. Most of the energy is delivered locally to the impact site, where it causes contusion and/or laceration of the scalp and depressed fractures of the skull, sometimes even bursting fractures. At the impact pole, the injury is largely confined to a depressed skull fracture. The global effect on the skull, in the form of transient high acceleration, is too small to generate the necessary negative pressures at the contralateral pole to cause cavitation, even if the head is unsupported when it is struck.

The most common impact site is the parietal region. Most of the other sites of impact occur when the victim, who will be injured by a blow, is lying on the ground and his head is therefore supported. If the head is resting on a hard surface when struck, it cannot be accelerated, so contralateral cortical hemorrhages are uncommon under such circumstances.

Cortical hemorrhages located on the side of impact are a direct result of the forces delivered by the blow. Light force induces discrete cortical hemorrhages morphologically indistinguishable from con-

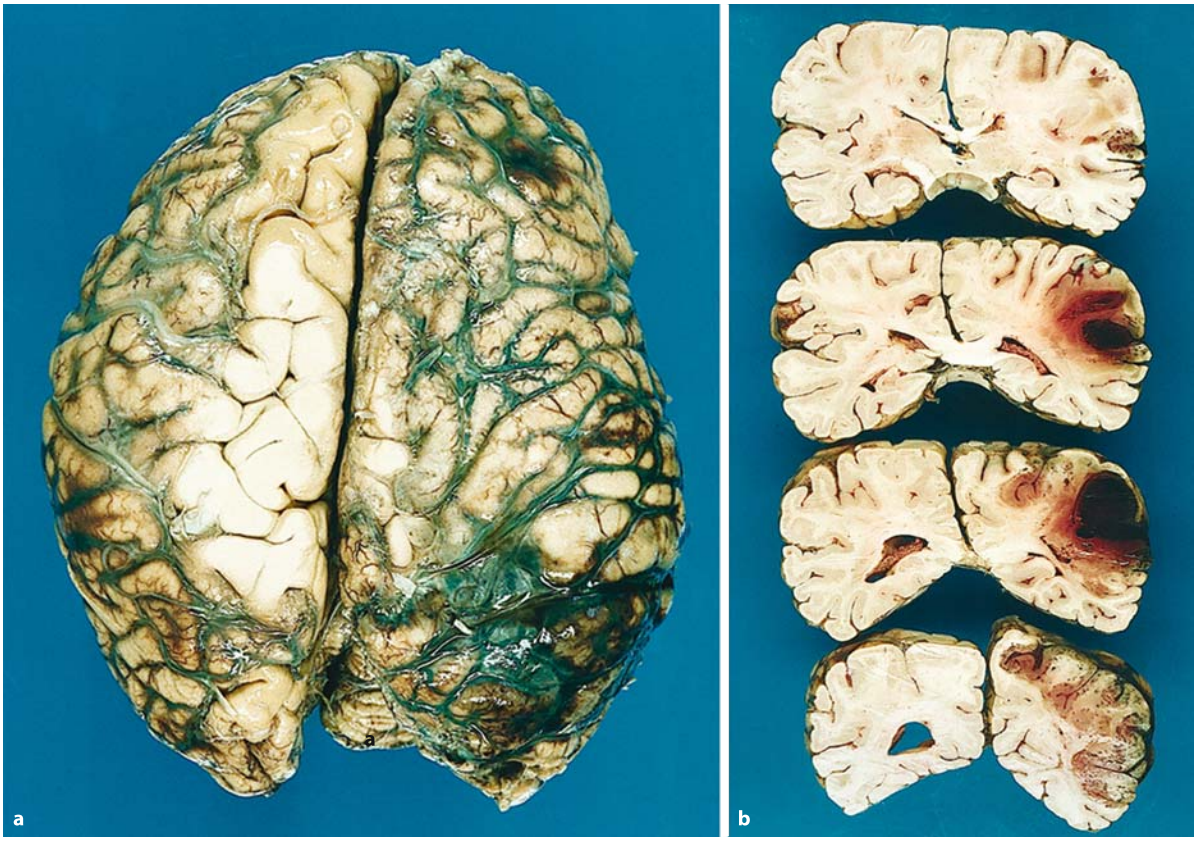

Fig. 9.5a, b. Ipsilateral hemorrhages caused by blow. **a, b** Lateral-parietal blow and corresponding focal cortical and intracerebral hemorrhage

tralateral hemorrhages. The greater the force, the more extensive the focal brain injury, with slight or severe depression fracturing of the skull. The fractured bone causes lacerations of the dura or leptomeninx as well as of the surface of the cortex. Depending on the force of the impact, destruction of brain tissue occurs with massive, space-occupying hemorrhaging. The brain injury can involve an entire hemisphere and lead to breaching of the blood–brain barrier and bleeding into the ventricular system.

There have been repeated attempts to establish morphological criteria for the differentiation between brain injuries induced by falls and by blows. Among the criteria discussed has been the formation of DAI (Adams et al. 1982; Geddes et al. 1997, 2000), which is more common after falls, i.e., after high acceleration loading (see also Oehmichen et al. 1997). In any given case, however, this criterion alone is not sufficient for reliable discrimination.

9.2.2 Cellular and Molecular Mechanisms

9.2.2.1 Cytological Reaction

The wounding of the brain (ipsilateral or contralateral) is characterized by extravasal red blood cells (Fig. 9.6). The cellular response following non-missile closed brain injury includes emigration of leukocytes and macrophages and the aggregation of thrombocytes. The earliest reaction is emigration of *polymorphonuclear leukocytes* (Fig. 9.7), which are attracted by endothelial release of L-selectin. Leukocytes release interleukins (IL) IL-1, IL-2, and IL-6, and tumor necrosis factor (TNF) as well as several lipid mediators (Biagas et al. 1992). Platelets release P-selectin and lipid mediators, while macrophages and activated microglia release L-selectin, IL-1, IL-2, IL-6 and lipid mediators, which are upregulated at the endothelial surface.

Another reaction to closed head trauma at the cellular level is the reactivity of mononuclear phagocytes, the so-called *microglial reaction*, which can be diffuse (Meyermann et al. 1997) or localized near to

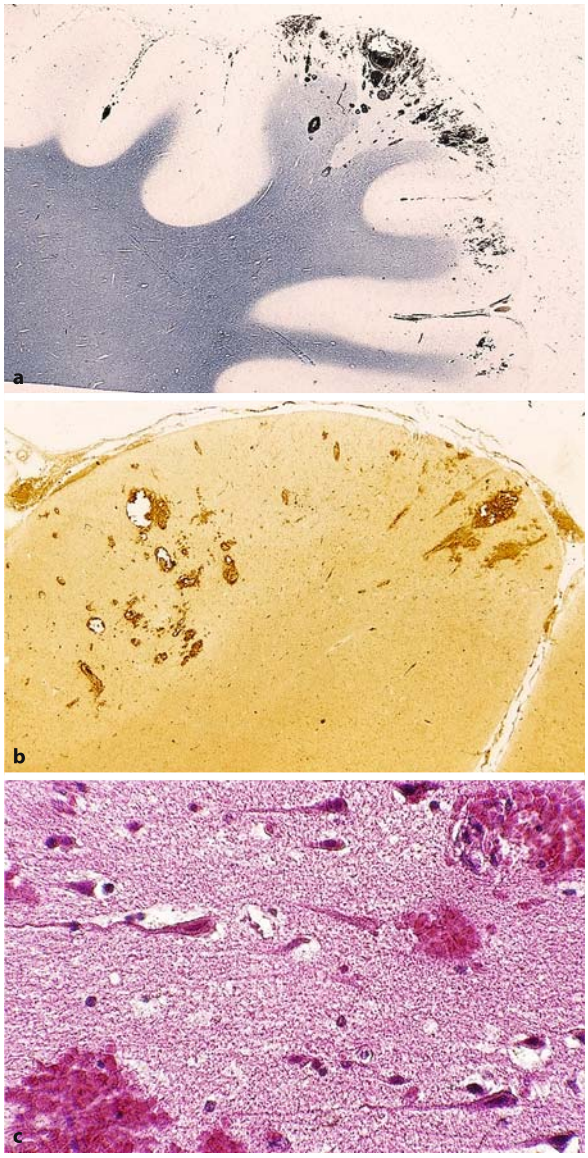

Fig. 9.6a–c. Cortical hemorrhages and their histological distribution at the crests of the gyri (**a** Gomori stain, **b** van Gieson stain, **c** H&E; magnification **a** ×100, **b** ×200, **c** ×1,000)

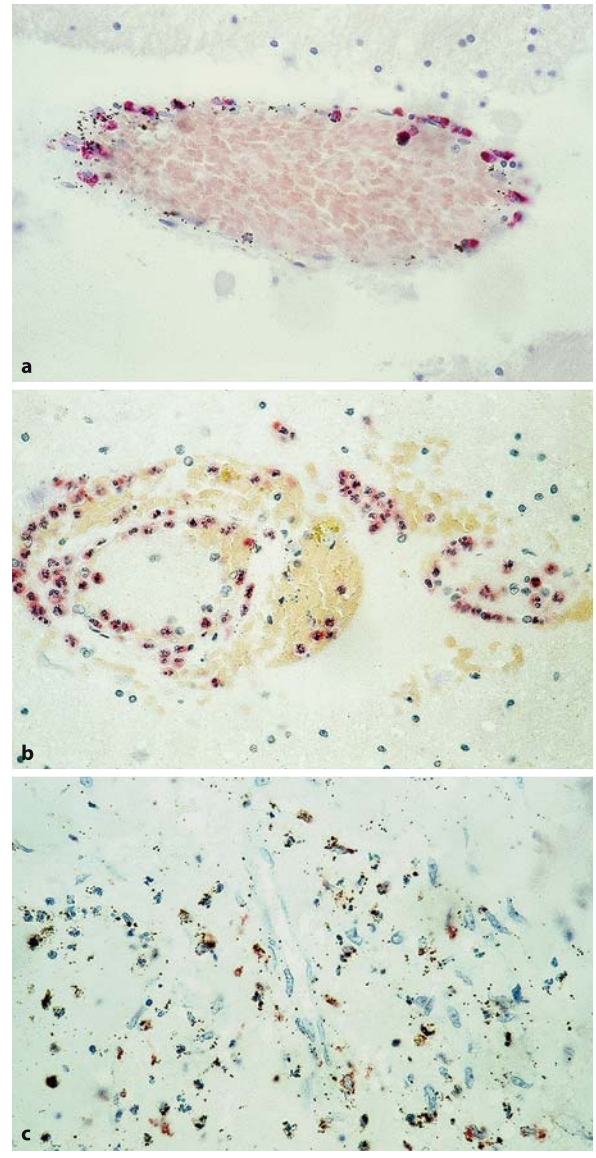

Fig. 9.7a–c. Leukocytic response. **a** Marginal leukocytes adhering at the inner vessel's wall; **b** emigrating leukocytes; **c** several leukocytes within the necrotic brain parenchyma (N-AS-DCIAE, magnification ×1,000)

the hemorrhage (Graeber et al. 1997) (Fig. 9.8). This reaction has been shown to follow a relatively consistent temporal course (Oehmichen and Raff 1980; Oehmichen et al. 1981, 1986; Lassmann 1997), but is unrelated to the site of axonal injury (Oehmichen et al. 1999a, b). An activation of resident microglia by upregulation of major histocompatibility complex (MHC) class II expression (Beyer et al. 2000), CD14 expression (Beschorner et al. 2002), as well as of the inducible nitric oxide synthase isoform (iNOS) have recently been shown, which results in an enhancement of their production of nitric oxide (Possel et al. 2000; Orihara et al. 2001).

The next phase is characterized by an activation and proliferation of *astrocytes* (Fig. 9.9). They provide structural, trophic, and metabolic support of neurons and modulate synaptic activity. Accordingly, the impairment of these astrocytic functions during the mechanical insult may critically influence the survival of neurons. The functions of astrocytes influence the glutamate uptake, glutamate release, free radical scavenging, water transport, and the production of cytokines and nitric oxide. Astrocytes may affect the ultimate clinical outcome by means of neurogenesis and synaptic reorganization.

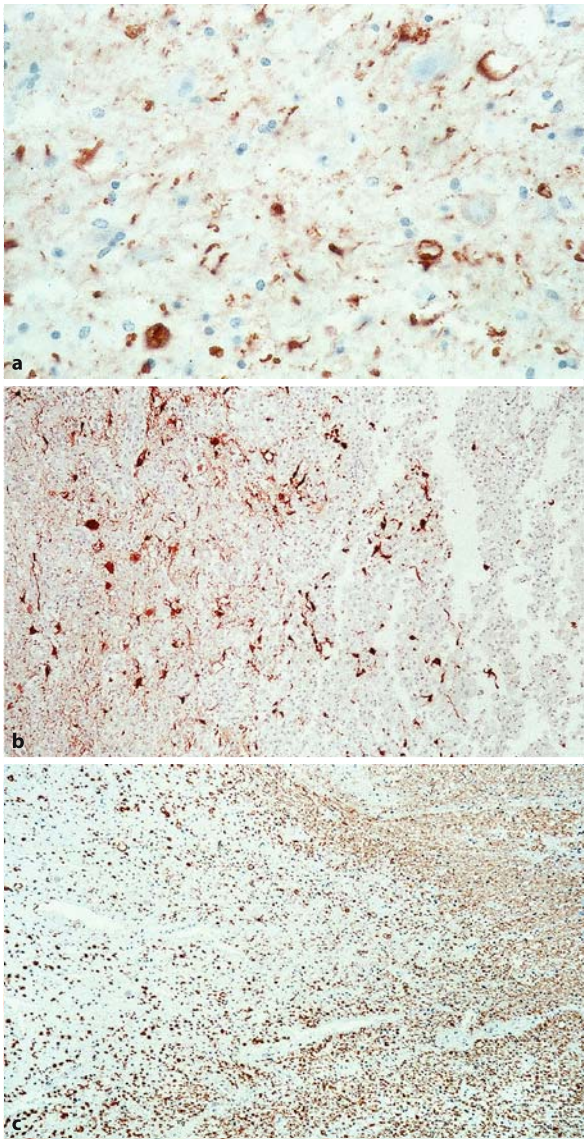

Fig. 9.8a–c. Macrophage response (immunoreactivity to CD68). **a** Early macrophage reaction at the site of the hemorrhage; **b** increase of number and immunoreactivity of macrophages; **c** massive invasion of macrophages replacing decomposed tissue (magnification **a** ×1,000; **b** ×500; **c** ×100)

Reactive alterations of astrocytes are characterized by the following criteria. At first, GFAP expression is upregulated only at the wound site, but later becomes widespread among astrocytes in the surrounding neuropil (Maxwell et al. 1990a, b) (Fig. 9.9a, b). The astrocyte activation proceeds very rapidly (Mandell et al. 2001) via the extracellular signal-regulated kinase (ERK) [mitogen-activated protein kinase (MAPK)] pathway. An in vitro model has demonstrated ERK/MARK activation within 2–10 min in cells near the wound edge. Injury-induced signaling to ERK/MAPK requires Ras, as demonstrated by specific blockade. Later the astrocytes are characterized mainly by a proliferation of fibers, exhibiting the features of so-called fibrous astrocytes.

Recently the regenerative activity of neuronal elements has also been discussed. Recent studies indicate the existence of progenitor cells and their potential neurogenesis in the subventricular zone and the hippocampus of the normal adult mammalian brain. Using markers for immature and mature astrocytes, activated microglia, neural precursors, and mature neurons, the proliferating cells did not express any of the cellular markers used, indicating that they have not yet begun to differentiate (Chirumamilla et al. 2002).

9.2.2.2 Necrosis

The pathogenesis and morphology of necrosis have been described above, as have the associated cytokine cascade and cell reactions (Chap. 4, pp. 56 ff). Here our remarks will be confined to the following issues.

Mechanical force with associated massive diffuse hemorrhage leads to a space-occupying situation in the cramped cranial vault. The resulting inadequate blood supply combines these factors to cause *ischemic cell necrosis*, including *primary neuronal death* (Kermer et al. 1999). This is accompanied by a breakdown of the transmembrane K^+/Na^+ ion pump due to a lack of ATP.

Expression of the *immediate early genes* (IEG) and release of cell adhesion molecules – heat shock proteins and cytokines – begin 30 min after wounding and can last for 6–12 h (Raghupathi et al. 1997). In the experimentally contused spinal cord, cytokine expression [*tumor necrosis factor* α *(TNF-α)*, IL-1β] was found to peak after 5–6 h (Semple-Rowland et al. 1997). When glial cells are exposed to injured or dead hippocampal neurons they release *TNF-α* (Viviani et al. 2000). This glial response may be induced by a primary neurodegenerative event involving the release of a neurospecific protein factor via activation of caspase.

The metabolic changes in the vicinity of brain contusion injuries were evaluated by means of proton magnetic resonance spectroscopy in comparison with histological alterations (Schuhmann et al. 2003). Creatine and phosphocreatine (–35%), *N*-acetylaspartate (–60%) and glutamate (–37%) immediately decreased after the incidence of MBI in the pericontusional zone and recovered at 7 days.

Another recent study (Stahel et al. 2000) found *TNF-α* and *IL-6* to exert an additional protective effect. The MBI-induced mortality of mice deficient in genes for these pro-inflammatory cytokines was significantly higher than that of wild-type animals. Since no differences were found in blood–brain barrier dysfunction, neutrophilic granulocyte infiltra-

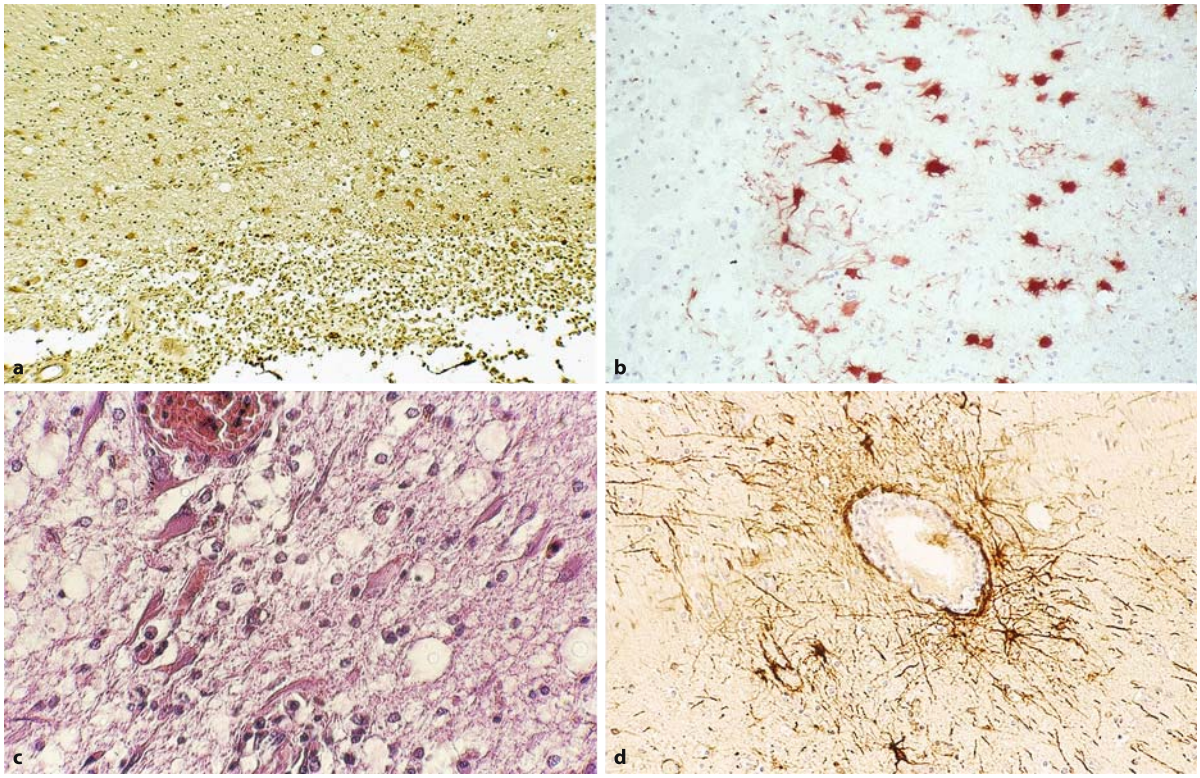

Fig. 9.9a–d. Astrocytic response. **a, b** Early response at the site of the hemorrhage demonstrating activated astrocytes (GFAP; magnification **a** ×100, **b** ×500); **c** demonstration of reactive astrocytes by H&E stain (magnification ×1,000); **d** the last stage of astrocytic reaction is characterized by increasing fiber production (GFAP; magnification ×500)

tion and/or neuronal cell death, the pathophysiological sequelae of the cytokines following MBI remain unexplained.

The cell reaction is indispensable for discriminating between necrosis and apoptosis: necrosis does not strike individual cells but entire areas supplied by the affected arterial vessels, i.e., cell groups and/or tissue areas. Necrosis is characterized by a primary immigration of neutrophils, followed by a secondary immigration of monocytes/macrophages and activation of resident microglia which scavenge the cell debris and myelin fragments in the necrotic area (cf. above – Chap. 3, pp. 28 f).

9.2.2.3 Apoptosis

MBI is regularly accompanied by apoptosis of neurons and glia (see also pp. 60 ff) together with the degeneration of cells demonstrating classic necrotic morphology (Clarke 1998; Raghupathi et al. 2000). Sharp et al. (1990) have shown that brain injury stimulates the *fos-antigens* and the *fos-dependent antigens*. The stimulation is mediated by *NMDA receptors*: brain trauma triggers the release of excitatory amino acids, which exert a depressive effect on the NMDA receptors (Smith and McIntosh 1995). The consequent depolarization stimulates the release of *fos* in the cortical neurons, enabling the neurons to adapt biochemically to the trauma. The primary trauma also activates specific genes belonging to the *bcl-2* gene family (which includes, e.g., *Bax, bcl-x*), which explains the phenomenon of apoptosis near the foci of hemorrhage (Yakovlev and Faden 1997).

Apoptosis begins 4 h after wounding and can be demonstrated for about 3 days thereafter (Yakovlev and Faden 1997). TNF-α and IL1-mRNA increase rapidly (20-fold) within 1 h after wounding. TNF-α levels begin to decrease again after 6 h, but IL6-mRNA levels continue to rise and do not normalize until after 3 days. A recent study found apoptosis occurring in white matter for as long as 1 year after setting head injury (Williams et al. 2001).

As described above, a cellular reaction after apoptosis is a rare occurrence. Neighboring cells phagocytose the cell debris. If there is extensive necrosis with a cellular reaction or a different type of inflammatory process, apoptotic leukocytes are phagocytosed by specific phagocytes, a phenomenon that has been termed "safe phagocytic clearance of dying, yet intact leukocytes undergoing apoptosis" (Platt et al. 1998). Rapid recognition, uptake, and degradation of the apoptotic leukocytes has been described.

9.2.2.4 ApoE-Genotype

It has been repeatedly (see pp. 105 f) shown that individuals differ in their reaction to (and prognosis following) closed brain trauma depending on their apolipoprotein E (*apoE*) *genotype* (Nicoll and Graham 1997). ApoE is thought to be responsible for the transportation of lipids within the brain maintaining structural integrity of the microtubule within the neurons and assisting with neural transmission. Possession of the apoE epsilon4 allele has been shown to influence neuropathological findings in patients who die from MBI, including the accumulation of amyloid β protein (Nathoo et al. 2003).

The number of apoE immunoreactive plaques has recently been shown to correlate with levels of β-amyloid 42(43) (Horsburgh et al. 2000). Additional evidence linking a history of brain injury and Alzheimer's disease comes from studies of retired boxers with dementia pugilistica subsequent to repeated brain injury (Roberts et al. 1990a, b). The apoE4 allele is the most important genetic determinant of susceptibility to Alzheimer's disease and acts synergistically with brain injury (Nicoll and Graham 1997). The suspected direct relationship between MBI and Alzheimer's disease (Gentleman and Graham 1997; Jordan et al. 1997; Teasdale et al. 1997) could not be confirmed in the recent large (6645 patients) prospective Rotterdam Study (Mehta et al. 1999). Moreover, the epsilon4 allele may either function as a risk factor for cognitive impairment in normal aging across a broad spectrum of domains or exert detectable effects early in a long prodromal Alzheimer disease trajectory (Bretzky et al. 2003). Moreover, from experimental and clinical brain injury studies it is evident that apoE plays an important role in the response of the brain to mechanical injury (Nathoo et al. 2003).

9.2.3 Pathology

The extent and type of clinical and morphological changes depend on the severity of injury.

9.2.3.1 Concussion Injury

The lowest grade of brain injury means "concussion" or "commotio cerebri," which produces a temporary loss of consciousness but no long-lasting neuronal deficits. The above mentioned definition (p. 177) of concussion is based largely on clinical findings (Congress of Neurological Surgeons 1966), its pathophysiological basis being yet poorly understood (McCrory and Berkovic 2001). The morphological appearance is characterized at most by signs pointing to a *slight increase in intracranial pressure*. Animal experiments have shown a temporary disturbance of the blood–brain barrier without attendant nerve cell loss (Povlishock et al. 1979). Marked or repeated mechanical injury of the brain produces submicroscopic *mitochondrial swelling* in the nerve cells and a *major breakdown in the blood–brain barrier*; these are sometimes the cumulative effect of repeated subthreshold blunt impacts (Bakay et al. 1977; Liu et al. 1979). Other experimental results suggest that shear strains within the brain caused by rotational accelerations can place physical stress on individual neurons (Holbourn 1945). Discussing all available theories, Shaw (2002) concluded in an excellent review that only the convulsive theory is readily compatible with all neurophysiological data and can provide a totally viable explanation for concussion injury. The chief tenet of the convulsive theory is that since the symptoms of concussion bear strong resemblance to those of a generalized epileptic seizure, then it is a reasonable assumption that similar pathological processes underlie them both.

It has recently been hypothesized that the functional failure associated with MBI is due in part to mechanoporation, the impact-induced deformation of the cell membrane's lipid bilayer resulting in ionic influx (Gennarelli and Graham 1998). The role of ion channel dysfunction is underscored by the finding that calcium channel subunit gene CACNA1A mutations are associated with fatal coma after minor brain wounding (Kors et al. 2001).

In this context, a further phenomenon is of interest: repetitive minor mechanical loadings to the brain have been shown to have a cumulative effect, especially in athletes engaged in contact sports such as American football and boxing (Cantu 1998) or in victims of repeated domestic violence (Roberts et al. 1990b), and child abuse (Duhaime et al. 1998; Lancon et al. 1998). Recently this phenomenon has been demonstrated in a new experimental model (Laurer et al. 2001). The risk of neurodegenerative disease in later life is elevated even if the initial injury did not produce long-lasting disability or impairment (Gentleman et al. 1993a, b; Jordan et al. 1997).

9.2.3.2 Contusion Injury

Contact-induced loading to the brain leading to tissue damage that induces cortical hemorrhages at the gyral crests is termed contusional injury. The term "contusion" is applied if the pia is not breached, the term "laceration" if it is torn. Contusional injuries and lacerations are both the result of the local brain tissue movements within the cranium (Graham et al. 1995). Mechanical loading to the head gives rise to neurological deficits and visible morphological

changes. The main injury is a *hemorrhage*, mainly of the *gyral crests of the cerebral surface* (Figs. 9.1–9.3, 9.6), especially of the gyri of the frontal basis, partly spreading to adjoining white matter. Macroscopically the hemorrhages appear streaked or pooled and are often confluent. The *microscopic changes* depend on *survival time* and the presence or absence of additional factors such as acidosis, hypoxia, hypotension, electrolyte disturbances, etc. The time-dependent morphological changes are useful in estimating the age of the hemorrhages, a common requirement in forensic pathology (see pp. 190 ff).

Homolateral cortical (focal) hemorrhages: cerebral *contusional injuries* are characterized by a combination of tissue and vascular disruption that is most severe at the crests of the gyri and extends into the white matter (Teasdale and Mathew 1996). Specific mechanisms of injury are associated with certain locations and patterns of contusional injury (see Sect. 9.2.1). Deformations of the skull creating a direct compressive strain exceeding the tolerance of the pial vessels and brain tissue will give rise to a contusional injury at the impact site (Fig. 9.1). Cortical hemorrhages opposite the impact site, formerly called *"contrecoup contusions"*, bear a morphological resemblance to their counterparts near the site of impact (Figs. 9.2–9.4).

The injury of the brain accompanying translational acceleration is primarily due to the differences in mass density of the skull and dura relative to the brain as described above, and not to strain deep within the brain as produced by angular acceleration. This explains why focal injuries such as cortical hemorrhages, intracerebral hematomas, and subdural hemorrhages do not always induce immediate loss of consciousness. The brain must be subjected to angular acceleration for diffuse axonal injury (DAI) and immediate loss of consciousness to occur (see Sect. 9.4).

9.2.3.3 Posterior Fossa Hemorrhage

Cerebellar cortical hemorrhages: cerebellar contusional injuries and hematomas result from substantial local pressure to the occipital area. The musculature of the neck, the massive occipital skull bone with its smooth and regular internal contours, the elastic tentorium of the cerebellum in combination with the "fluid cushions" of the subarachnoid cisterns and fourth ventricle constitute a "buffer" that greatly reduces the energy acting upon the cerebellum. Dorsal cerebral and cerebellar contusional injuries and hematomas are therefore much less frequent than cortical hemorrhages in other regions of the brain. But every infratentorial hemorrhage is capable of causing an obstructive hydrocephalus and herniation of cerebellar tissue into the foramen magnum and incisura tentorii. Therefore, the sequelae of posterior fossa hemorrhages may be fatal.

Cerebellar cortical hemorrhages were found in about 12% of 152 autopsies of victims of MBI (Gurdjian 1972). They occur in the gyral crests of the cerebellar surface, usually at the occipital poles. Clinical symptoms associated with cortical hemorrhages of the cerebellum include: ataxia, cerebellar flaccidity, dysarthria, dysmetria, resting and motor imbalance, elevated intracranial pressure, headache, stiffness of the neck, vomiting, and nystagmus. Primary *intracerebellar hematomas* are extremely rare. The paucity of symptoms renders clinical diagnosis difficult. Roentgenography often frequently reveals fracture of the occipital bone.

Posterior fossa *epidural hemorrhage* (EDH) comprise only 1.2–1.7% of all MBI cases in hospitals. The bone deformation caused by local impact to the occipital region can lead to a separation of the dura mater, with detachment of the sinus and superficial venous vessels. A posterolateral impact can produce a diastasis of the lambdoid or occipito-mastoid sutures or a fracture running between the midline and medial segment of the transverse sinus. Fractures of the posterior fossa are observed in 64% of posterior fossa EDHs (Glowacki 1991).

Cerebellar subdural hemorrhage (SDH) in the posterior fossa, a consequence of acceleration mechanisms, is associated with tearing of veins along the cerebellar surface. These tears are caused by the same biomechanical effects underlying SDH of the cerebrum and have a high mortality rate, especially in the acute stage.

9.2.3.4 Scar Formation

Degradation and scavenger mechanisms of the injured tissue and extravascular blood create a cystic cavity in the form of a glial-mesenchymal scar (Figs. 9.9–9.13) as well as a broad mantle of marked demyelination. On the margins, thin remnants of the molecular layer often extend beyond the shrunken schizogyric alteration on the cerebral surface (Fig. 9.12a, b). These marginal zones of the cortex often possess mineralized (ferruginated) neurons and astrocytes (Fig. 9.13). Gentleman et al. (1992) described diffuse β-amyloid-precursor-protein-positive plaques in some cases of extremely severe MBI after survival times of only 3 days.

9.2.4 Dating of Cortical Hemorrhages

Forensic practice often requires dating of contusional (and intracerebral) hemorrhages (cf. Müller 1930; Lindenberg and Freytag 1957; Krauland 1973;

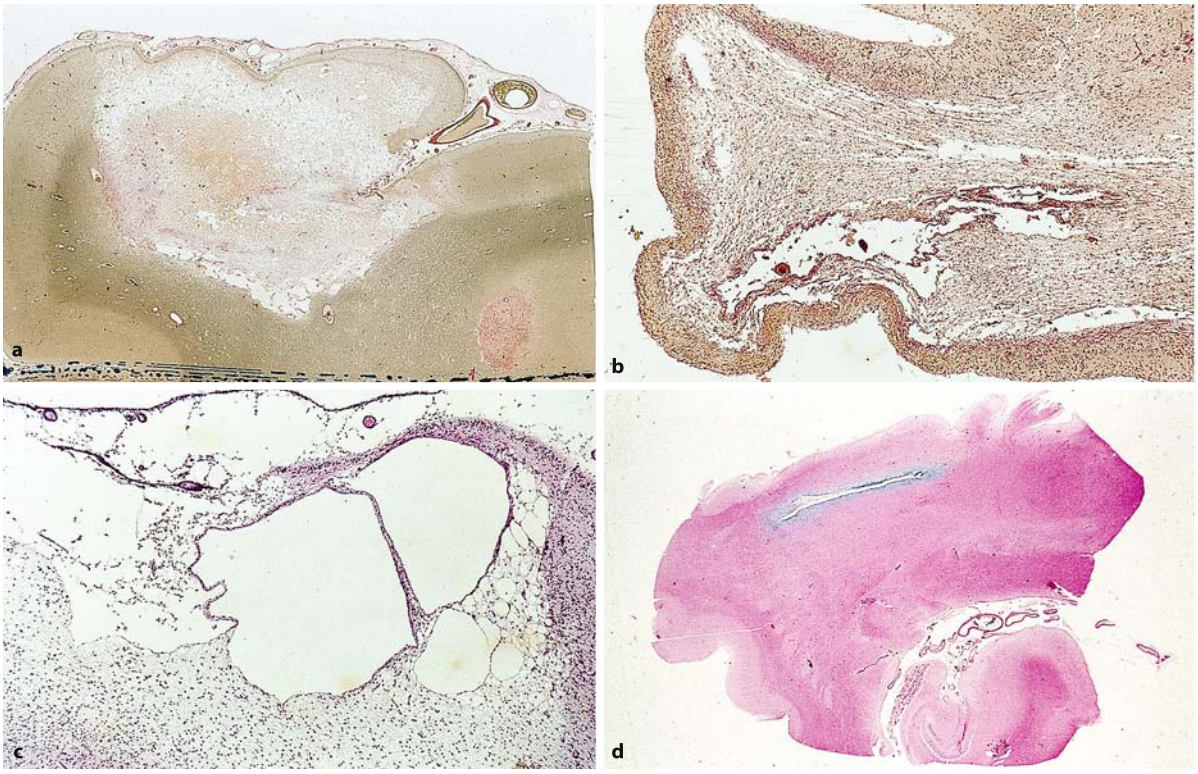

Fig. 9.10a–d. Scar formation process. The end phase of reactivity is characterized by a cystic scar produced by glial and collagenous fibers (**a, b** van Gieson, **c** H&E, **d** Prussian blue reaction; magnification **a–d** ×10)

Oehmichen and Raff 1980; Oehmichen et al. 1981; Oehmichen 1990; Hausmann 2002). A temporal classification is possible within certain limits based on neuronal degeneration and the leukocyte, glial cell, and mesenchymal reactions.

Analysis of more than 300 cases of mechanically induced cortical hemorrhage produced detailed statistical data regarding the individual phenomena, which will only be dealt with briefly here (cf. Oehmichen et al. 2003). The results may be transferred to timing problems in instances of intracerebral hemorrhages – within certain limitations. The temporal course is given in Table 9.4 and the following observations were made.

Primary mechanically induced hemorrhage is followed by three phenomena that occur simultaneously: (1) red blood cell flooding, (2) degeneration of neurons, axons, and white matter, and (3) emigration of leukocytes.

Red blood cells (Fig. 9.6) are the hallmarks of a vessel tear caused by mechanical injury. The degradation of the erythrocytes takes time and depends on the extent of the bleeding. Because of spontaneous rebleeding, which cannot be definitively ruled out, intact red blood cells are present for nearly 5 months after the initial blunt impact, but only in very rare cases.

The changes in the *degenerating neurons* (Fig. 9.14) consist of a cloudy swelling and/or a shrinkage and nuclear pyknosis. They become visible within the first few minutes after external violence to the brain. Ischemic nerve cell injury is uncommon. Over the ensuing hours and days, the neurons disappear, in part without a reaction, in part in the form of a satellitosis (after 4 h and 45 min at the earliest). Sometimes, however, they remain in loco and are mineralized in situ (ferruginated) for 6 days to several years.

Between 10 and 70 min after wounding, *extravasal polymorphonuclear leukocytes* (neutrophils) (Fig. 9.7) may appear within and around the hemorrhage. This phenomenon is especially conspicuous if perivascular bleeding is accompanied by neuropil destruction, i.e., if the hemorrhages are associated with destruction of brain tissue at the site of impact. The earliest neutrophilic emigration is seen as a reactive process in contusion injuries associated with subarachnoid hemorrhage. The number of neutrophils decreases during the first 3 days after wounding.

Macrophages and/or *activated microglia* (Fig. 9.8) are seen within 11–12 h (Oehmichen 1978). Their number increases during the ensuing 7–14 days, then their numbers decline again. In many instances, macrophages can still be demonstrated in the vicinity of the scar tissue years later.

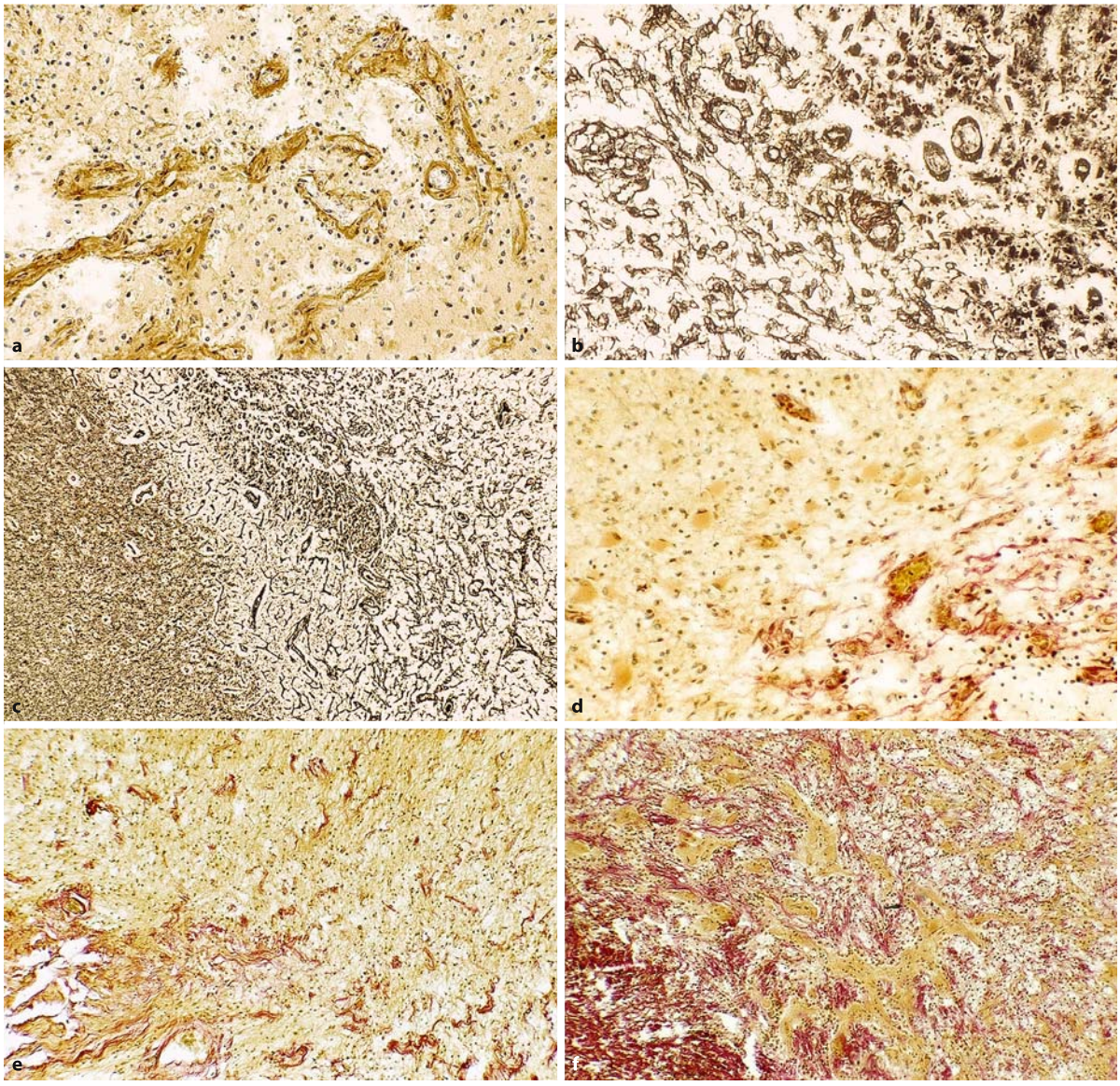

Fig. 9.11a–f. Scar formation process. **a, b** Endothelial proliferation associated with macrophages; **c–f** different stages of an increase of glial and collagenous fibers (**a, d, e, f** van Gieson stain; **b, c** Gomori stain; magnification **a, b, d** ×500, **c, e, f** ×100)

The behavior of *lipid-containing macrophages* over time is a function of the type of fat they contain (Oehmichen et al. 1986). The lipid within the macrophages is the result of myelin degradation. Using a myelin stain such as Luxol fast blue (Fig. 9.15) myelin-containing macrophages (Fig. 9.15b) are demonstrated. Intracellular neutral fat first appears 17 h post impact (Fig. 9.16a). Immunohistochemical demonstration of myelin debris (Lassmann 1997) can provide further information regarding the temporal course of the phagocytic process in brain macrophages.

1. In the acute phase of myelin breakdown, as a result of the traumatic event, the presence of immunoreactivity for both myelin oligodendrocyte glycoprotein (MOG) and myelin-associated glycoprotein (MAG) within macrophages is a reliable marker.
2. During the further digestion of myelin within macrophages the minor myelin proteins, such as MOG and MAG, are lost. The macrophages contain degradation products reactive for myelin basic protein (MBP) and proteolipid protein.
3. After 1–2 weeks, all myelin proteins have been degraded and macrophages contain only neutral lipids (Oil Red O). This stage may last up to 6 months. Other markers of early macrophage activation are the antigens 27E10 and MRP14 (Brück et al. 1995).

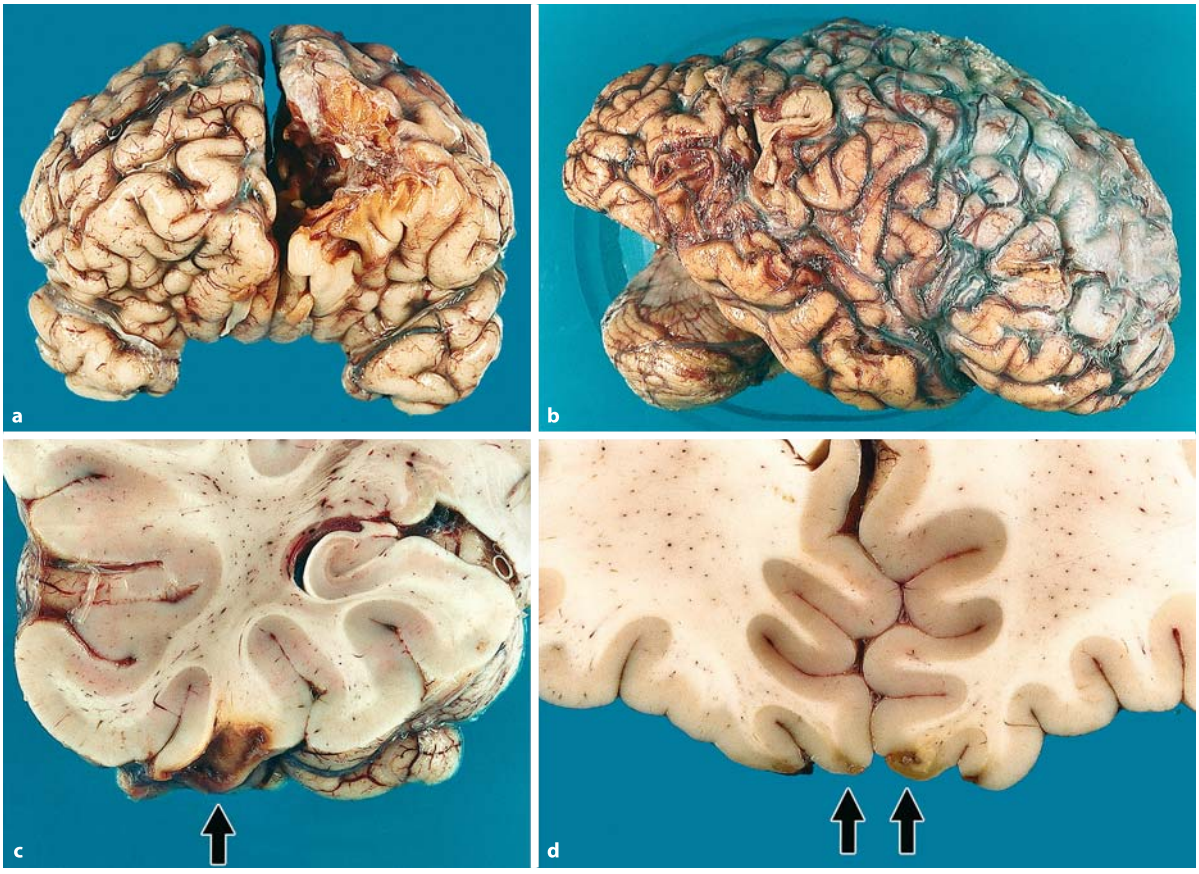

Fig. 9.12a–d. Macroscopic aspect of the final stages of cortical hemorrhages. **a** Cystic alteration of the left frontal pole with rust-colored mesenchymal tissue; **b** schizogyric alteration of the lateral parts of the right occipital, parietal, and temporal lobe; **c** cystic defect of the crest of the inferior temporal gyrus; **d** discrete color alteration at the crests of both the rectal and pararectal gyri as an indication of an old mechanically caused cortical hemorrhage

Hemosiderin-containing macrophages (Fig. 9.17) are easy to date since they almost always appear after 4–5 days, in rare cases after 3 days (Oehmichen 1976). *Hematoidin* as well as *hematoidin-containing macrophages* (Fig. 9.18) also follow a regular temporal course, becoming evident in frozen sections within 3–4 days, in paraffin sections after 12 days (Laiho 1995).

Some of the first signs of vital phenomena are alterations caused by *axonal injury* (Fig. 9.19), which can be demonstrated in single cases as early as 105 min after impact (Blumbergs et al. 1995) by expression of β-amyloid precursor protein (β-APP) by injured axons, and regularly after 3 h (in our own material after 2.75 h). The reperfusion during resuscitation may succeed in extraordinary cases to make axonal flow possible: in one case, a 20-min survival time was followed by a 90-min resuscitation attempt, which led to the incipient expression of β-APP in axons (personal observations; see also Gorrie et al. 2002).

As described by Zhao et al. (2003) *astrocytes* are marked by a loss of GFAP immunohistochemistry in rat ipsilateral hippocampal CA3 neurons within 30 min to 4 h after a traumatic event. Reactive astrocytes (Fig. 9.9) express GFAP and sometimes vimentin after only a 7-h survival time (Chen and Swanson 2003). Hypertrophic astrocytes can be demonstrated in the early days after wounding of the brain, in H&E-stained slides after several days. Primarily activated GFAP-expressing astrocytes evolve into fibrocytic astrocytes beginning on the sixth day post-impact, and by the conclusion of the degradation process they have formed a glial-mesenchymal scar.

Endothelial proliferation (Fig. 9.11) first becomes evident through the expression of proliferation markers on the third day after wounding. *Collagenous fibers* and *fibrosis* (Fig. 9.10) appear during the first 5 days and increase over the ensuing weeks. They constitute the end product of the healing process, namely a cystic scar.

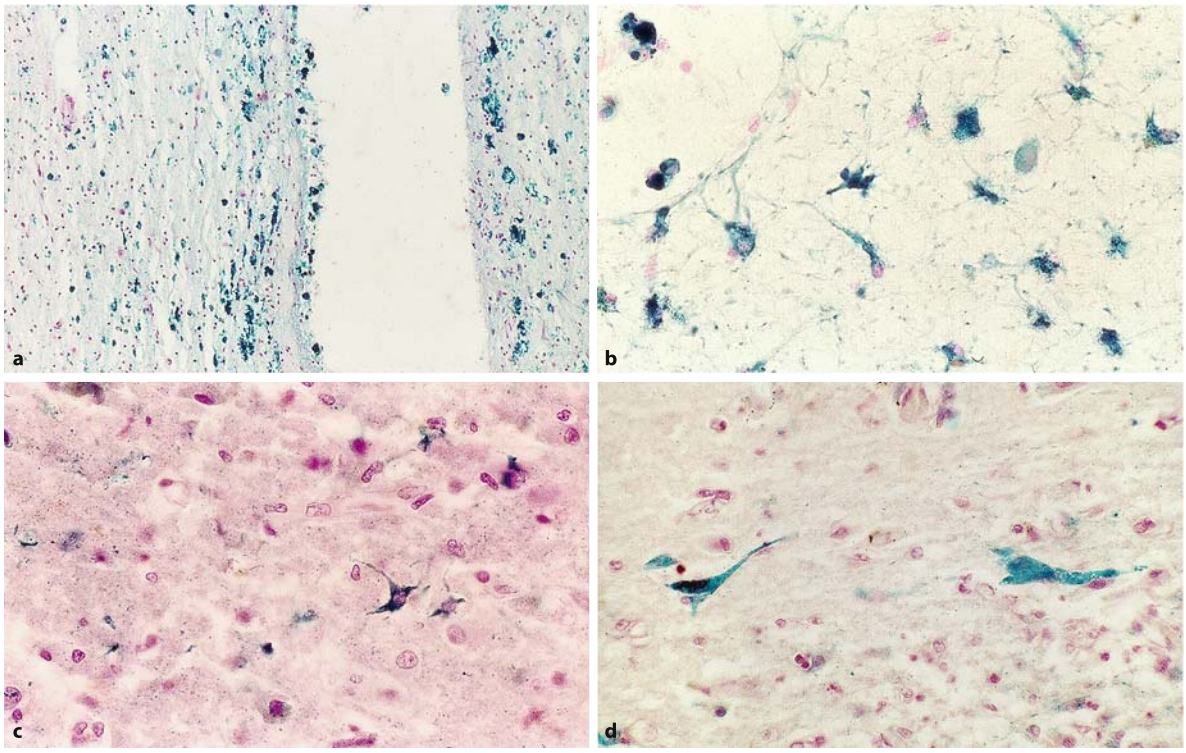

Fig. 9.13a–d. Mineralized astrocytes (**a, b**) and neurons (**c, d**) at the marginal zone of old brain wounds after MBI (**a–d** Prussian blue reaction; magnification **a** ×200, **b, c** ×500, **d** ×1,000)

9.3 Intracerebral Hemorrhages

9.3.1 Classification

External mechanical loading-induced primary intracerebral (and intraventricular) hemorrhages are more common than once thought. However, intracerebral hemorrhages may also sometimes occur spontaneously – i.e., without external violence – in the form of hypertensive massive hemorrhage (Chap. 28, p. 546) or the rupture of microangiomas (pp. 557 ff) or aneurysms (pp. 547 ff). Since external violence-induced and *spontaneous intracerebral hemorrhages* often have the same localization and since tracing the ruptured vessels can be difficult, the differential diagnosis must sometimes be based on other evidence, e.g., on the case history, on the influence of mechanical forces and its absence, on the demonstration of galeal hemorrhages or on the proof of additional cortical hemorrhages and/or the phenomenon of an association of homolateral and contralateral wounding of the brain.

Primary mechanically induced intracerebral hemorrhages originating in but not confined to the cortex (Fig. 9.20) occur in about 15% of all cases of MBI. Such hemorrhages often do not reach the brain surface, they rarely occur singly, and are typically located *in the depths of the hemispheres* (Jennett and Teasdale 1981).

Primary impact-induced intracerebral hemorrhages are also to be differentiated from secondary, i.e., delayed, "traumatic" intracerebral hemorrhages. Primary intracerebral and intraventricular hemorrhages result directly from mechanical force (positive/negative pressure, impulsive loading: traction and shearing forces). Secondary hemorrhages may also be caused by mechanical force, the primary injury being slight weakening of vessel walls; or a primary thrombosis is followed by ischemia in the area supplied by the occluded vessel; or violence-induced hemorrhagic shock results in disseminated intravascular coagulation (DIC) that gives rise to a blood coagulation disturbance.

The types of mechanically caused intracerebral hemorrhages are distinguished according to their localization and – partly – according to their pathogenesis:

1. Cortical hemorrhages (see Fig. 9.3–9.6) arise mostly from multiple ruptures of small arteries and arterioles in the cortex (Aa. corticales).
2. White matter shearing injuries (Fig. 9.20c), affecting the Aa. medullares: these injuries are rare and obviously can be caused in a manner similar to cortical hemorrhages (cf. Prokop and Göhler

Table 9.4. Dating of cortical hemorrhages according to cytologic and histologic criteria. Source: Oehmichen et al. 2003

Histomorphologic alterations	Observation period		Total number of examined cases during the observation period	Number of cases with morphological alterations	Relative frequency of the observation (expressed in %)	Estimated limits of confidence (Pearson and Tukey 1965) (expressed in %)	Distribution-free tolerance intervals with 95% reliability (expressed in %)
	First appearance	Last appearance					
Column	**1**	**2**	**3**	**4**	**5**	**6**	**7**
RBCs	1 min	150 days	305	237	77.70	72.6–82.3	98.0
Polymorphonuclear leukocytes	5 min	110 days	304	131	43.09	37.5–48.9	96.4
Macrophages (Ms)	11.5 h	58 years	305	223	73.11	67.8–78.0	97.9
RBC-containing Ms	12 h	150 days	303	145	47.85	42.1–53.6	96.8
Hemosiderin-containing Ms	4.2 days	44 years	305	162	53.11	47.3–58.8	97.1
Hematoidin	12 days	1 year	304	36	11.84	08.4–16.0	87.5
Lipid-containing Ms	17 h	30 years	220	118	53.64	46.8–60.4	96.0
Fibroblasts	4.4 days	9 years	305	104	34.10	28.8–39.7	95.5
Endothelial cells	3.9 days	53 years	305	149	48.85	43.1–54.6	96.9
Collagenous fibres	5 days	58 years	305	118	38.69	33.2–44.4	96.0
Gemistocytic astrocytes	7 h	35 years	305	139	45.57	39.9–51.3	96.6
Fibrillary gliosis	6 days	58 years	305	87	28.52	23.5–33.9	94.7
Hemosiderin-containing astrocytes	5 days	53 years	305	101	33.11	27.9–38.7	95.4
Neuronal destruction	1 min	150 days	305	183	60.00	54.3–65.5	97.4
Neuronophagy	4.8 h	125 days	305	67	21.97	17.4–27.0	93.1
Axonal swelling	2.8 h	125 days	49	19	38.78	25.2–53.8	77.4
Axonal balls	15 h	44 years	282	143	50.71	44.7–56.7	96.7
Mineralization of neurons	6 days	44 years	303	36	11.88	08.5–16.1	87.5

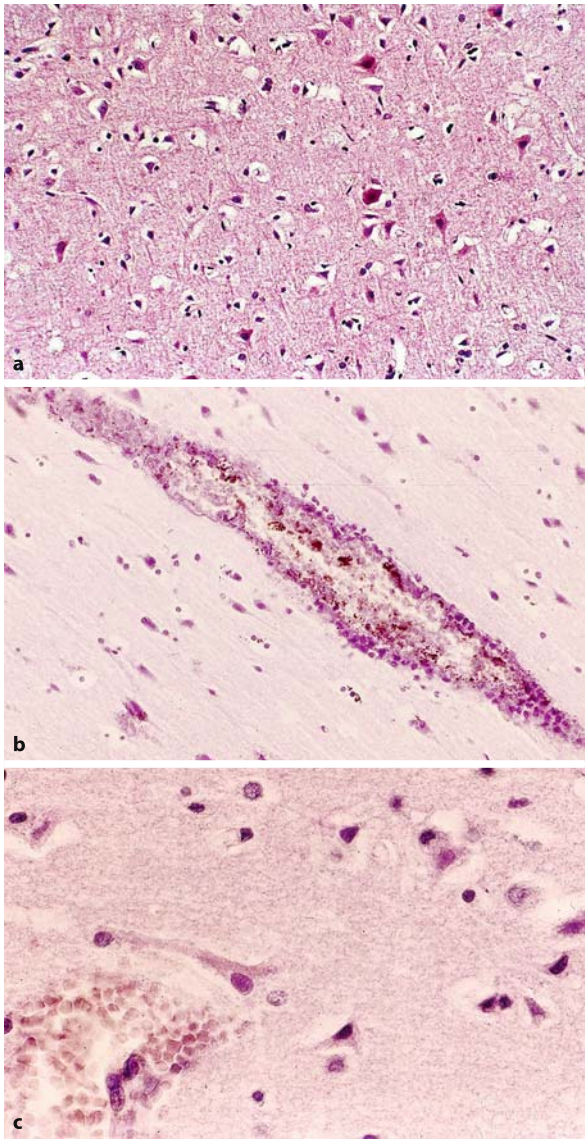

Fig. 9.14a–c. Degenerating neurons in mechanically caused cortical hemorrhages characterized by pericellular spaces, neuronal shrinkage,homogenous nucleus and dark-red staining of the cytoplasm (H&E stain; magnification **a, b** ×500, **c** ×1,000)

1976; Krauland and Bratzke 1980); they are associated with impact. The lesions can be homolateral, contralateral or disseminated.

3. "Gliding contusions" are a special form of hemorrhage (Fig. 9.21) usually caused by angular acceleration and occurring in the white matter of the first frontal gyrus (Adams 1992). They are – with exceptions – associated with SDH and/or DAI.
4. Cleft-like hemorrhages of the external capsule (Fig. 9.22) are commonly associated with acceleration mechanisms and thus frequently seen in combination with DAI.
5. Spherical hemorrhages in the basal ganglia (Fig. 9.20c) remain puzzling as, despite numerous hypotheses, no clear explanation yet exists as to their origin (Krauland 1982; MacPherson et al. 1986). Adams et al. (1986) have been able to show that patients with this type of hematoma rarely experience a lucid interval, and that gliding contusion injuries and DAI are often revealed on examination. They appear to have suffered diffuse brain injury caused by extreme mechanical forces.
6. Intraventricular hemorrhages which result from extremely severe impact in most instances cause a rupture of the subependymal veins.

9.3.2 Pathology and Differentiation

The morphology of intracerebral hemorrhage depends on its localization and extent as well as the specific histological-cytological reaction elicited by it. The localization and extent of the hemorrhage depend on the severity of the effecting violence applied, and the cellular reaction on the survival time (see also pp. 190 ff). The ruptured vessel(s) sometimes can be detected morphologically by careful examination of serial sections. The detailed histological search for ruptured vessels is usually a frustrating process, since the vessels within the hemorrhage can often no longer be traced. If they are found, the rupture in the vessel wall will be associated with fibrin deposits, possibly also aneurismatic dilatation of vessels' walls and reactive cells, such as macrophages and hemosiderin-containing macrophages (cf. Krauland 1982).

Two important sets of criteria for discrimination between different causes of intracerebral hemorrhages bear emphasizing:

1. Primary mechanically caused hemorrhage versus spontaneous hemorrhage.
   A primary mechanically caused hemorrhage is characterized by the following:
   - The age, since younger patients rarely suffer hypertonic massive hemorrhages or hyalinosis of the intracerebral vessels.
   - Bruising of the scalp, indicating impact.
   - The absence of pathological alteration of vascular walls (atherosclerosis, hyalinosis, etc.) and hemorrhagic diathesis.
   - The presence of additional, unequivocally mechanically induced hemorrhage, e.g., cortical hemorrhages on gyral crests.
2. Primary mechanically caused hemorrhages versus secondary hemorrhages (i.e., delayed mechanically caused hemorrhage, see Gentleman et al. 1989). Often the primary mechanically induced hemorrhage will overlap with a secondary

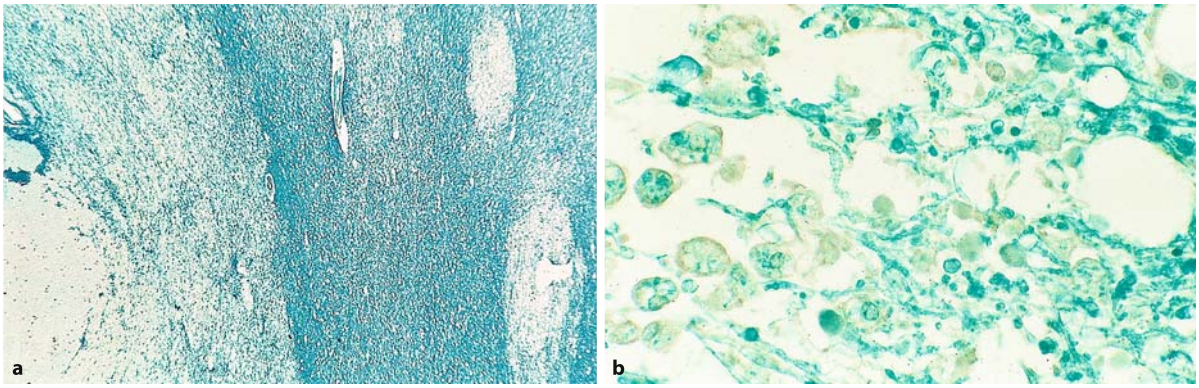

Fig. 9.15a, b. Myelin-containing macrophages (Luxol fast blue). **a** As a result of the ischemic process associated with a closed brain injury demyelination takes place (magnification ×100); **b** an increase of macrophages results from demyelination and the macrophages will contain intracytoplasmic blue-colored myelin (magnification ×1,000)

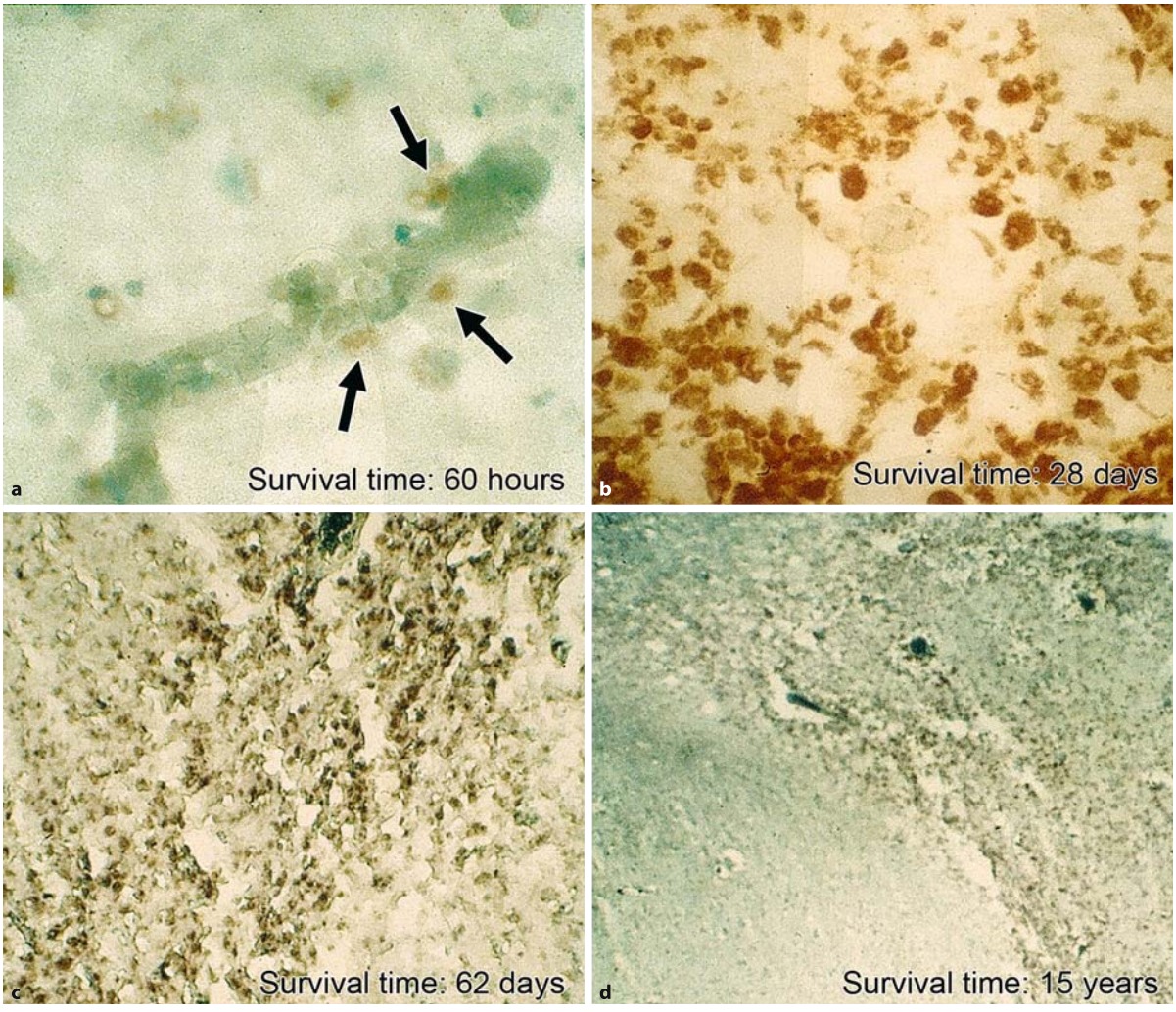

Fig. 9.16a–d. Lipid-containing macrophages (oil red O). The extent of lipid phagocytosis depends on the survival time after the traumatic event. **a** Single lipophages are seen perivascularly (magnification ×1,000); **b** several macrophages contain fat (magnification ×500); **c, d** a maximum of fat-containing macrophages is demonstrated at the border zone of hemorrhagic necrosis (magnification **c** ×300, **d** ×100)

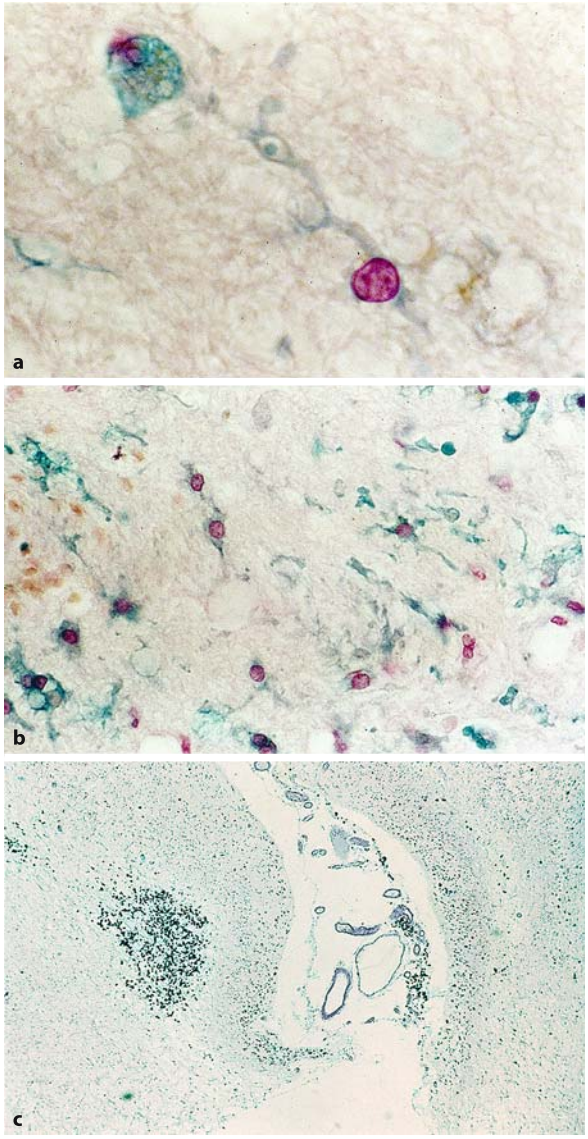

Fig. 9.17a–c. Hemosiderin-containing macrophages (Prussian blue reaction). **a** Very early ameboid-reactive macrophages containing erythrocytes and hemosiderin are seen (magnification ×1000); **b** hemosiderin-reactive macrophages which are characterized by processes and have the features of resting microglia (magnification ×500); **c** aggregated as well as diffusely distributed siderophages are demonstrated (magnification ×50)

hemorrhage due to DIC, increased blood pressure, or decreased intracranial pressure resulting from a subsiding posttraumatic brain edema. For a primary mechanically caused hemorrhage the following additional criteria must be considered:

- Clinical observations: disease course free of acute worsening of cerebral symptoms in the absence of other plausible pathophysiological explanations.
- Clinical and pathological symptoms of a primary or secondary coagulopathy have to be ruled out.
- Histological changes on the margin of the hemorrhage as well as at the site of the vessel rupture (if found), which are consistent with the survival time.

3. Mechanically induced delayed apoplexy.
   A form of secondary hemorrhage often mentioned in the literature is the so-called Bollinger's Spätapoplexie. If the primary injury is survived for weeks, months or years, hemorrhagic events can occur that obviously are causally linked to the initial trauma. Sometimes the link with the traumatic event must be assumed, although a direct causal connection cannot be confirmed. To do this however the following criteria must be met:
   - The hemorrhage must originate from a vessel located near the original site of the injury. The cause can be, for example, a loading-induced aneurysm.
   - Vascular disease capable of causing massive bleeding must be ruled out.
   - Illness-related or estrogenic coagulation disturbances must also be excluded.

In an individual case, it can be exceedingly difficult to distinguish between a primary injury and delayed apoplexy.

9.3.3 Brain Stem Hemorrhages

Classification and Pathology. Hemorrhages located in the brain stem have distinctive characteristics according to the biomechanical background, the corresponding clinical deficits, and the differential diagnosis. Primary mechanically induced brain stem hemorrhages are to be distinguished from secondary herniation-induced hemorrhages. Primary brain stem hemorrhages may be induced either by contact (skull fracture versus brain tissue) or – rarely – by non-contact, i.e., by indirect forces.

Clinical Features. Brain stem injuries have a *poor* prognosis; only a few cases survive (Fig. 9.23d), most cases die shortly after the occurrence of a hemorrhage. The surviving cases are partly characterized by a protracted coma. Clinically the following changes stand out, depending on the extent of the hemorrhage:

- *Midbrain syndrome*, characterized by loss of consciousness, increased muscular tension, spasms, atypical movements, minor respiratory, cardiac, circulatory and temperature dysregulation combined with impairment of eye movement and unreactive pupils.
- *Bulbar syndromes* are characterized by deep coma, slack muscle tonus, disturbed cardiac, cir-

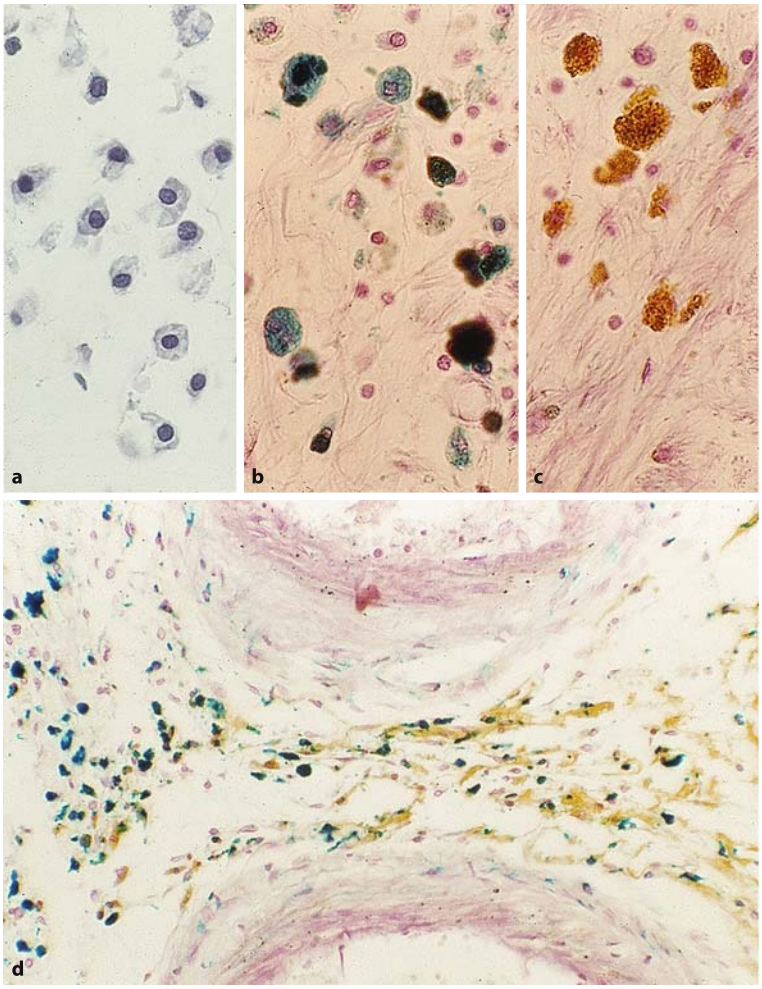

Fig. 9.18a–d. Hemosiderin and hematoidin as well as hemosiderin- and hematoidin-containing macrophages (Prussian blue reaction). While the first phase of the macrophage reaction will be an aggregation of ameboid macrophages without demonstrable phagocytized material (**a**), the second phase is characterized by siderophages (**b**), and the third phase by hematoidin-containing macrophages (**c**); during the last phase siderophages and hematoidin (**d**) may simultaneously be demonstrable (magnification **a–c** ×1000; **d** ×500)

culatory, and respiratory regulation; the sleep-wake rhythm is retained, postural and control reflexes are responsive, and there is an absence of reaction to external stimulation although the eyes are open.

- *Coma vigile* and/or apallic syndrome.
- *"Locked-in" syndrome* with tetraplegia involving cranial nerve palsy and loss of the sleep-wake rhythm with intact vertical eyeball and eyelid movement, but without loss of consciousness.

9.3.3.1 Primary Brain Stem Hemorrhage

According to Bratzke (1981) and Krauland (1982), mechanically induced (primary) hemorrhages at the base of the cerebral peduncles, at the base of the fourth ventricle, in the interpeduncular fossa, and/or in the rostral portion of the pons are primary loading-induced (non-contact) hemorrhages. They are thought to result from rotational acceleration-induced ruptures of small arteries and roots of Galen's vein. If there is an increase in supratentorial pressure, however, axial displacement of the brain stem can induce venous congestion and extravasation from the great cerebral vein, with a consequent overlapping of the primary and secondary hemorrhages (cf. Bratzke 1981).

Primary (contact) hemorrhages tend to be located at the margin of the midbrain (Bratzke 1981) (Fig. 9.23a) and are often associated with fractures of the base of the skull (Dirnhofer and Patscheider 1977). Most victims survive only briefly (Krauland 1982), although a few cases with long survival times have been reported.

In addition to hemorrhages, which are generally also *macroscopically* apparent, *necroses* and *axonal ruptures* can occur in the brain stem as well – in the absence of local hemorrhage in the brain stem. Acceleration loadings subject the brain stem to massive shearing forces, which upon rotation can lead – as described above – to tears of axons resulting in DAI as well as tears at the branching of the large basal arteries and thus to traumatic subarachnoid hemorrhage (SAH).

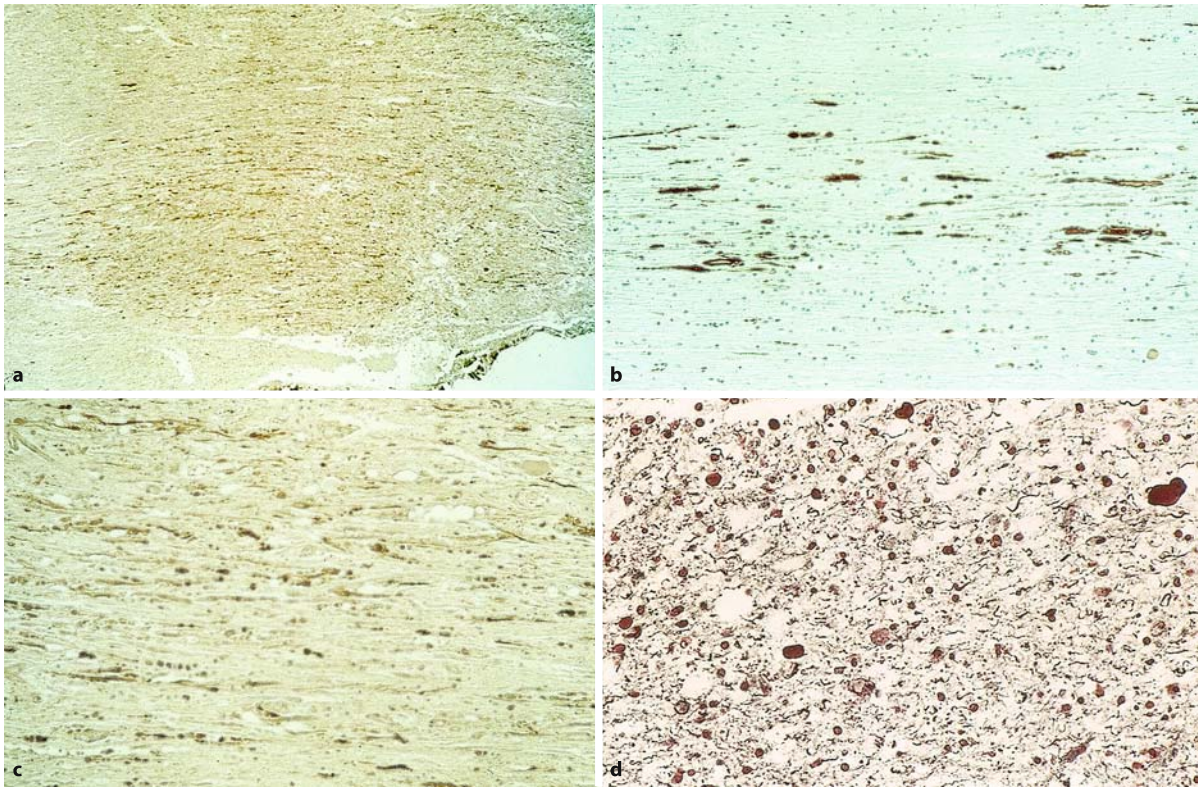

Fig. 9.19a–d. Axonal injury as demonstrated by antibody against β-APP after a survival time of >1.5–3 h for the first time (**a** magnification ×200; **b, c** magnification ×500), and by **d** silver technique (magnification ×500)

A distinction must be made between primary and secondary mechanically induced brain stem hemorrhages known under the terms of *Duret-Berner hemorrhage*: this is a microscopic hemorrhage near the third and fourth ventricles. Duret assumed that they are the result of an acute increase in intracranial pressure and of a contusion of the CSF with the ventricle wall. Today it is thought this represents a non-specific finding not attributable to mechanical processes (Unterharnscheidt 1993a, b). This is to be distinguished from the bleeding termed "Duret hemorrhage" in the American literature (Alexander et al. 1982; Knight 1996), which is a hemorrhage secondary to herniation of the midbrain and pons (see below).

9.3.3.2 Secondary Brain Stem Hemorrhage

Secondary brain stem hemorrhages are caused by a rapid increase in axial pressure produced by supratentorial space-occupying processes such as dura hemorrhages, intracerebral hemorrhages or severe cerebral edema (cf. Chap. 7, p. 123). Those expanding processes can unilaterally or bilaterally compress, displace, and distort the brain stem (Fig. 9.23b, c; see also Figs. 4.8a, 4.11a, 7.10e). Stretching of the upper pontine arteries and veins results in ischemia. Additional distortion leads to rupture and hemorrhage into the rostral portion of the pons and the midbrain. Sudden decompression of the intact ischemic pons may cause bleeding into the necrotic tissue. Lesions or masses that slowly expand or decompress permit adaptive reactions that may prevent subsequent massive hemorrhage. A further factor may also play a role, namely structural degeneration secondary to mechanical loading at a distant portion of the cerebrum, a supratentorial hemorrhage for example. A non-mechanically induced increase in axial pressure with a space-occupying process such as edema, tumor or spontaneous hemorrhage may also result in brain stem hemorrhage (an American type of "Duret hemorrhage").

Pathogenically, secondary brain stem hemorrhage is explained as follows:

- Venous congestion leads to bleeding in the middle portions of the brain stem. The hemorrhages are often located between the caudal parts of the substantia nigra and aqueduct. They occur if the arterial blood supply remains intact while venous drainage is impeded by the arrested supratentorial circulation (Matakas 1975). The *morphology* is characterized by bleeding and/or necrosis in the center of the brain stem, including lateral parts

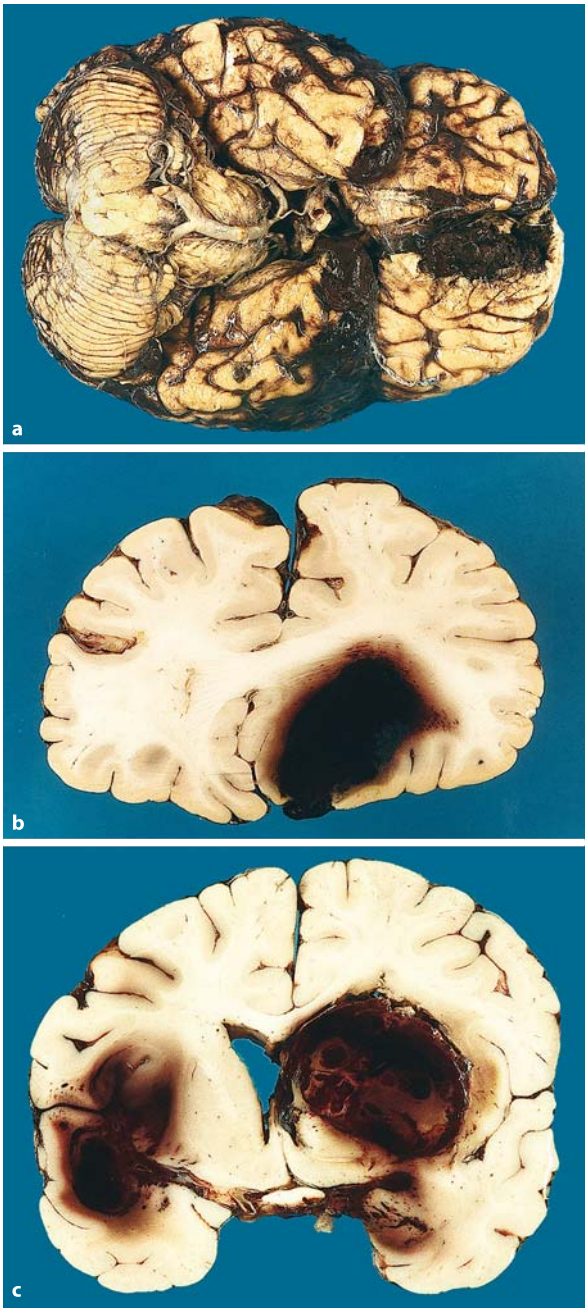

Fig. 9.20a–c. Intracerebral hemorrhages – two cases. **a, b** Extensive subarachnoid hemorrhage associated with an intracerebral hemorrhage, originating from a mechanically induced cortical hemorrhage at the frontal basis. **c** Two centers of hemorrhage – in the white matter (*left*) and in the basal ganglia (*right*)

of the pons (Fig. 9.23b), or of the periventricular tissues (Fig. 9.23c).

- The herniation process leads to tonsile strain of the horizontal running small arteries which supply the brain stem by pressure and capillaries will rupture.

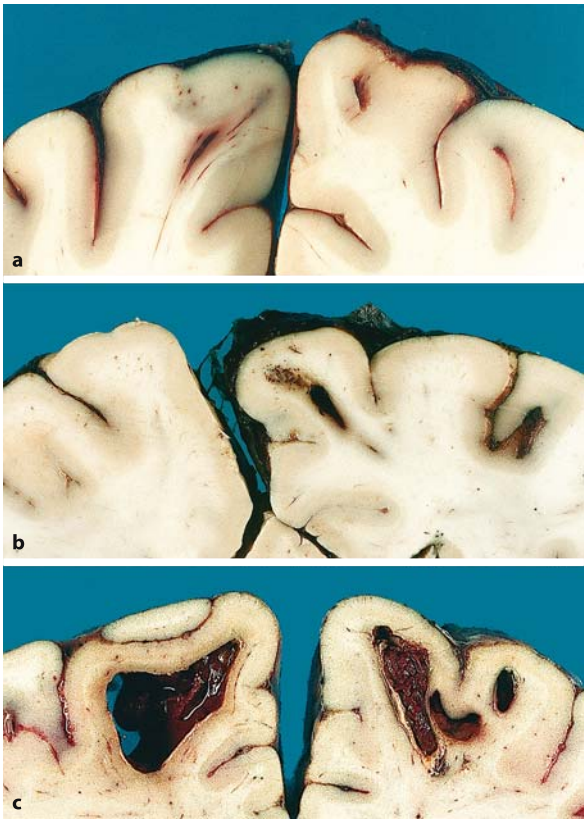

Fig. 9.21a–c. "Gliding contusions" in three cases as demonstrated by cleft-like hemorrhages in the white matter of the first frontal gyrus

9.3.4 Intraventricular Hemorrhage

Intraventricular hemorrhage requires extremely severe external violence to the head and carries a poor prognosis (LeRoux et al. 1992). In some instances, it is caused by impact along the sagittal plane of the head that increases the minor axis and thus the ventricular diameter. The resultant deformation of the skull can generate tensile strain of the subependymal veins. In rare cases, intraventricular hemorrhage can result from rupture of venous vessels of the fornix, corpus callosum, choroid plexus, and/or – very rarely – of subependymal arterial vessels. Intraventricular hemorrhages are almost always associated with DAI and tissue-tear hemorrhages, suggesting an additional mechanism involving angular acceleration-induced shear strain.

Intermediary Hemorrhage: (see the next section, Sect. 9.4).

Herniation Hemorrhage: (see below and Sect. 6.4.5).

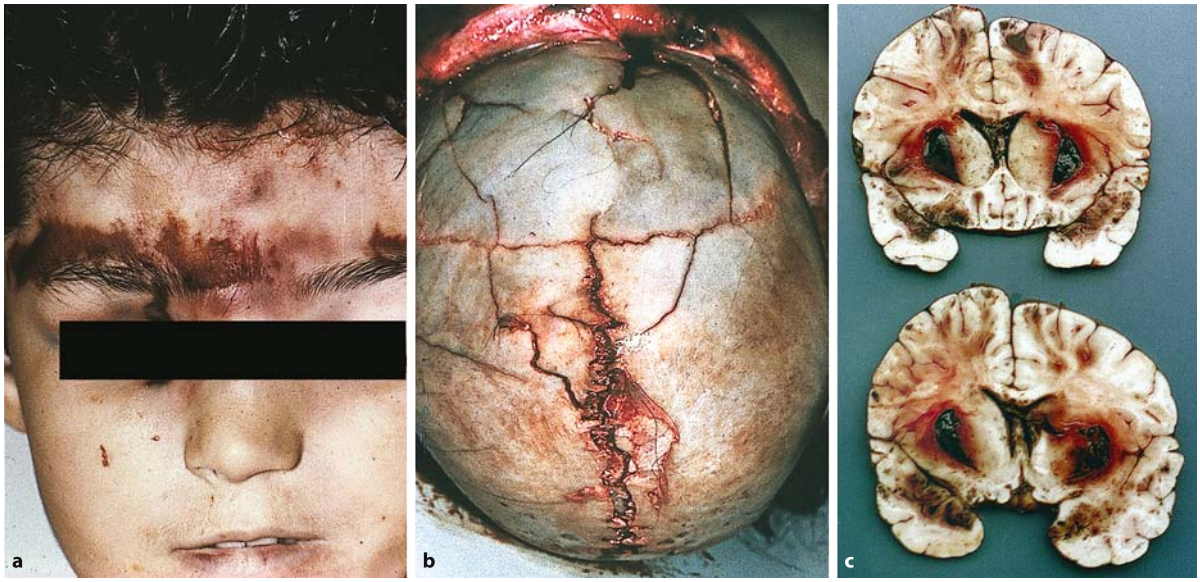

Fig. 9.22a–c. Massive, symmetric hemorrhages with cleft-like hemorrhages in both the external capsules (**c**), as the sequelae of an accelerating impact to the forehead by a car (**a**), with multiple fracture lines of the frontal bone (**b**)

9.4 Diffuse Brain Injuries

From a *clinical point of view* diffuse MBI is characterized in the post-wounding state by primary and secondary functional disturbances of the CNS. Diffuse mechanically induced injury may progress to permanent disability or to a fatal outcome.

These clinical phenomena are caused by *morphologic changes*, termed variously "intermediate lesions" (Lindenberg and Freytag 1960), "shearing injury" (Zimmermann et al. 1978), "inner cerebral trauma" (Grèeviæ 1982), "diffuse lesions of the white matter" (Strich 1961), and "diffuse axonal injury" (DAI) (Adams et al. 1982). Other entirely non-specific factors also contribute to the functional state of the CNS, particularly mechanically induced disruption of the blood–brain barrier, ischemia, and vascular injury. Several additional systemic influences also play a role, including electrolyte dissociation, acidosis, hyperhydration, dehydration, embolic processes, etc.

The macroscopic morphology is sometimes characterized by *brain swelling* and *hemorrhagic lesions*, which are located in the deep white matter, centered on the midline structures, usually in the periaxial, periventricular, and peduncular areas, or which occur as so-called gliding contusion injuries. The absence of such macroscopic findings does not rule out severe ischemia, edema or DAI. Microscopically, destruction of white matter by focal edema and demyelination are often seen in combination with axonal injuries, along the junction of gray and white matter.

A detailed study of the incidence and morphological picture of diffuse brain injuries was published by Graham et al. (1995; see also Adams et al. 1977) (Table 9.2).

9.4.1 Edema

Local edema may be induced directly by cortical hemorrhage. Experimentally it could be shown that an impact load creates an immediate *increase in the cerebral blood supply*, followed a few minutes later by a drop in cerebral blood flow to one-third of its normal volume; normalization begins after 40 min (Nilsson and Nordström 1977). During the brief initial increase in cerebral blood flow the oxygen supply to the brain increases; but this does not compensate for the subsequent drop in blood flow however. Among the sequelae is a disturbance of the blood–brain barrier, attributable in part to vasomotor paralysis leading to vasodilatation and vasogenic edema.

The presence of edema (Richard 1991) can be easily detected by computed tomography as early as 20 min after an external traumatic event (Kobrine et al. 1977). The pathogenesis of trauma-induced cerebral edema is poorly understood, but microthrombosis and chemokine influences may play a role. Depending upon how severely the blood–brain barrier is disrupted and the extent of tissue destruction, elevated *enzyme activity* can be demonstrated in the cerebrospinal fluid (Liu et al. 1979). Likewise, the severity of injury determines the amount of increase in *plasma catecholamine levels* (Nayak et al. 1980). Like

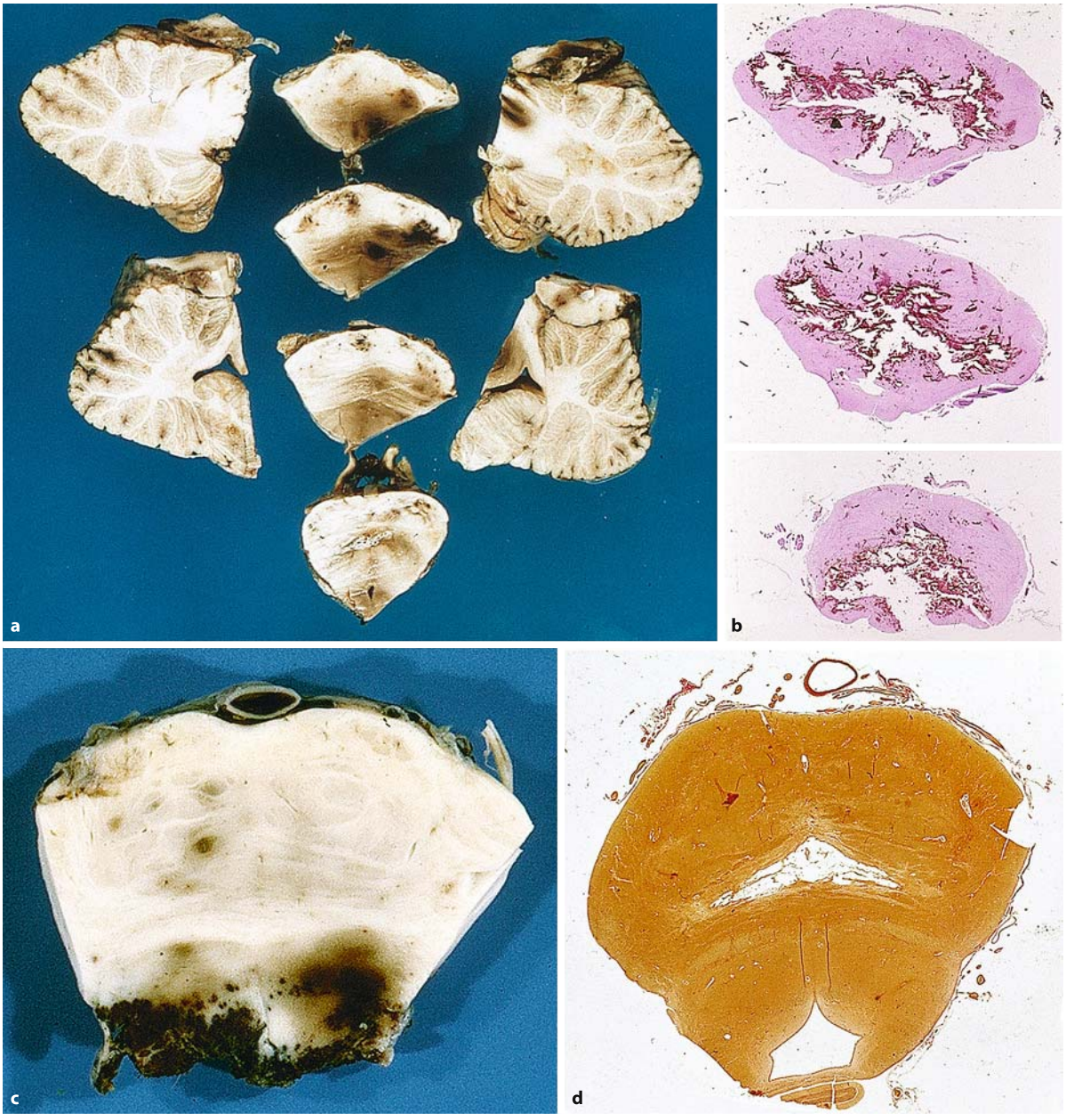

Fig. 9.23a–d. Brain stem hemorrhage. **a** Primary brain stem hemorrhage which is associated with fracture of the right part of the basal skull (primary contact injury); **b** acute secondary brain stem hemorrhage in the center of the pons, as well as **c** in the periventricular tissue associated with intraventricular hemorrhage; **d** cystic alteration in a case with secondary midbrain hemorrhage which was survived for several years

hyperglycemia, glycosuria, and increased *amino acid secretion*, they can be attributed to mechanical loading of the hypothalamic region and brain stem.

There exists a close association between edema of one cerebral hemisphere and ipsilateral SDH. Diffuse edema of both central hemispheres tends to occur only in children and adolescents (Graham et al. 1989a). It is not known why some patients exhibit increased intracranial pressure due more to the congestion created by the paralysis-induced vasodilatation than to disturbance of barrier function (see Chap. 4, pp. 42 ff).

Secondary changes caused by edema can be more important for understanding the development of clinical signs, especially the psychopathology of the post-contusional syndrome (see p. 105) and of the fatal process, than the primary injury. Morphologically, secondary sequelae of edema are found in the following regions of the brain (see also pp. 51 ff):

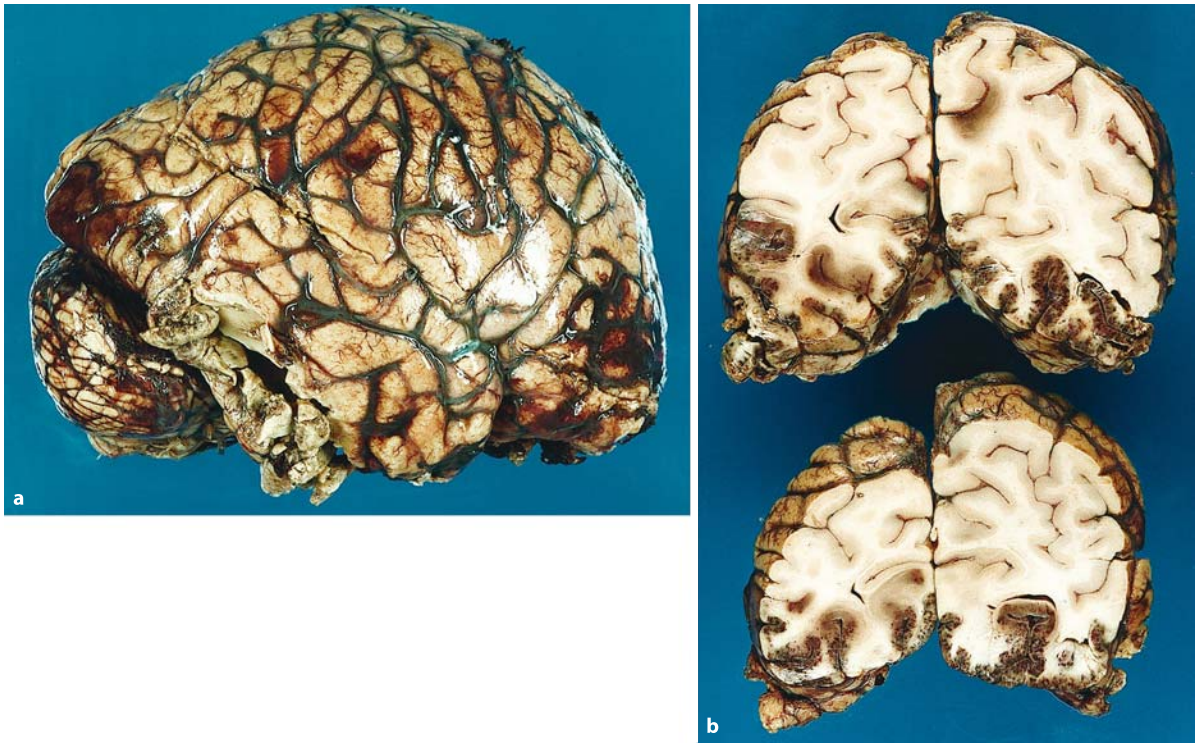

Fig. 9.24a, b. Bilateral secondary hemorrhagic infarct of the base of the temporal and occipital lobe caused by massive supratentorial mechanically induced brain swelling, which causes a compression of the occipital cerebral artery

- In the *mediobasal cortical areas* of the temporal lobes ("Liebermeister's furrow," which is caused by a rise in supratentorial pressure).
- In the *contralateral margins of the base of the cerebral peduncles* due to supratentorial pressure on the tentorial notch produced by unilateral displacement; the *localization* is diagnosed clinically by the presence of homolateral pyramidal signs.
- At the *top of the corpus callosum*, notched by the free edge of the falx cerebri and – with lateral displacement – notching of the cingulate convolution, sometimes combined with hemorrhage in the crest of the cingulate gyrus.
- In the *basal cortex of the temporal and/or occipital lobes* (uni- or bilateral), with possible extension to all associated cortical areas of these two brain lobes as a *hemorrhagic infarct* attributable to transient (or incomplete) compression of the occipital cerebral artery (Fig. 9.24, see also Fig. 8.10).
- In the case of infratentorial pressure, on the *dorsal surfaces of the cerebellar hemispheres* notched by the free edges of the cerebellar tentorium.
- In the *midbrain*, necrosis and bleeding caused chiefly by venous congestion in the medial sections of the pons.
- On the *cerebellar tonsils* resulting from a rise in supra- and/or infratentorial pressure with necroses; the tonsils may be hemorrhagically infarcted or exhibit necrotic changes due to herniation (Oehmichen 1994).
- A special type of late white matter alteration is a demyelination (Fig. 9.25) which is caused by perifocal or traumatic edema. The edema may be associated with a mechanically caused hemorrhage.

9.4.2 Ischemia

MBI gives rise to neuronal loss in the hippocampus, cortex, thalamus, and cerebellum independent of the sites of hemorrhages (Kotapka et al. 1992; Ross et al. 1993). A bilateral loss of hippocampal neurons, for example, was observed in 85% (Kotapka et al. 1992) or 90% (Graham et al. 1978) of fatal head injury cases as early as 48 h post-wounding.

Morphological signs of ischemia are more common in the basal ganglia and hippocampal area than in the cerebellar or cerebral cortexes. In a significant proportion of cases the ischemia is due to poor post-accident management, i.e., impossibility of an adequate stabilization of circulation or delayed re-

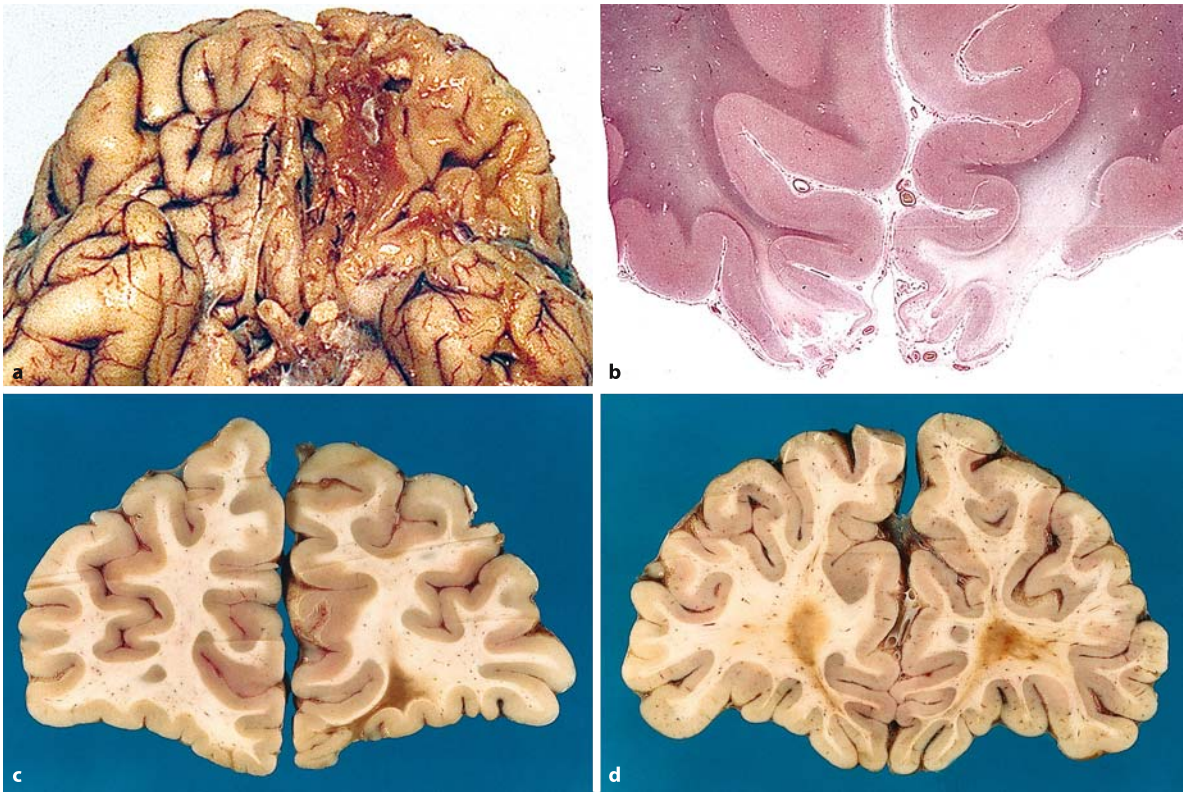

Fig. 9.25a–d. Demyelination caused by mechanical brain injury. **a** Close to the injury site there are schizogyric alterations, which are remnants of cortical hemorrhages in the frontobasal brain surface; **b** the demyelination is histologically seen, caused by perifocal edema; **c, d** moreover a demyelinating process also occurs without a primary hemorrhage as a result of edema necrosis (**b** van Gieson stain, magnification ×5)

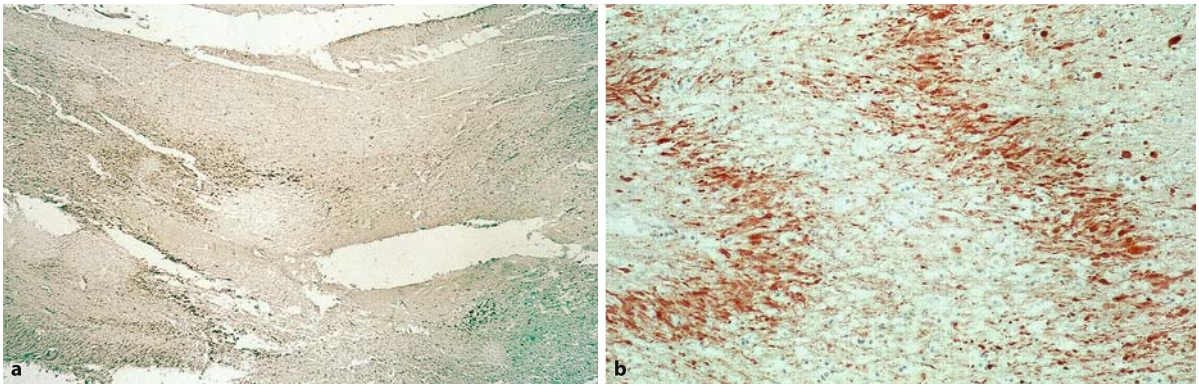

Fig. 9.26a, b. Diffuse axonal injury as demonstrated by axonal swelling and axonal bulbs in the corpus callosum (**a**) and midbrain (**b**) (β-APP reactivity; magnification **a** ×100, **b** ×1,000)

lease of cerebral compression from intracerebral hematomas and/or failure to properly treat respiratory disturbances, cardiac arrest, status epilepticus (Graham et al. 1989b) or hypotonia. The main predictors of mortality 12 months post impact are the duration of hypotension, pyrexia, and hypoxia (Jones et al. 1994).

9.4.3 Axonal Injury

Axonal injuries (AI) occur both in the area of the bleeding (focal axonal injury) and at remote sites. In the latter instance they sometimes occur as diffuse axonal injury (DAI – see Povlishock 1992; Gennarelli

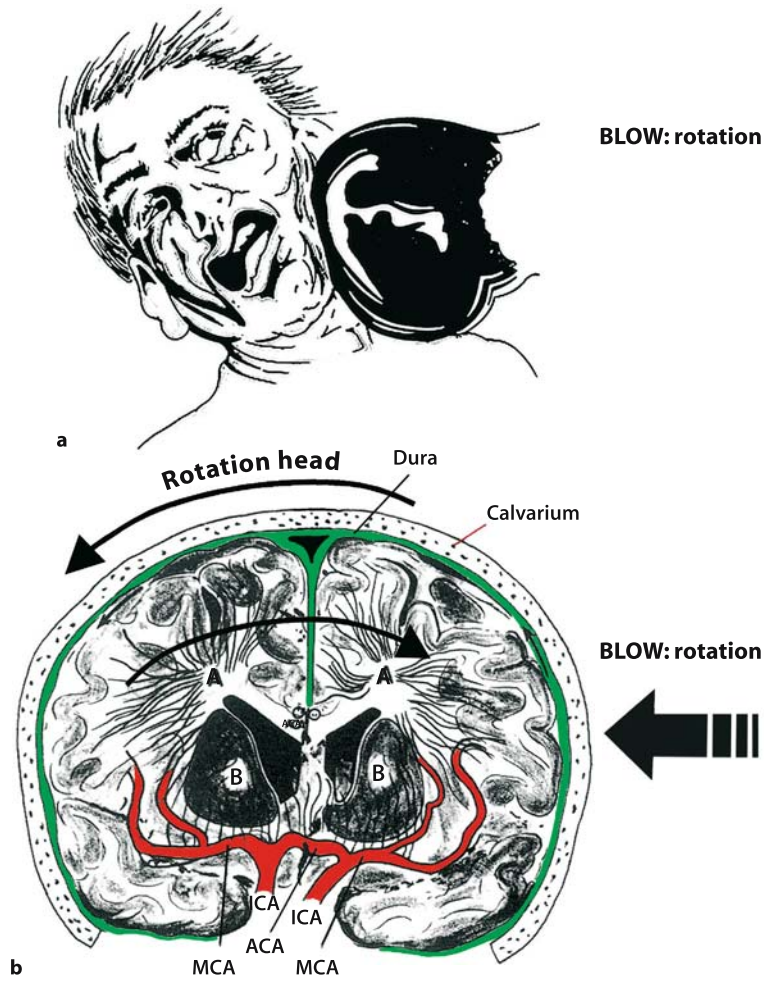

Fig. 9.27. Diffuse axonal injury is caused by angular and/or translational acceleration (*ACA* anterior communicating artery, *B* basal ganglia, *ICA* internal carotid artery, *MCA* middle cerebral artery)

et al. 1998) concentrated along the midline structures, e.g., in the corpus callosum, septum pellucidum, fornix, tela chorioidea (Blumbergs et al. 1995), and in the midbrain, pons, and hippocampus (Adams et al. 1982) (Fig. 9.26). Today's immunohistochemical methods (β-APP – Gentleman et al. 1993a, b; Sheriff et al. 1994) can consistently demonstrate axonal injuries 105–180 min after wounding (Oehmichen et al. 1997). In two children, axon swelling was visualized by Gorrie et al. (2002) in the internal capsule after only 35–45 min of survival. Moreover, there is a significant correlation between axonal swelling size and survival time (Wilkinson et al. 1999) as confirmed by Leclercq et al. (2002). However, Leclercq et al. (2002) suggest the large variability in swelling size within individual cases and the heterogeneity of the original trauma seriously comprise the utility of such information in the timing of lesions.

However, axonal injuries are sometimes a delayed phenomenon due to interruption of intra-axonal transport (Povlishock 1997). Expression of β-APP in particular is not an indication of axonal transection at all and not all β-APP-positive axons are irreversibly damaged (Povlishock 1997).

DAI is caused by angular or rotational and/or translational acceleration following impact of the head, which exposes the axons to transient tensile strain (Fig. 9.27). Impact as well as acceleration of the head can generate impulsive loading of sufficient magnitude to produce DAI (Gennarelli and Meaney 1996). The severity of DAI correlates with the magnitude, duration, and speed of onset of the angular acceleration as well as the direction of head motion (Gennarelli and Meaney 1996). DAI is produced by longer acceleration loading than that which generates SDH and is caused by the head colliding with a relatively soft, broad object (e.g., an automobile dashboard – see Gennarelli and Thibault 1982). Equivalent magnitudes of angular acceleration applied to the primate head readily induced DAI if accelerated laterally, less readily upon oblique or sagittal acceleration.

DAI is the result of shear and/or tensile strains caused by the brain tissue movements in contrast to the static structures of falx and tentorium during angular acceleration occasioned by lateral movement of the brain tissue (Gennarelli and Meaney 1996). The prognosis for functional recovery depends largely on the extent and location of DAI.

Tissue-tear hemorrhages are sometimes associated with severe DAI and constitute small areas of hemorrhage located parasagittally in the deeper regions of the brain (Strich 1961). Because gray matter is denser than white matter, the interface between them is particularly susceptible to shearing forces generated by angular acceleration. Geometric irregularities of the skull, intracranial partitioning membranes such as the falx cerebri and tentorium, and the plane of motion of the head all help to determine the location of these lesions. As discussed above, tissue-tear lesions in the frontoparietal white matter are termed "*gliding contusion injuries*" (see Fig. 9.21).

Axonal injuries also occur secondary to hypoxic injury, which may also be the consequence of an impact (Jellinger 1977; Kaur et al. 1999; Oehmichen et al. 1999a, b; Niess et al. 2002). It is sometimes impossible to determine retrospectively whether the axonal injury is primary or secondary. Secondary axotomy in most cases is delayed until some hours after wounding of the brain (Maxwell et al. 1993). In addition to axonal injuries, which have been relatively well studied, a mechanical dendrite injury is also possible but has been studied by only a few authors (Li et al. 1997).

9.4.4 Vascular Lesion

Diffuse forms of vascular lesions are:

1. Mechanical lesions, which can lead to disseminated hemorrhages.
2. Vascular spasms, which reduce the regional (or the total) blood flow within the brain.
3. Microthrombi, which give rise to secondary ischemia.

Primary mechanically induced intracerebral hemorrhages occur in the form of disseminated petechiae located mainly in the white matter of the frontal and temporal lobes as well as in the brain stem (Adams 1992). They probably result from acceleration mechanisms associated with rupture of minute vessels.

Ischemic lesions secondary to vasospasms: the temporary increase in cerebral blood supply that immediately follows brain wounding as well as the hemorrhages lead to more or less extensive generalized spasms of the brain vessels (see above). The 1000 times greater affinity of ferrous heme for nitric oxide, a potent vasodilator of cerebral vessels, than to oxygen has led to the concept that hemoglobin scavenges nitric oxide and produces delayed cerebral vasospasm (Pluta et al. 2001). It is not known how long the spasms last, or what factors influence their duration. Rather than inducing changes in vessels, the spasms cause secondary, variably severe regional hypoxic (and edematous) changes.

Thrombus formation (Fig. 9.28) is a special form of diffuse MBI (Keimowitz and Annis 1973; Goodnight et al. 1974; Drayer and Poser 1975; Hekmatpanah 1987). The area around cortical hemorrhages almost always contains a few thrombosed vessels, the lesions are caused by local vessel wall damage, and mechanically induced microaneurysms. One of the most common responses to tissue damage is the aggregation of platelets and formation of thrombi (Weller et al. 1983), apparently due to the aforementioned temporary generalized vasospasms (Cervós-Navarro et al. 1984; Susi and Walls 1990; Suzuki et al. 1990), sometimes acting in combination with the sequelae of DIC (Keimowitz and Annis 1973).

Obrenovitch and Hallenbeck (1985) showed that cerebral microthrombosis reduces blood flow to the brain, disrupts the blood–brain barrier, and inflicts structural damage on neurons and glial cells. Huber et al. (1993) demonstrated a major increase in fibrinous microthrombi in human brains following severe MBI, especially 2–9 days after wounding of the brain.

Microthrombi may also be influenced by an increase in platelet-activating factor (PAF), a biologically active phospholipid reputed to be a mediator in central nervous system injury (Feuerstein et al. 1990). The formation of microthrombi, aggravation of brain edema (Ishige et al. 1987), and cerebral hypoperfusion (Arvigo et al. 1985; Dickman et al. 1991) are all thought to be triggered in part by PAF (Snyder 1989; Feuerstein et al. 1990).

As already mentioned above a *secondary arterial occlusion* may follow compression by a supratentorial space-occupying process, i.e., edema, hematomas, tumors, etc.; a compression of the posterior cerebral artery in association with unilateral or bilateral uncal herniation often causes a hemorrhagic infarct of the occipital lobe (Fig. 9.24).

9.4.5 Boxing Brain Injury (Punch Drunk Syndrome)

Impact has been implicated as a cofactor in the genesis of a number of progressive degenerative diseases (Strich 1976): dementia of *Alzheimer's type* (Hollander and Strich 1970), *Pick's disease* (Kosaka et al. 1982), *Parkinson's disease* (Grimberg 1934), *amyotrophic lateral sclerosis* and *Creutzfeldt-Jakob disease* (Behrmann et al. 1962). The inner and outer atrophies as well as the neuronal loss are thought to result from single or repeated episodes of subarachnoid hemorrhage.

Of special interest in this regard is the examination of the brains of former *boxers*, both amateur and professional, who have suffered *repeated knock-outs*. They are especially likely to develop both neurological symptoms and *progressive dementia* (Corsellis 1989) years after the last boxing-related traumatic event. A

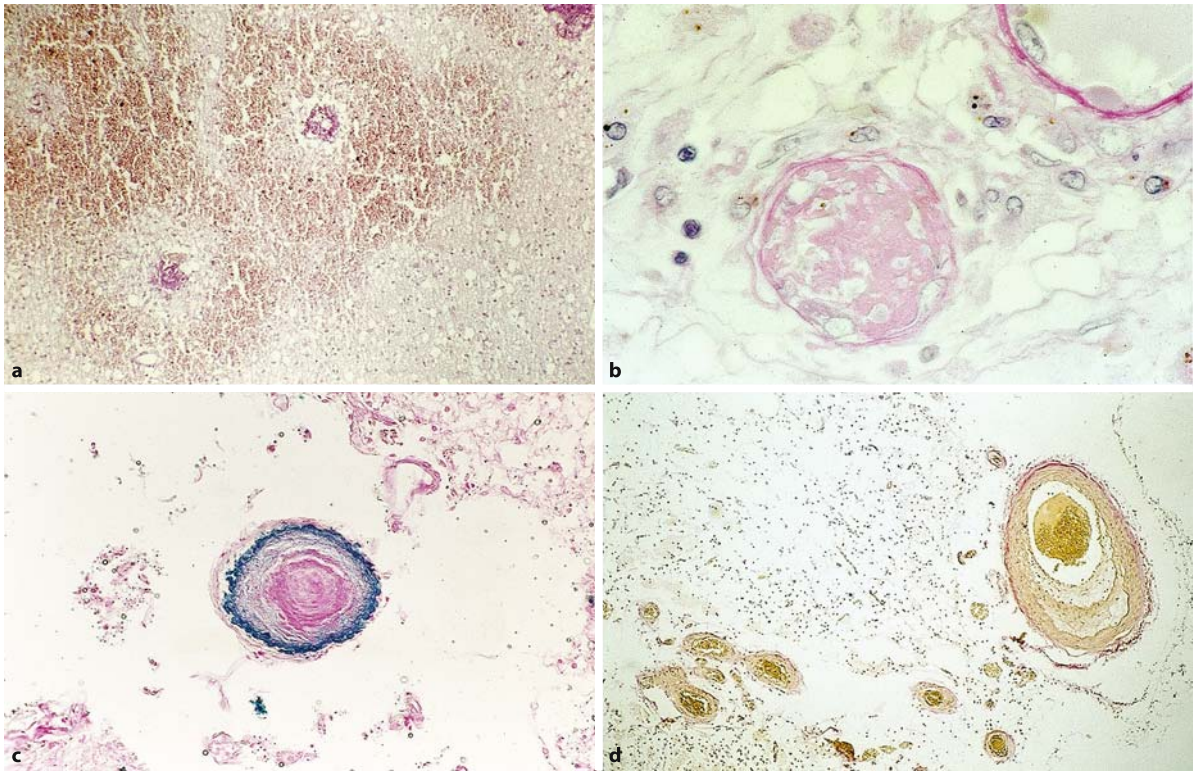

Fig. 9.28a–d. Vascular lesions near mechanically caused hemorrhages. **a, b** Intravasal fibrin precipitation (**a** H&E, magnification ×100; **b** PAS, magnification ×1,000); **c** thrombotic occlusion of an arterial vessel (Prussian blue reaction, magnification ×300); **d** angiostenosis of an artery within a posttraumatic cyst (van Gieson stain, magnification ×300)

detailed examination of 15 brains of boxers (Corsellis et al. 1973) revealed conspicuous changes in the *septum pellucidum* with enlargement of the cavum and *fenestration of the interventricular septum*. In a few cases the adjacent fornices and corpus callosum were thinned, there was a *loss of nerve cells in the cerebellum*, *degeneration of the substantia nigra*, and numerous *neurofibrils* in the nerve cells of the cerebral cortex and brain stem. Senile plaques were almost entirely lacking. A subsequent reexamination of the same 15 brains confirmed the presence of *amyloid-beta protein* (β-A4-amyloid) in the form of diffuse senile plaques in the cortex, revealing a close resemblance to dementia of Alzheimer's type (Roberts et al. 1990a, b; Tokuda et al. 1991; Gentleman et al. 1992).

The new imaging techniques allow one to visualize preclinical signs of chronic, repetitive head blows. Performing diffusion-weighted imaging in 24 boxers, Zhang and his team (2003) measured the diffusion values. This team stated that the values in the boxer group were significantly higher than those measured in the control group. The most common MR finding in the boxer group was a volume loss inappropriate to the age followed by cavum pellucidum, subcortical white matter disease, and periventricular white matter disease. These global findings can exist even when routine MR findings are normal.

9.5 CNS Involvement in Mechanical Injury without Primary Brain Injury

Even without primary mechanical injury of the CNS, the brain can be involved and affected by a generalized multiple impact injury (poly-traumatization), mainly the sequelae of hemorrhagic shock, embolism, and/or ischemia. *Edema* and/or *ischemic/hypoxic damage* are discussed elsewhere (pp. 202 f and 204 f).

9.5.1 Fat Embolism

Pathogenesis. As a consequence of bone fracture or crush injury to fat tissue in the pulmonary circulation a massive invasion of fat droplets can occur, increase the vascular resistance and lead to *subsequent right ventricular failure*. If this condition is survived, after an interval of 18 h to 4 days the patient is at risk of a cerebral fat embolism, which can ultimately lead to death or contribute to the fatal event. If fat emboli pass through a patent foramen ovale of the heart or pulmonary arteriovenous shunts, the fat droplets

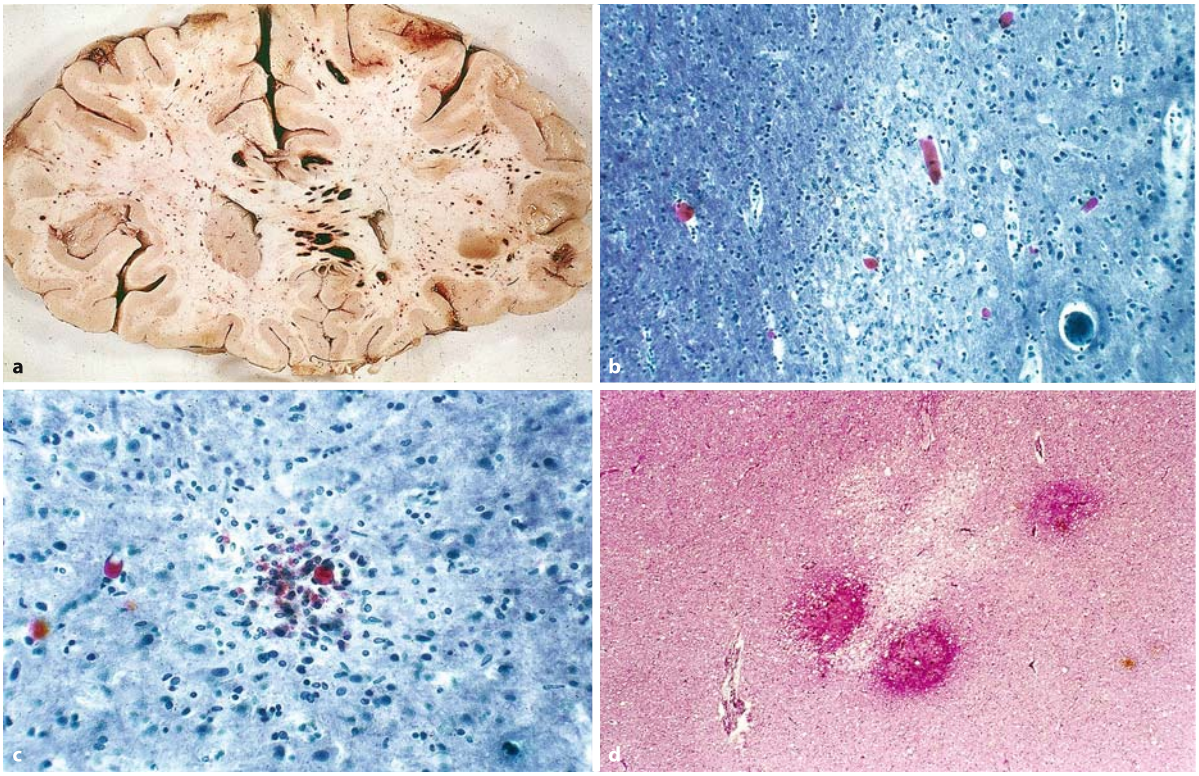

Fig. 9.29a–d. Fat embolism as demonstrated (**a**) macroscopically (purpura cerebri) as well as histologically (**b, c**) by means of oil red O stain and (**d**) by H&E stain. Fat droplets are seen intravascularly (**b**) and are characterized by phagocytosing macrophages (**c**); paraffin-embedded tissue demonstrates spheric hemorrhages associated with edema (magnification, **b, c** ×500; **d** ×100)

can be transported to the systemic circulation (cf. Mellor and Soni 2001).

Clinical Features. Cerebral fat embolism gives rise to *uncharacteristic cerebral symptoms* which are reminiscent of a differential diagnosis of *brain edema*. If there is an initial loss of consciousness, intervening neurologic signs cannot be detected, thus masking the cerebral fat embolism. Psychopathological changes such as an acute-onset *confusional state*, *clouding of the sensorium*, and *cerebral convulsions* are just as much symptoms of a fat embolism as are symptoms of generalized embolism, such as *petechial bleeding* in the skin of the trunk. Because the mortality associated with cerebral fat embolism is very high, the appearance of its symptoms must be regarded as predictive of a poor prognosis (Henn 1989).

Neuropathology. Macroscopically (Fig. 9.29), brain slices exhibit numerous *punctiform hemorrhages* located mainly in the white matter of the cerebrum and typically described as *purpura cerebri*. In the cerebellum, the cortex and white matter are equally affected. Most cases also exhibit signs of a *brain edema*. Microscopically, *annular* or *ball-shaped hemorrhages* are seen and the central vascular lumen is occluded by fat droplets. If the embolism is survived for days, *fat-* or *siderin-containing macrophages* appear perivascularly. After survival of several months, *circumscribed perivascular glioses* appear, with myelophthisis and expansion of the interior CSF spaces (internal hydrocephalus). This must be interpreted as the result of edema and hemorrhage-induced demyelination. An intermittent clinical course can occur (Henn 1989), exhibiting various time-dependent reactive changes.

Differential Diagnosis. A few cases of *cerebral purpura without fat embolism* have been reported. They featured either a *disseminated intravascular coagulopathy* (DIC) with vessel thrombosis, a release of tissue thrombokinase from the injured organs, or a trauma-induced spasm of the small vessels (see above). The differential diagnosis in cases of purpura must include *mercury poisoning* with subsequent endothelial injury (arsphenamine or Salvarsan therapy) as well as hypothermic purpura cerebri.

9.5.2 Air Embolism

If there is a traumatic opening of large veins near the heart, air can enter the circulatory system as a result of

the negative blood pressure within the venous system. Similarly, a rapid increase in atmospheric pressure (e.g., in caisson disease) can result in a release of gas bubbles by blood and tissue, or the lung vessels may be ruptured and atmospheric gas will be aspirated by the ruptured vessels. The bubbles then enter the circulatory system. In venous air embolism the gas is first demonstrable in pulmonary vessels, but it can pass through the lungs by arteriovenous shunts or patent foramen ovale and enter the vessels of the brain. Morphologically, a massive brain edema and a bubble-like (spherical) gap can be demonstrated in the lumen of the vessels (see also Chap. 12, pp. 260 ff).

9.5.3 Vascular Injury

Mechanically induced vascular injuries are rare (for survey see Dowling et al. 1995). A violent blow to the common carotid artery (Fig. 7.26), during a physical alteration or boxing match for example, can produce injury of the endothelial cells with consequent thrombosis. Less common is the formation of an intramural aneurysm with subsequent thrombosis (Peiffer 1977), or the mechanically induced dissection of a vessel wall with subsequent thrombosis leading to a cerebral embolic process. Thromboses of the basilar artery and, especially of the arteries of the upper cervical spine, can also be induced by mechanical loading of the head (Krauland and Stögbauer 1961; Mastaglia et al. 1969). Mechanically induced subarachnoid hemorrhage is discussed above (pp. 139 ff), as are carotid-cavernous fistulae (p. 145), which can be caused by both penetrating and non-penetrating wounding to the brain, usually by blunt impact (Halbach et al. 1989). Vasospasms can also lead to regional or generalized circulatory disturbances.

9.5.4 Coagulation Disorders

Violent mechanical insults of brain tissue can lead to major systemic coagulation abnormalities (Hoots 1995), particularly DIC. In animal models, minor experimental brain injury resulted in the formation of microthrombi in the brain and lungs of rats. Marbet and Griffith (1986) demonstrated the generation of thrombin in vivo and its subsequent inactivation by the major thrombin inhibitors. Pretreatment with ATIII cofactor heparin inhibited development of the tissue thromboplastin-induced DIC.

Following mechanical brain wounding, the release of thromboplastin into the circulation with associated activation of factor VII is accompanied by extensive endothelial injury; contact factor pathways are activated and platelets are released (Kaufman and Mattson 1985). A pathway is thus established for amplification of clotting mechanisms, resulting in thrombotic occlusions and possible DIC-induced hemorrhage. There is evidence that the presence of coagulopathy is predictive of delayed brain injury (Stein et al. 1992) and prognostic outcome, as supported by data from a large cohort study of head injury victims (Olson et al. 1989).

9.5.5 Ischemic Injury

Local hypoxia occurs in the area of acute cerebral hemorrhage (see above). A recent study measured total the cerebral blood flow, cerebral oxygen consumption, and the oxygen extraction fraction using positron emission tomography in 19 patients 5–22 h after onset of hemorrhage. Although the overall cerebral blood flow and cerebral oxygen consumption were found to be significantly reduced, the authors (Zazulia et al. 2001) found no evidence of local ischemia in the perifocal area. In contrast to these observations, diffuse ischemic injury as a secondary phenomenon is commonly known and is discussed elsewhere.

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Injuries of Spine and Spinal Cord 10

10.1 Basic Principles

Injuries of the spine and spinal cord can be caused by a *traffic accident*, *fall*, *stabbing*, *gunshot*, *or* by *accidents* in *sport* or *work*. The spinal cord is protected from blunt force injury by the surrounding – predominantly muscular – soft tissue, the vertebrae, and the spinal dura mater. While the segmental architecture of the bony spinal column allows *flexibility of movement*, it exposes the spinal cord to *perforating injury* through the spaces between the vertebrae. The *nerve fibers radiating off the spinal cord* are additional places of lesser resistance (*loci minoris resistentiae*) where the nerve fibers themselves are vulnerable to mechanical loading such as traction and compression.

The extradural space of the *spinal canal* contains *fatty tissue* and a *venous plexus*. The *spinal cord* itself is *soft* and relatively *inelastic*, making it and its roots susceptible to even slight compression or bending of the spinal canal.

10.1.1 Epidemiology

Despite the enormity of its impact on the individual and its vast social and economic significance, little was known until recently of the epidemiology of spinal cord injury (SCI). In a survey of the literature from 1960 to 1978 (see also Köning et al. 1987; Unterharnscheidt 1992; Lobosky 1995), Kraus (1986) detailed the methodological difficulties encountered in assessing the epidemiology of SCI due to the variety of methods used for data collection and the lack of uniform terminology and definitions (see also Köning et al. 1987).

The incidence of a given type of injury is defined as the number of occurrences in a given population in a discrete geographical region within a specific time frame. Findings from The National Head and Spinal Cord Injury Survey of 1974 (Kalsbeek et al. 1981), from Southern Australia (Simpson et al. 1981) and Virginia (Rimel 1981) indicate that 10–20% of all hospital admissions for neurotrauma are for SCI. Bracken et al. (1981) studied the incidence of long-term hospitalization (15 days or more) for acute SCI in the USA over an 8-year period from 1970 to 1977. The overall 8-year incidence was 40.1 per million population (standard error: 8.3). Kraus (1986) reported incidences ranging from 14 to 50 per million population in Canada, Australia, and the United States. This variability is probably due to the diver-

sity of the applied definitions and methods of ascertainment.

Three more recent books based on the Model Systems National Spinal Cord Injury Data Base (USA) were comprehensively and critically reviewed by Stover et al. (1995): "Spinal cord injury statistics" (1982), "Spinal cord injury: the facts and figures" (1986), and "Spinal cord injury: clinical outcomes from the model systems" (1995). Because the model system covers only 15% of annual SCI cases in the USA, its data are incomplete. In 1988, about 177,000 institutionalized and non-institutionalized SCI patients resided in the USA (Harvey et al. 1990), amounting to 721 per million of the population.

To estimate the incidence of SCI in the former Federal Republic of Germany (FRG) Köning et al. (1987) extrapolated from data on the 25.7 million persons insured by the "Allgemeine Ortskrankenkasse" (1983) in 1983. The estimated incidence of SCI in Germany for that year was 66 per million. Not included in the study were patients covered by workman's compensation. Compensation was granted in 316 cases of injury of the vertebral column involving spinal cord lesions. The overall incidence was about 12 per million persons insured. Of the total of 316 victims of SCI, 133 died (42%). This finding concurs well with that of Kraus et al. (1975), who reported 294 fatalities out of 619 cases of SCI (47%). Of the 133 fatal cases in the Köning et al. (1987) study, 80% died at the site of accident. The prevalence of SCI, i.e., the total number of cases, has been estimated at approximately 906 per million population (Meyer et al. 1991). In general, young adult males are at greatest risk of SCI in a given population.

The *age distribution* of SCI is similar in all studies (Kraus et al. 1975; Bracken et al. 1981; Kalsbeek et al. 1981; Levi 1996): the incidence peaks between the ages of 15 and 24 years, decreases during middle age, and rises again after age 55. The age distribution is similar in both sexes. *Females* have a remarkably lower incidence than males in all age groups.

The major *causes* of acute SCI were summarized by Lobosky (1995). He reported that about 50% of cases are caused by traffic accidents, 15–20% by falls, 15–20% by interpersonal violence, and 10–15% by sports and recreational activities. Traffic accidents were the most frequent cause of SCI in all studies, comprising 30–50% of cases (Clifton 1983; Meinecke 1983; Köning et al. 1987; Levi 1996), followed by falls.

10.1.2 Anatomy

The *vertebral column* is composed of 33 vertebrae: 7 cervical, 12 thoracic, 5 lumbar, 5 fused sacral, and 3–5 fused coccygeal vertebrae. The non-fused vertebrae are separated by cartilaginous intervertebral discs. The typical vertebra is comprised of a body and an arch, between which the spinal cord lies. The arch consists of the pedicles, which form the spinal canal, and the lamina, which constitutes its roof or posterior limit. The morphologies of the vertebrae comprising the upper cervical spine [occiput – C1 (= atlas) – C2 (= axis)] are described in detail below (pp. 233 ff).

The spinal cord and cauda equina are covered by the *meninges*, i.e., the dura, the arachnoid, and the pia mater. The vertebral canal is lined by the ligamentum flavum and the dorsal longitudinal ligament. The *epidural space* is relatively wide in diameter and contains adipose tissue, arteries, and Batson's epidural venous plexus.

The *spinal cord* extends from the occiput (medulla oblongata) to the lower border of the first lumbar vertebra or the upper border of the second lumbar vertebra, the conus medullaris and the cauda equina. Thirty-one pairs of spinal nerves leave the cord as anterior and posterior roots. The eight cervical roots exit the cord and traverse in an almost horizontal plane to enter the intervertebral foramen. But the vertebral column is much longer than the spinal cord. Thus, below this level, the roots take a progressively more vertical route, coursing inferiorly to enter their respective intervertebral foramina one or two vertebral levels inferiorly. The spinal cord itself ends at the lower border of L1 and hence all nerve roots here must necessarily descend a considerable distance in the cauda equina to reach their intervertebral foramina.

In the spinal cord, the *gray matter* is composed of centrally located groups of neurons, which are seen as a butterfly shape in cross-section. The anterior columns contain motor neurons, the posterior columns contain sensory relay neurons. The intermediate or lateral columns in the thoracic and upper lumbar cord contain nerve cell bodies belonging to the sympathetic nervous system. Hence the anatomical term thoracolumbar for the sympathetic nervous system, contrasting with the craniosacral outflow for the parasympathetic nervous system, due to efferents being limited to leaving the CNS via the cranial or sacral nerves. The *white matter* consists of ascending and descending myelinated fiber tracts, the most important of which are the descending lateral corticospinal tract (motor), the ascending lateral spinothalamic tract (pain and temperature sensation), and the ascending dorsal columns posteriorly (touch, vibration, and proprioception).

Blood reaches the spinal cord mainly by the anterior spinal artery, which runs along the cord in the anterior median fissure. Two posterior spinal arteries originate from the posterior inferior cerebellar arteries. The anterior spinal artery supplies the anterior two-thirds of the spinal cord, the posterior

spinal arteries supply the remainder. The anterior and posterior spinal arteries receive blood from the rostral feeder arteries, the radicular arteries originating in one or both vertebral arteries of the neck, from the thyrocostocervical trunk of the subclavian artery, and, below the level of T3, from the segmental intercostal and lumbar arteries.

10.1.3 Pathophysiology

In most instances, blunt mechanical loading (compression) produces no externally visible changes in the spinal cord. Petechial hemorrhages usually begin at the center of the cord. This is followed by a central hemorrhagic necrosis, chromatolysis, and acute swelling of nerve cells. In later stages there is resolution of the hemorrhage with tissue softening and phagocytosis, followed by cavitation and partial replacement of destroyed neural tissue by glial scarring.

The spinal cord can suffer *primary* damage if surrounding bony and soft tissues and/or penetrating objects directly inflict the nervous tissue and vasculature, as commonly seen in fracture-dislocation of the spine. The traumatic event initiates a *secondary* cascade of biochemical events that adds to the resulting injury. In some instances of mild mechanical loading, i.e., *commotio medullae spinalis*, the loss of function is transient and unaccompanied by significant morphological changes.

The spinal cord – unlike the brain – has a clear capacity for *regeneration*, with collateral sprouting and formation of new synapses as well as regeneration of transected axons if provided with an appropriate growth environment. A variety of growth inhibitory proteins are known to block axon regeneration (for review see McKerracher 2001). Frustrated regeneration in the spinal cord can be detected by demonstration of axonal bulbs using antibodies against β-amyloid precursor protein (β-APP – Li et al. 1997).

Massive traumatic violence to the spinal cord resulting in a complete disconnection of the cord usually causes the immediate cessation of all functions of ascending and descending pathways. In addition to paralysis and loss of deep tendon reflexes, sensation and autonomic function are eliminated below the level of injury, a stage of injury known as "*spinal shock*" (Guttmann 1976; see also Stauffer 1987; White and Panjabi 1990; Unterharnscheidt 1992). Spinal shock usually lasts 24–72 h, at which time the reflex function of the cord will have completely recovered. During spinal shock, the bowel and bladder are paralyzed, with consequent urinary retention and ileus. Without vasomotor control, blood pressure falls, and sweating is absent below the level of injury. The loss of vasoconstriction impedes temperature control. With complete resolution of the spinal shock, reflex activity returns but motor and sensory functions only recover if the insult to the cord has produced mild or moderate injury. Even then, complete recovery is rare.

The disabilities caused by SCI are largely confined to functions caudal to the horizontal plane of injury, and include:

1. Impairment or loss of voluntary motor activity
2. Impairment or loss of sensory function
3. Impairment or loss of volitional control of bladder and bowel emptying, leading to incontinence

Suprasacral injury can cause:

4. Reflexogenic movements and muscular hypertonicity manifesting as *spasticity* (i.e., upper motor neuron syndrome, due to corticospinal tract impairment)

Injury of the *sacral cord* (i.e., lesions of *conus medullaris*) or to the *cauda equina* produces:

5. *Flaccid* paresis (i.e., lower motor neuron syndrome)

SCI can also lead to long-term or permanent impairment of autonomic functions (e.g., of pelvic organs, vasomotor, and sensorimotor control) as well as to metabolic and hormonal derangements of potentially pathogenic significance.

10.1.4 Clinical Features

For the purpose of standardization, the American Spinal Injury Association (ASIA 1992; Ditunno et al. 1994) put forth the following definitions of some fundamental terms related to SCI:

Tetraplegia. Impairment or loss of motor and/or sensory function, i.e., impairment of function of the arms, the trunk, legs, and pelvic organs, due to damage of neural elements in the cervical spinal cord.

Paraplegia. Impairment or loss of motor and/or sensory function secondary to damage of neural elements within the thoracic, lumbar or sacral (but not cervical) segments of the spinal cord. In paraplegia, function of both arms or both legs is spared. The term also refers to *conus medullaris* and *cauda equina* injuries, but not to neurological impairment due to lumbosacral plexus lesions, or peripheral nerve lesions outside the spinal canal.

Complete Injury. Total loss of sensory and voluntary motor function due of injury to neural elements within the lowest sacral segment. According to this definition, even if voluntary motor function and sen-

sory perception are partially preserved caudal to the neurological level of the injury, it can still be classified as neurologically complete if the sensorimotor loss in the most caudal segment is complete.

Incomplete Injury. Partial preservation of sensory and/or motor functions below the neurological level of injury, including the lowest sacral segment. Preserved motor function is confirmed by the presence of voluntary contraction of the external sphincter upon digital examination. Sacral sensation includes sensation at the anal mucocutaneous junction plus deep anal sensation.

Conus Medullaris Syndrome/Cauda Equina Syndrome. Injury of the sacral cord (conus) and the lumbar nerve roots within the spinal canal. Cauda equina syndrome reflects injury of the lumbosacral nerve roots within the spinal canal. Both syndromes usually involve *areflexive* bladder, bowel, and lower limbs. Sacral segments may retain certain reflexes, including bulbocavernosus and micturition reflexes.

10.1.5 Biomechanical Aspects

Compressive or tensile stress to the spinal column by external violence can dislodge the *spinal cord* in the sagittal or lateral direction or cause it to rotate around the longitudinal or lateral axes. The medulla oblongata, which contains the neuronal centers for regulation of respiration and circulation, is located at the craniocervical junction. Mechanical loading to the cervical spine therefore can result in acute central death.

The *biomechanics* of injury of the spinal column and cord have been the subject of several monographs (Breig 1978; Saternus 1979; Saternus and Oehmichen 1984; Sances et al. 1986a, b; Tucci et al. 1992; Unterharnscheidt 1992). Four anatomical structures account for the stability and flexibility of the spinal column:

1. Vertebrae
2. Intervertebral discs
3. Ligaments
4. Muscles

The spinal column is susceptible to the following types of mechanical loading:

- Compression
- Tension
- Bending
- Axial rotation
- Shearing

The physical properties of its anatomical structures largely determine the functional biomechanics and failure tolerances of the spine (Panjabi and White 1978).

The *intervertebral discs* possess a nucleus pulposus surrounded by an annulus fibrosus comprised of concentric layers of connective tissue fibers. Whereas intervertebral discs are relatively stable against the aforementioned biomechanical loadings, the *ligaments* (anterior and posterior longitudinal ligaments as well as the ligamentum flavum) have a certain physical stability that depends on the age of the victim (Nachemson and Evans 1968) and that may be disrupted depending on the range and type of loading (Tkaczuk 1968).

The *vertebral body* is a roughly cylindrical mass of cancellous bone contained in a thin shell of cortical bone. Measurement of the mechanical load-bearing capacities and strength of the vertebral bodies disclosed marked differences from the first cervical to the fifth lumbar vertebra, differences attributed to their morphological, functional, and biomechanical adaptation to the progressively increasing loads to which they are subjected. Adult vertebral bodies also exhibit anatomical variation, foramina for the vertebral arteries in the cervical region, for example, articular facets for the ribs in the thoracic vertebrae, etc. Adult vertebral strength decreases with age, especially after age 40. Bell et al. (1967) could show an inverse relationship between their ability to tolerate stress and the age-related decline in osseous tissue of the vertebrae.

The vertebral bodies and the intervertebral discs are responsible for the mechanical stability and elasticity of the spinal column in most physiologic situations. An axial load is transmitted from the superior end-plate of a vertebra to the inferior end-plate via the cancellous core and the cortical shell. The stiffness coefficients of each motion segment were calculated by Panjabi and White (1978).

With its ligaments intact but devoid of muscle an adult human cervical spine has a tension failure tolerance of about 2,400 N in the upper and of 1,800 N in the lower part, as found by postmortem cervical spine tests (Van Ee et al. 2000). As verified by modeling, the cervical musculature under maximal stimulation increased the tolerance from 1,800 N to 4,200 N. Optimized anthropometric and physiologic modeling data resulted in a whole neck tolerance of 3,100 N and 3,700 N for the relaxed neck and the neck with maximal activated muscles, respectively (Chancey et al. 2003). The muscles and complex neuromuscular controls provide the stability of the trunk in a given posture and produce movements during physiologic activity. Adult cervical spine injury tolerance to compressive impact loading has been investigated by experiments with dissected human cadaver spines (Carter et al. 2002). They measured an axial force at failure of about (3,300±700) N.

The length of the *spinal canal* changes upon physiological flexion, extension, and lateral bending. The cross-sectional area also changes with physiological axial rotation and horizontal displacement. The *spinal cord* itself is supported and protected by surrounding soft-tissue structures: fat tissue and venous vessels, ligaments, dura mater, the subarachnoid space filled with spinal fluid. Although highly flexible when subjected to small loads, the spinal cord provides considerable resistance before failure.

10.2 Spinal Cord Injury (SCI)

10.2.1 Subdural and Epidural Hemorrhage

The covering of the spinal cord resembles that of the brain both anatomically and functionally. At the great occipital foramen the inner dural layer of the cerebral dura becomes the spinal dura mater within the spinal canal, while the outer layer continues to function as the periosteum.

But the propensity for subdural and epidural hematoma of the spinal cord is inverse to that in the brain. Whereas subdural hematoma is easily produced in the cranial cavity from venous bleeding of subdural bridging veins, and epidural hematoma is difficult to produce because of the necessity of the arterial bleed to dissect the dura from the inner aspect of the skull, spinal cord epidural hematoma is easy to produce by bleeding from the epidural venous plexus and spinal cord subdural hematoma is rare.

The spinal *extradural space* is confined by the dura and the ligamentum flavum and anterior and posterior longitudinal ligaments. The diameter of the spinal cord channels is two- to three-fold greater than that of the cross section of the spinal cord (Scarff 1960). The dorsal portions of the extradural space contain fat tissue and an extensive venous plexus. The subdural space is confined by the arachnoid of the spinal cord and the interior dural sheet.

Dural bleeding in the spinal canal, especially subdural hemorrhage (SDH), is rare (Bohlman and Cook 1982). Classified according to their temporal course, such hematomas are acute (<1 week), subacute (1–3 weeks), and chronic (>3 weeks).

Dural hemorrhages are usually caused by spinal column injuries: among nearly 100 patients with SCI, Holzer and Kloss (1962) observed epidural bleeding in 3.2%, SDH in 4.3%, and combined epidural and SDH in 7.5%. Spontaneous dural hemorrhages unassociated with any type of mechanical violence do occur and are usually related to blood coagulation disorders. Dural hemorrhages can also be of iatrogenic origin, caused in most cases by lumbar puncture or spinal anesthesia. Even mechanically induced dural hemorrhages without additional spinal injury are occasionally seen. Extremely rare, and related to coagulopathy when they occur, are cases of spontaneous *spinal extradural hematoma* with mainly dorsal and/or dorsolateral hemorrhaging, without impact and without blood coagulation disturbances (Horne and Mueller 1977).

Mechanically induced and spontaneous epidural hemorrhages (EDH), which are often associated with ruptures of the dorsal parts of the intervertebral discs, are usually venous and spread diffusely (Fig. 10.1a); in rare cases they displace and compress the spinal cord (for overview see Bruyn and Bosma 1976). The extreme acceleration forces seen in shaken baby syndrome affect the head, cervical spine, and the craniocervical junction, in most cases producing epidural and SDH unassociated with injury of the bony, cartilaginous or spinal portions of the cervical columns (see Chap. 25, pp. 500 f).

Spinal SDH are – as said above – often seen in combination with vertebral fractures (Anagnostopoulos and Gortvai 1972; Edelson 1976) and subarachnoid spinal bleeding, but not exclusively (Fig. 10.1b, c). SDH can surround and compress the spinal cord like a cuff that leads to progressive degeneration, mainly of the dorsal columns (Edelson et al. 1974). In a few reported cases, compression fracture has led to secondary circulatory impairment that caused complete necrosis of the affected spinal cord segments (Oehmichen and Meissner 1999).

Aneurysms of the subarachnoidal vessels along the spinal cord are almost unknown. Subarachnoid hemorrhage is caused by contusions, accelerations or other types of mechanical violence to the spine (Fig. 10.1d), and may be associated with subdural spinal hemorrhages or may be secondary due to a intracranial subarachnoid hemorrhage.

10.2.2 Penetrating SCI

The hallmark of penetrating SCI is perforation of the dura mater spinalis caused by stabbing or gunshot, by a needle (during, e.g., lumbar puncture, Dick 1992), or even by displaced fragments of the vertebrae. SCI can result in complete or partial paralysis below the lesion. Rare under civilian conditions, penetrating SCI are common under wartime conditions, during the Korean and Vietnam wars for example (Simpson et al. 1981).

As with open brain injury, infection is one of the major complications of open injuries of the spinal cord. Spinal subdural, epidural, or subarachnoid infections, abscesses and empyemas can develop, the

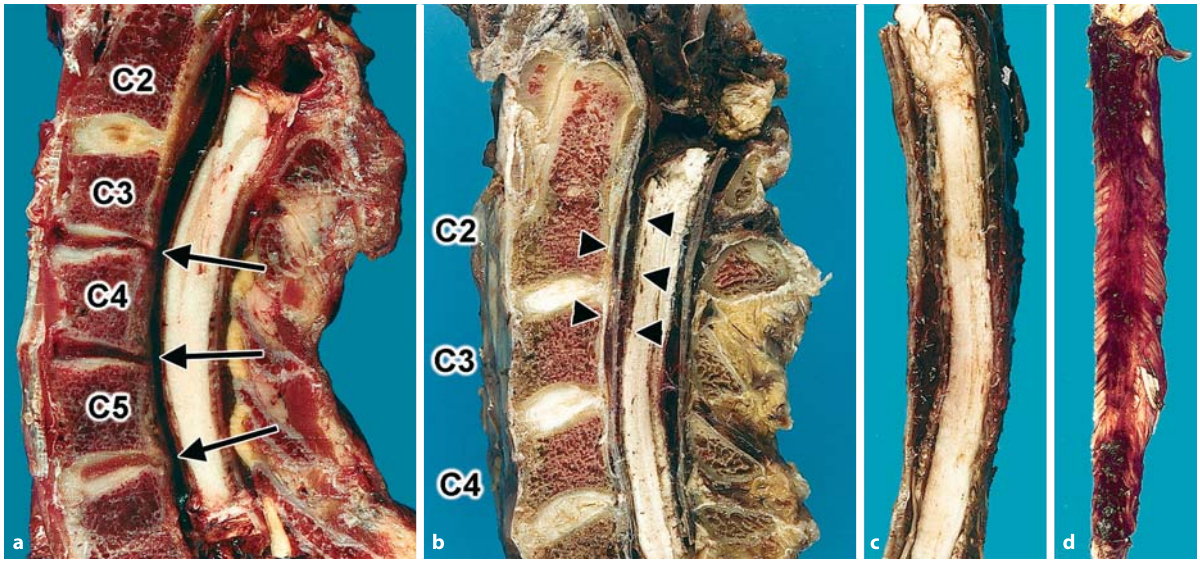


Fig. 10.1a–c. Spinal dural hemorrhages. **a** Epidural hemorrhage associated with hemorrhages of the intervertebral discs (*arrows*) as a result of acceleration; **b, c** sudden unexpected subdural hemorrhage (*arrowheads*) within 4 days after suffering mechanical brain injury (*MBI*); **d** spinal subarachnoid hemorrhage caused by acceleration, which is associated with a basal subarachnoid hemorrhage of the brain

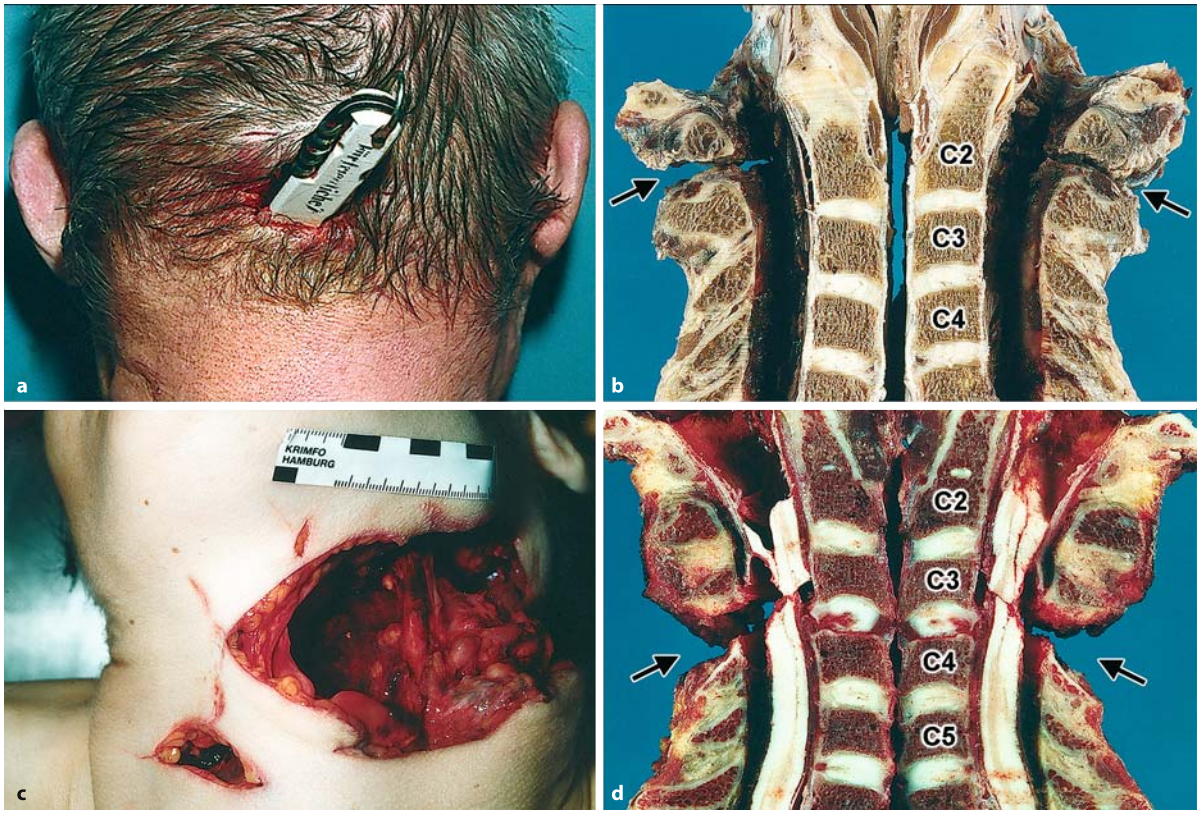


Fig. 10.2a–d. Stab wounds of the spinal cord. **a, b** Incision wound in the neck of a schizophrenic victim demonstrate the suicidal process which finally leads to a disconnection of the spinal cord in combination with an epidural hemorrhage. **c, d** A homicidal stabbing of the frontal neck is associated with a disconnection of the cervical spine and cervical cord caused by a laterodorsal incision

inflammation usually originating in local infectious processes, e.g., osteomyelitis. Penetrating SCI carries the risk of spinal purulent meningitis or subdural abscess (Klaue 1948; Reihsaus et al. 2000). In hospital, dural puncture (Lucas et al. 2000), spinal or epidural anesthesia (Horlocker 2000), or epidural catheterization (Wang et al. 2000) can be the inadvertent cause of penetrating SCI and secondary inflammation, in most instances an epidural abscess.

10.2.2.1 Stab Wound

If the spine near the dorsal part of the atlanto-occipital joint (Fig. 10.2a, b) is stabbed, the consequent injury of the caudal medulla oblongata often results in immediate apnea and death. The other segments of the spine are protected by the vertebral spines, which overlap like roof tiles. In single cases the stabbing of the spinal cord will also be the result of incision wounds of the frontolateral as well as dorsolateral neck (Fig. 10.2c, d). At most, a knife or other sharp object can enter the dorsolateral part of the spinal canal, producing an asymmetrical lesion (Courville 1950; Lipschitz 1976), i.e., the wound runs at an angle that causes paralysis on the side of action. The opposite side of the spinal cord is sometimes also affected. Stabbing of the spinal cord will injure the dura, leptomeninges and vessels, the lesion spreading via bleeding. The vascular lesion may result in a secondary, more severe ischemic necrosis of the spinal cord.

The salient *clinical feature* of penetrating SCI is a modified hemisection of the cord, giving rise to a more or less typical Brown–Séquard syndrome. *Morphologically* the cord injury can range from a small localized lesion to complete transection. Bleeding is usually minimal except from epidural veins. Complete disruption of the upper cervical cord due to spinal fracture may be fatal.

10.2.2.2 Gunshot Wound

Gunshot injuries of the spinal cord (Yashon 1976) always involve injury of the bony column. Injury of the spinal cord itself may be caused by the projectile (Fig. 10.3), by bony fragments, or by both. Once lodged in the spinal canal, the projectile and/or its fragments can move within it (Arasil and Tascioglu 1982; Tanguy et al. 1982) and thus cause paresthesias and motor paralysis – possibly also lead poisoning – even after prolonged survival times. High-velocity projectiles create shock waves that are capable of inflicting injury of tissue without actually penetrating it (Kirkpatrick 1988). Klaue (1948) distinguished three types of gunshot wounds of the spine:

1. Perforating wound, in which the missile transverses the spinal column and cord.
2. Penetrating wound, in which the missile enters the spinal canal but remains within it.
3. Depressed wound, in which the missile fails to enter the spinal canal and ricochets externally or takes an external tangential course with or without piercing the dura and inflicting direct or indirect damage to the cord.

Jellinger (1976) described four types of gunshot-related cord injury:

1. Direct lesions caused by passage of the missile through the spinal canal irrespective of whether it touches the cord or not. Damage to the cord is maximal.
2. Compression or laceration of the cord by displaced bone fragments or due to blast effects; the cord escapes direct damage.
3. Secondary damage to the cord caused by intramedullary, intrathecal or perithecal hemorrhage, or by edema, compressive forces, or vascular and circulation deficiencies.
4. Lesions occurring in parts of the cord remote from the actual site of wounding; hemorrhages, edema, spongy changes, necrosis, and central cystic cavities being especially prominent in cases of spinal concussion injuries.

Gunshot wound-induced pathological changes of the *spinal cord* feature partial or complete transection of the cord. The histological appearance of the mechanical insult includes liquefaction, necrosis of the lacerated tissue, and hemorrhages with tissue destruction. A latent period is followed by reactive changes, including leukocyte emigration and axonal swelling. As macrophages clean the wound of necrotic material, repair processes begin that leave a mesenchymoglial scar or cyst.

10.2.2.3 Disruption of the Craniocervical Junction

As already mentioned, disruption of the spinal cord at the craniocervical junction is a type of open SCI that almost invariably results in instant death. It is often associated with intentional killing of a victim who is powerless to resist due to physical restraints or threat. It is caused by the types of execution carried out in the Holocaust (Kucharski 1998) and, more recently, during the Kosovo conflict (Pozgain et al. 1998; Sprogoe-Jakobsen et al. 2001).

The injury can involve complete transection of the lower brain stem and/or upper cervical cord with unilateral or bilateral disruption of the vertebral arteries. This type of injury has been reported after extreme hyperextension (retroflexion) of the cervical spine usually followed by sudden death (Hinz and Tamaska 1968). Transection of the cervical cord with dural tears has been found as a complication of birth

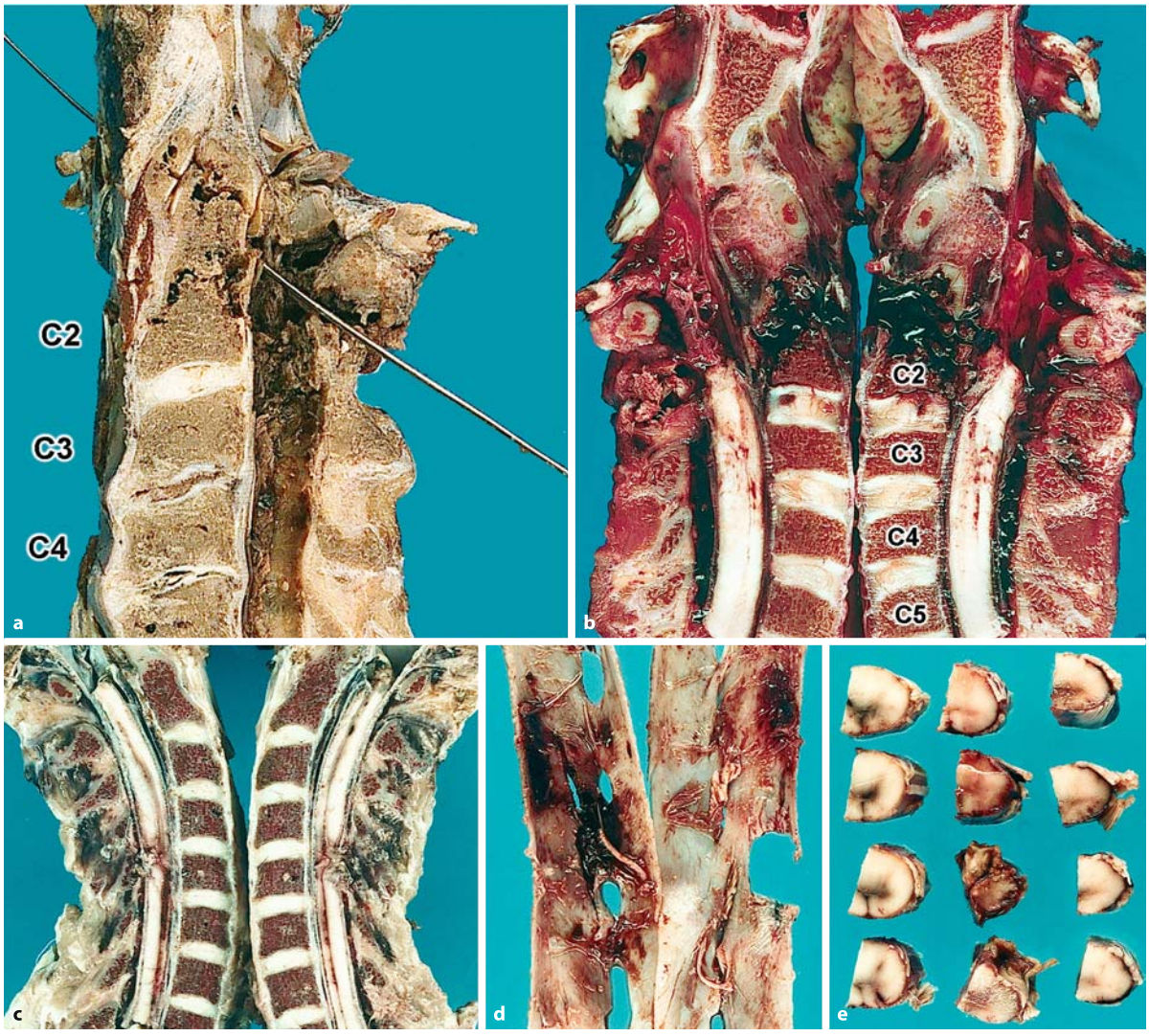


Fig. 10.3a–e. Gunshot injury of the spinal cord (three cases). **a, b** Perforating wounds of the cervical spine passing through the spinal canal as well as the spinal cord. Gunshot injury of the cervical spine and cord (**c**) associated with penetrating wound of the spinal dura (**d**) and a hemorrhagic destruction of the spinal cord (**e**)

injury during breech extraction and may sometimes be fatal.

10.2.2.4 Pathology of Penetrating Injury

The spinal cord injuries caused by stabbing and gunshot differ in their morphologies. Stab wounds are clearly delimited while gunshot wounds are more ragged and destructive. Each type of wound has three zones of destruction (Peters 1955):

1. Zone of primary destruction containing cell and tissue debris.
2. Zone of irreversible damage containing cell fragments, swollen neuronal and glial processes, and protein-rich fluid.
3. Zone of reversible tissue damage, i.e., of peritraumatic edema with swollen astroglia (without disruption of cellular membranes) and shrunken, darkly stained neurons.

Each of these zones contains time-dependent reactive changes described by Noack et al. (1971) (see also Jellinger 1976). The wound healing process consists of three phases:

Phase of destruction: during the first 2 h after wounding a non-proteinaceous fluid originating from disrupted blood vessels fills the extracellular spaces.

Phase of resorption: astrocytes develop progressive changes within 24–36 h; between 36 and 48 h phagocytes appear in the wound and astroglia undergo progressive changes. Proliferation of endothe-

lial cells and capillaries begins 8–10 days after the traumatic event.

Phase of repair: after destroyed cells and tissue debris are removed by scavenging macrophages, glial-mesenchymal formation increases over a period of 3–4 weeks. Fat- and/or hemosiderin-bearing macrophages are seen within the network of fibers, resulting in collagenous thickening of the meninges and dura.

Secondary lesions include edema and degeneration of ascending and descending fiber tracts (see above). As mentioned above, open spinal cord trauma entails the possibility of secondary infections. Spinal extradural and subdural empyemas are rare complications of penetrating SCI, observed by Klaue (1948) in only 6% of his 85 cases of spinal cord wounds in World War II. Another rare complication of open cord trauma is leptomeningitis. Infection of the spinal cord parenchyma accompanied by severe edema is found on the margins of the wound. Abscesses localized around retained foreign bodies were found by Klaue (1948) in only 3.5% of spinal cord wounds.

10.2.3 Closed Cord Injury

Closed SCI usually result from the mechanical stress created by a broad area of impact to the spine. When the load cross section is rather small as compared to the square diameter of the cross section an open cord injury will result, commonly associated with a fracture or dislocation of the spine (Klaue 1969). The static conditions of the spine and cord make the lower cervical region and the thoraco-lumbar junction the most common sites of mechanically induced damage. A distinction is made (Jellinger 1976) between direct and indirect SCI:

- Direct SCI is caused by blunt or penetrating violence inflicting space-occupying osseous or ligamentous damage (dislocation of vertebra and disc, etc.).
- Indirect SCI results from blunt violence transmitted to the cord without space-occupying damage to the spine (an impact with relatively small load cross section to the spine).

In every case of moderate or severe head trauma an associated cervical spine trauma must be confirmed or excluded. The incidence of cervical spine trauma in head-injured patients ranges from 4% to 8% (Holly et al. 2002). Holly et al. (2002) found that 24 of 447 head-injured patients (=5.4%) suffered a cervical spine injury, 14 of the 24 (=58.3%) sustaining spinal cord injuries, 14 injuries in the occiput-C3 region. A pathological-anatomical study to complement this clinical study has yet to be published.

10.2.3.1 Biomechanical Aspects

Four mechanisms of spine injury can be distinguished; in most cases a combination of these forces is involved, i.e., the fourth alternative (Jellinger 1976):

- *Flexion* (Fig. 10.4a) *and deflexion* (Fig. 10.4b–d) created by ventroflexive and retroflexive forces: cause transverse shear, longitudinal shear and tension. This is the most frequent mechanism of cervical spine injury (see below).
- *Compression* produced by longitudinal forces acting on the column in falls on the head, or bottom: the result may be flattening of vertebral bodies (Fig. 10.4e) and/or fracture of the end-plates.
- *Rotation* generated by torsional forces resulting in unilateral or bilateral dislocation, fracture dislocation of the vertebral body and/or its processes (Fig. 10.4f). This is the principal mechanism of injuries at the lumbar or thoracolumbar level.
- *Combined mechanisms*: pure flexion or extension forces are often insufficient to produce ligamentous rupture, dislocation, or fracture dislocation (Gosch et al. 1972). Closed injuries are thus frequently caused by a combined mechanism (see Fig. 10.5).

A further – fifth – indirect mechanism is to be mentioned:

- A blunt and non-penetrating blow to the lateral or posterolateral neck area, e.g., by the puck during competitive ice hockey, which leads to sudden death (Maron et al. 2003). The death was attributed to dissection and rupture of the vertebral or internal carotid artery leading to massive subarachnoid hemorrhage with rapid accumulation of blood within basilar cistern, Sylvian fissures and ventricles, as well as brain stem herniation.

10.2.3.2 Clinical Features

The victim of an acute injury of the cervical or upper thoracic area of the spine may go into a state of sympathetic *spinal shock* (Guttmann 1976; Stauffer 1987). The cord distal to the level of injury enters a state of areflexia. For a short period of time (6–24 h), the victim will exhibit areflexia with hypotonia and a "sympathectomy" effect. The vascular tree dilates and blood accumulates in the peripheral vasculature. Typically, the patient's blood pressure drops to 90 mmHg systolic over 50 or 60 mmHg diastolic in the absence of a rapid pulse. Reflexes begin to recover after 24 h and between 48 h and 72 h after the blunt impact the vasculature begins to contract. A patient in spinal shock can die suddenly, especially if high cervical SCI coexists with pontomedullary

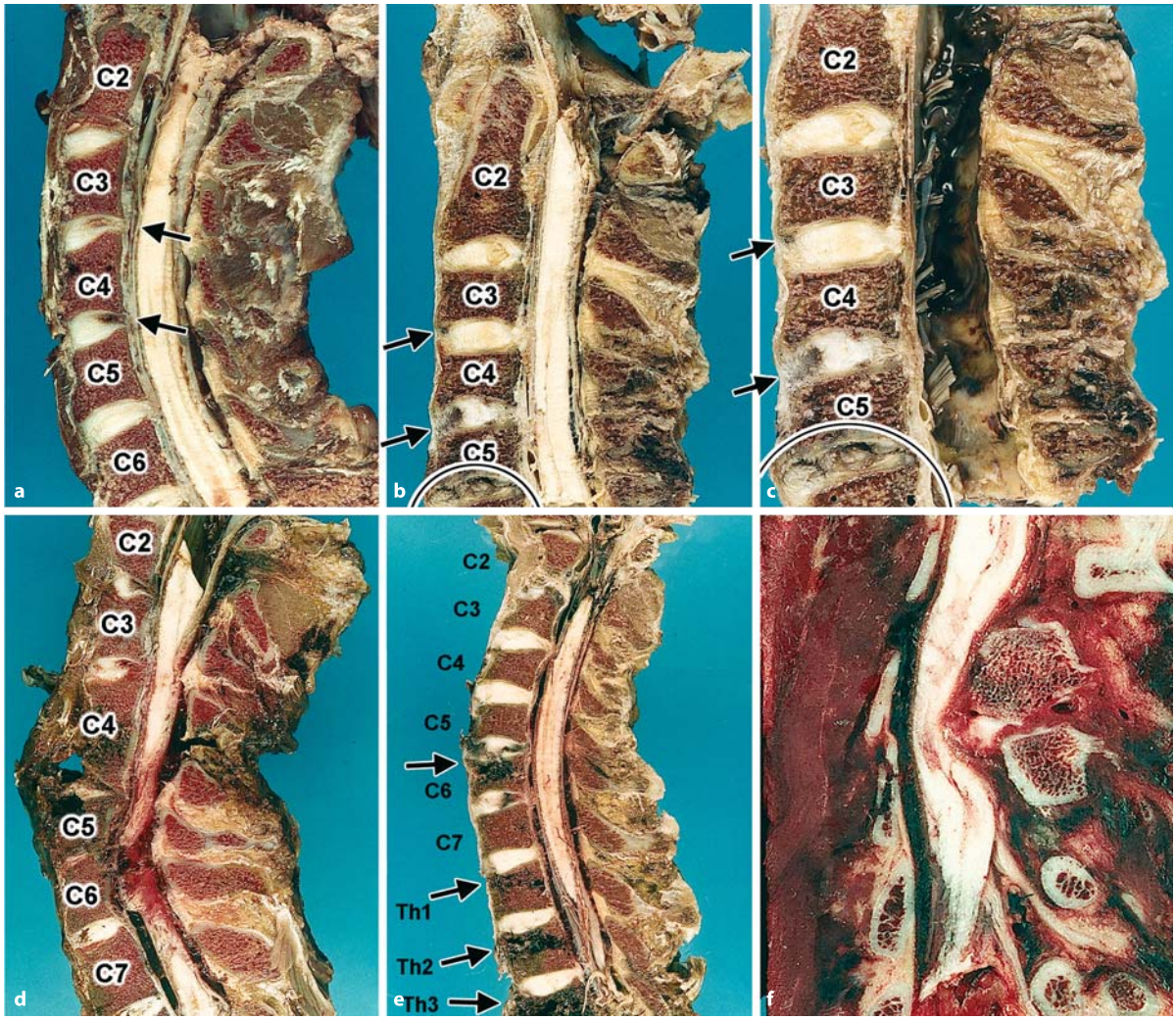


Fig. 10.4a–f. Morphology of different biomechanical mechanisms leading to closed spinal cord injuries. **a** Flexion injury as demonstrated by dorsal hemorrhages in the intervertebral discs between C3/C4 and C4/C5 (*arrows*); **b, c** hyperextension caused ventral hemorrhage in the intervertebral disc between C3/C4 and C4/C5 (*arrows*) and a rupture of the disc C5/C6 (*circle*) as well as an epidural hemorrhage; **d** deflexion injury associated with fractures of C4 and C5, a compression of the spinal cord and epidural hemorrhages; **e** compression caused fractures of several vertebral bodies (*arrows*): C6, Th1–Th3; **f** rotation induced asymmetrical fractures of vertebral bodies and their processes associated with compression of the spinal cord

or other brain stem injury (Braakman and Penning 1976; Leestma et al. 1983).

The *chronic* (and acute) *neurological* (sensory and motor) *deficits* depend on the segment of the cord that is injured. In adults, the spinal cord ends at the inferior aspect of the L-1 vertebra. The injured spinal cord segments, therefore, do not correspond with the vertebral bony segment level.

10.2.4 Neuropathology

Commotio spinalis and *concussio spinalis* are relatively minor, reversible injuries of the spinal cord. Neither macroscopic nor specific microscopic alterations are to be seen.

10.2.4.1 Contusional Injury of the Cord

Commonly the term "*contusio spinalis*" designates all primary mechanical alterations of the cord and its coverings caused by blunt violence to the cord. Spinal cord contusion injuries also include all non-disruptive injuries without evidence of continuing compression but those more severe than reversible functional disturbances are referred to as concussion injuries (Jellinger 1976).

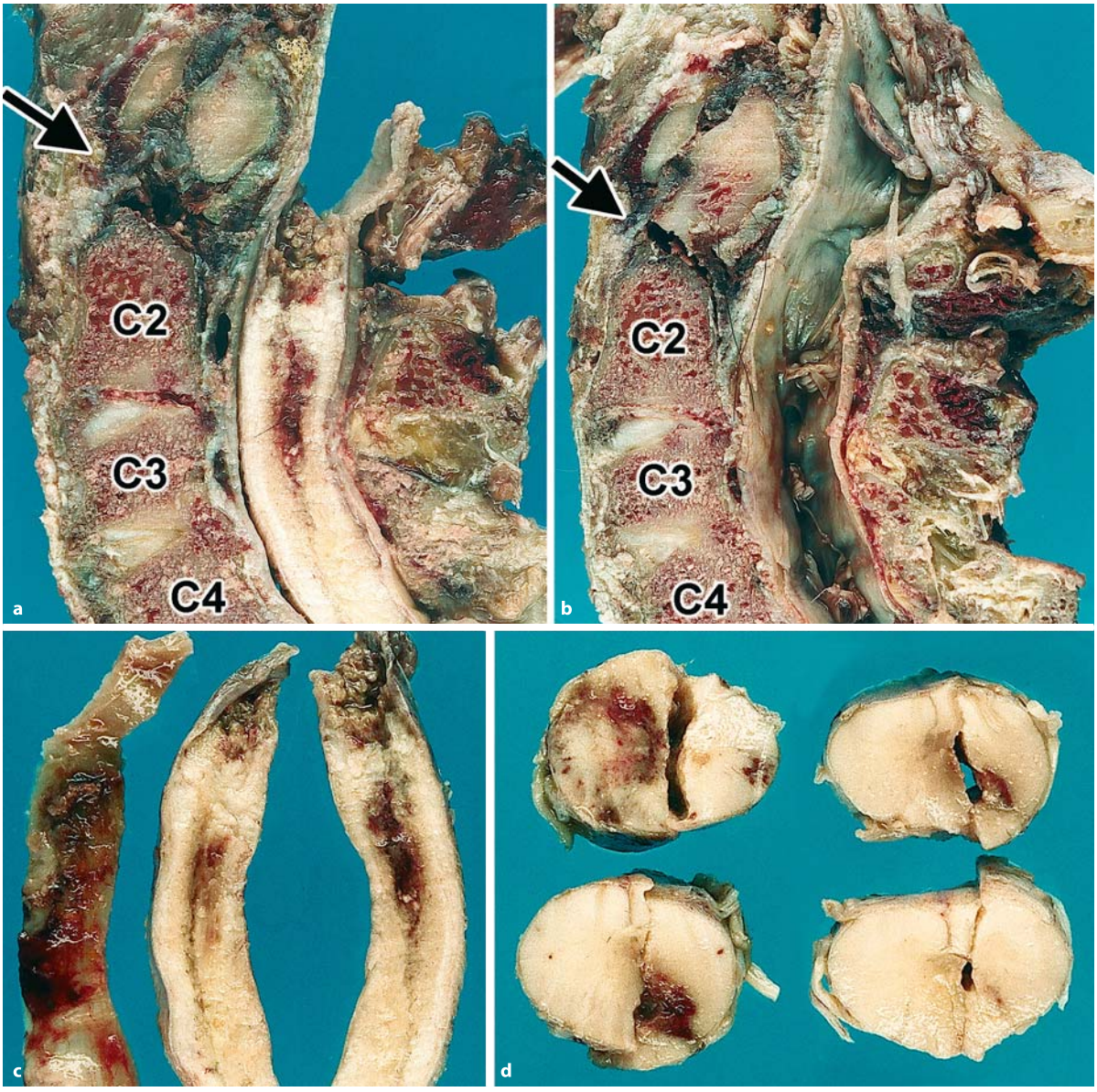


Fig. 10.5a–d. Fracture of the dens axis (*arrows* in **a**, **b**) and intraspinal hemorrhage as a result of a combined retroflexion and rotation around the *z*-axis: **a** Spine and spinal cord in situ; **b** occipito-cervical junction and fracture of the dens axis; **c** epidural hemorrhage and intraspinal hemorrhage; **d** intraspinal hemorrhage

This type of SCI features intramedullary hemorrhage and/or edema (Fig. 10.6a). The histological alterations extend the lesion for several segments both above and below the original site of injury. The bleeding involves the central gray matter, particularly the ventral portion of the posterior horn and the central canal, i.e., central cord necrosis or myelomalacia. Most cases exhibit a combination of hemorrhage and necrotic liquefaction of the central parts of the cord.

During the first 2 h after the impact, the first reactive changes arise: congestion, edema, and homogenization of vessel walls with leakage of plasma into the perivascular spaces (Wolman 1965) as well as leukocyte reaction (Fig. 10.6b). The periphery of the primary injury is characterized by rostral and caudal *axonal swelling and axonal bulbs* (Fig. 10.6c–f). Dendrite injury (Fig. 3.2) is also seen as marked by the absence of immunoreactivity to microtubule-associated protein 2 (Map2 – see Fig. 10.7a, b) (Li et al. 1997). An extensive demyelination occurs (Fig. 10.7c, d). Retrograde and W*allerian* (= *anterograde*) *degenerations* are evident (Hughes 1978). The adjacent neuropil features a pronounced spongy gliosis.

Four inflammatory phases are seen:

1. Hemorrhage and neuronal necrosis
2. Blood cell reaction

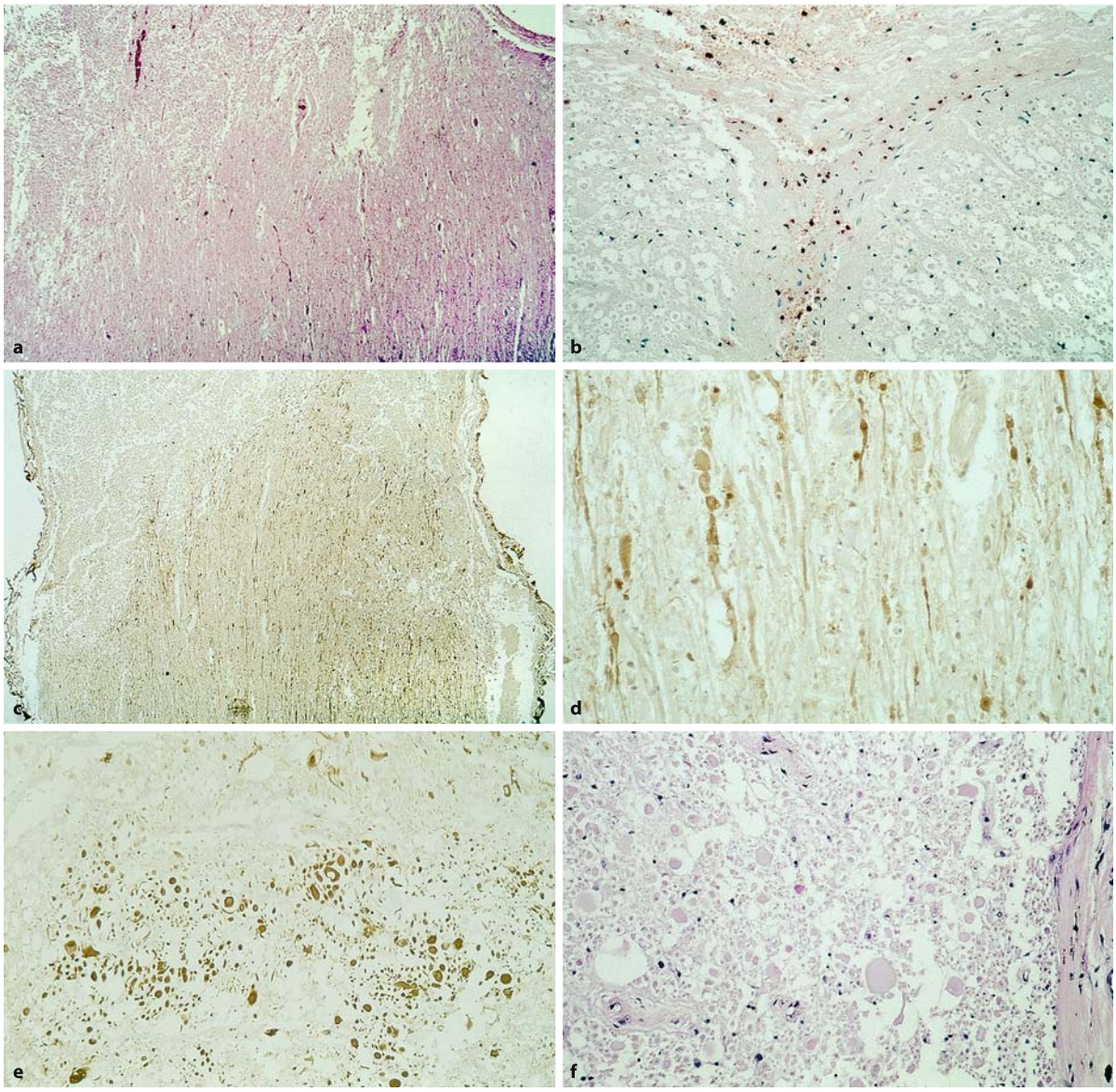


Fig. 10.6a–f. Contusion injuries of the spinal cord. **a** Edema (H&E, magnification ×100); **b** emigrating leukocytes as demonstrated by means of naphthol AS-D chloroacetate esterase (magnification ×300); **c, d** axonal injury as demonstrated by β-APP immunohistochemistry in longitudinal sections (magnification **c** ×30, **d** ×300); **e, f** axonal injury as seen in cross sections (**e** β-APP, **f** H&E; magnification ×500)

3. Proliferation of resident cells (mesenchymal and glial reaction) and/or resolution
4. Scarring process including production of glial and collagenous fibers

The *phase of hemorrhage and neuronal necrosis* is characterized by axonal injury. The hemorrhages occur mainly in the gray matter and produce a hematomylia as a result of hemorrhage and necrosis within the axial center of the cord. The zone of necrosis soon spreads, apparently due to edema. Neutrophilic leukocytes emigrate within 1 h, lymphocytes and macrophages appear after 12 h or more. Macrophages scavenge the tissue debris.

The hallmark of the early *blood cell reaction phase* is an incipient astrocytic reaction (gliosis) occurring at the margins of the lesion 24–36 h post impact. Demyelination spreads and macrophages invade. Lipophages and siderophages appear within the necrotic tissue, which gradually diminishes and is replaced by proliferating gliomesenchymal tissue. Endothelial proliferation develops at the margins; this is associated with a fibroblastic and collagenous reaction (granulation tissue, as in the rest of the body tissues) and gliotic changes (unique to CNS tissue) constitut-

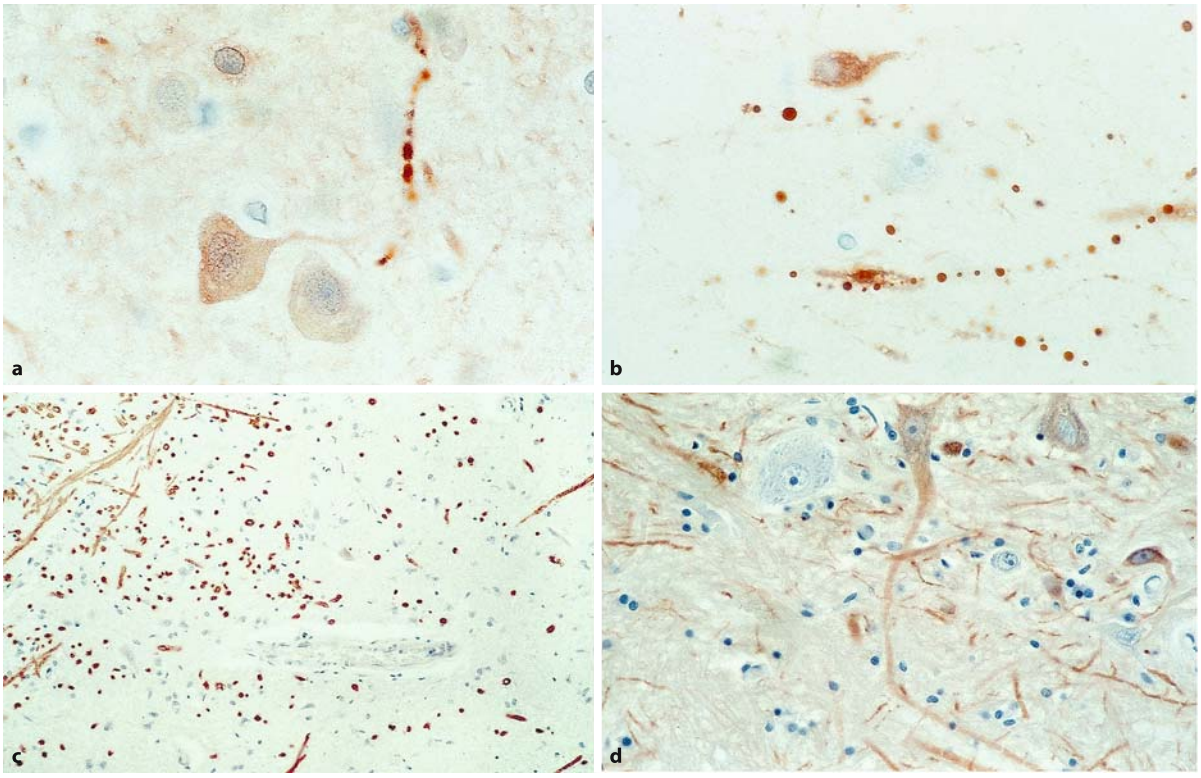


Fig. 10.7a–d. Loss of dendrites and demyelination. **a, b** Dendritic loss as demonstrated by a loss of MAP2 expression; **c, d** demyelination as demonstrated by a loss of myelin basic protein expression (magnification ×1,000)

ing the so-called gliomesenchymal scarring process, which originates in the mesenchymal tissue components of the perivascular tissue, the leptomeninges, and the local glia. The mechanical insult to the axons causes axonal injury at the margins, which resembles that seen in MBI (Fig. 10.6c–f).

During the *proliferation phase* the myelin sheaths are destroyed (Fig. 10.7c, d) and removed by macrophages; the dendrites are lost as well as MAP2-reactivity of spinal neurons (Fig. 10.7a, b). Signs of secondary (Wallerian) degeneration in distal ascending and descending long tracts appear: above the lesion (rostral or cranial part of the cord to the injury), fiber loss occurs in the posterior columns. This will occur in the fasciculus gracilis and, to a variable degree, the fasciculus cuneatus, depending on whether the interruption is above, at, or below the cervical enlargement. Spinothalamic and spinocerebellar tract degeneration is more difficult to discern. Caudal to the lesion, the corticospinal tracts degenerate. At the level of the lesion, secondary degeneration of the neurons then begins, with central chromatolysis (axonal reaction) after spinal root transection (Fig. 3.1c).

The *final* (*scarring*) *phase* commences 3–6 weeks after wounding in some cases and involves mechanically induced syringomyelia, which leaves a cavity surrounded by glial tissue within the center of the spinal cord. In a few cases the cavity extends rostral and/or caudal to involve regions unaffected by the initial trauma. Clinically the patient develops syringomyelic symptoms (central cord syndrome). In some patients, the cord is completely converted into a dense fibrous band and the surrounding dura becomes thickened with remnants of hemorrhage. In others, tissue fluid flow is impeded from the spinal cord, and the syrinx within the cord enlarges progressively over time (post-traumatic syringomyelia).

10.2.4.2 Compression Injury of the Cord

Chronic or acute narrowing of the spinal canal by more than 50% compromise of the free antero-posterior diameter entails the risk of compressing the cord (Scarff 1960). The acute compression caused by impact (Fig. 10.8a, b) results in an acute neurological deficit of the involved motor and/or sensory axons in the cord. Chronic lesions of the cord may be caused by survival after impact-induced compression (Fig. 10.8c, d), as well as by congenital diseases of the vertebral column (achondroplasia), by neoplastic proliferation (Schwannoma, meningioma, carcinoma), by osteogenic degeneration (spondylosis, osteoporosis), by cartilaginous degeneration (protrusion of the intervertebral disc), by inflammatory diseases (spondylitis), or by iatrogenic events (myelograph-

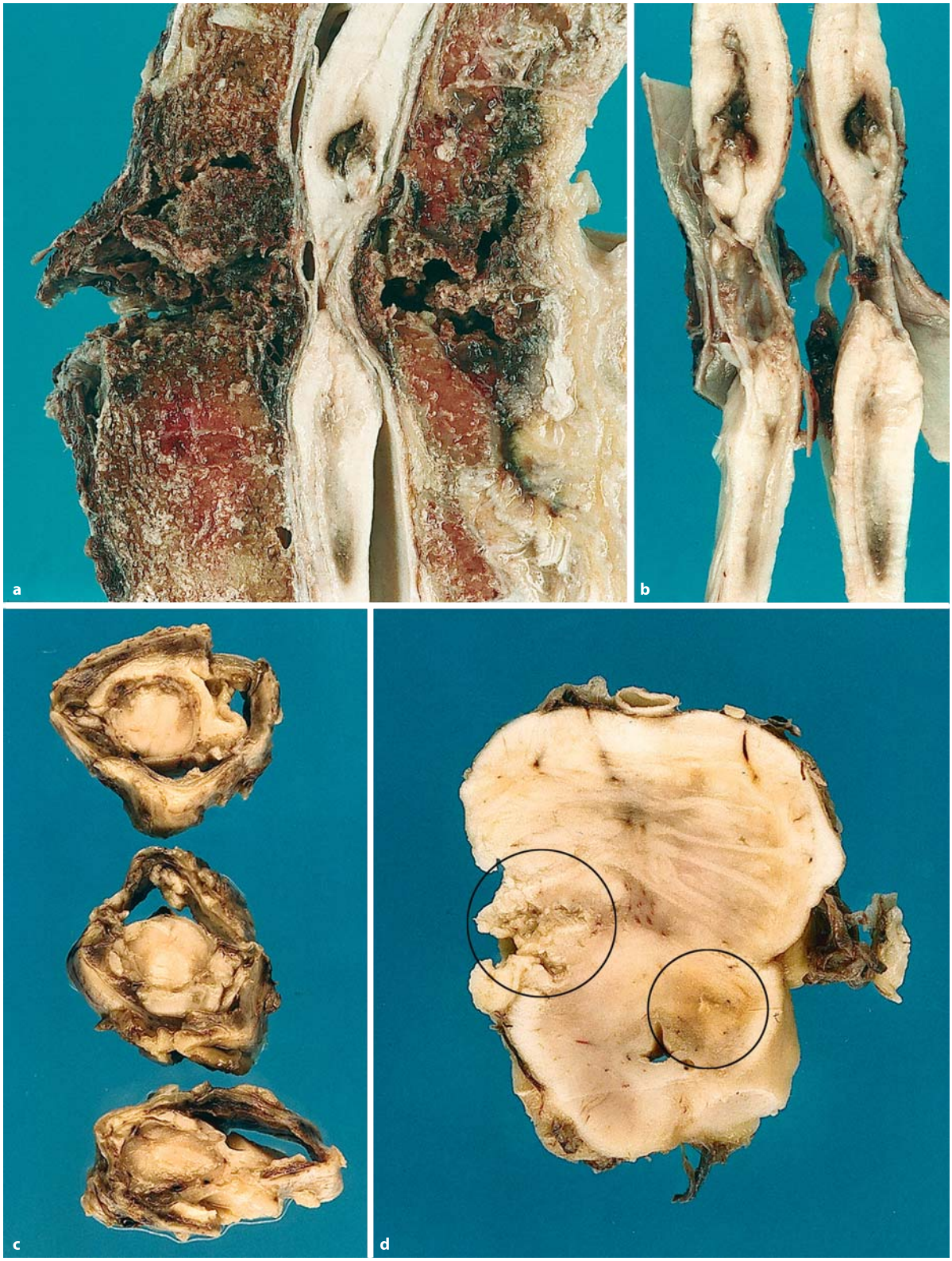


Fig. 10.8a–d. Mechanical spinal injury. **a, b** Acute compression injury associated with fracture of the spine, hemorrhages within the central parts of the spinal cord and softening of the compressed segment of the spinal cord; **c** scarring process as demonstrated by an intraspinal necrosis of white and gray matter; **d** necrosis of the periventricular pontine tissue associated with ascending degeneration of nerve fibers (circles)

ia). A secondary ascending alteration may be a focal necrosis in the medulla or pons (Fig. 10.8d). The cord may also be displaced and compressed by chronic subdural hemorrhage (Oehmichen and Meissner 1999): a compressive myelopathy may develop as a result of relatively prolonged intrinsic compression of the cord by encroachment on the space of the vertebral canal or by protruding intervertebral discs (Fig. 10.9).

Neuropathology. The pathological changes induced by compression of the cord derive largely from impairment of the intrinsic circulation (Hughes 1992). The early phase is marked by venous compression leading to venous stasis and edema. The myelin sheaths become swollen, conferring a vacuolated appearance of the white matter. A further increase in compression leads to necrosis and cavitation of the cord, particularly in the center of the cord. The last phase is characterized by a gliotic scar involving gray and white matter, with preservation of some of the axons. Wallerian (secondary degeneration) will result in ascending and descending fiber tracts at all levels distal to the lesion (see above). If the compression is only minor, the local decrease in blood flow can be compensated by autoregulatory mechanisms involving dilation of vessels and formation of collaterals at the site of compression (Palleske et al. 1970).

10.2.4.3 Vascular Myelopathy

Causes. Individual vessels and the spinal circulation are among the first tissue components to react to mechanical forces and thus contribute to the pathological and clinical sequelae of acute impact and compressive myelopathy. In rare cases, primary vascular involvement (arterial and/or venous disease) and/or systemic circulatory processes (prolonged hypotension and/or hypoperfusion) without compression can produce segmental or generalized cord lesions. Thus spinal cord ischemia attributable to a circulatory disturbance can occur in patients with aortic atherosclerosis or dissecting aortic aneurisms.

Neuropathology. The pathological changes associated with vascular myelopathy are comparatively uniform, depending largely on the cause of the underlying vascular disease. The gray matter is especially susceptible to circulatory disturbances. Thus, the necrosis induced by hypotension or a dissecting aortic aneurysm occurs mainly in the central areas of the cord, the areas dominated by white matter remaining well preserved. A thrombosis of the anterior spinal artery will usually result in necrosis of the anterior white matter as well.

Venous infarction of the cord is rare due to the highly anastomotic epidural venous plexus (Batson's plexus); its diagnosis is clearly warranted only in patients with extensive intramedullary venous thrombosis associated with hemorrhagic infarction, patients with carcinoma for example. The infarcted area in these cases involves multiple levels of the posterior and central portions of the cord (Rao et al. 1982).

Brain dead patients (patients with respirator brain, also termed, more accurately, non-perfused brain) exhibit a special form of hemorrhagic infarction of the upper cervical cord. The necrotic brain tissue, which has been deprived of oxygen and blood, is clearly demarcated from and rejected by the viable spinal cord tissue (Schneider and Matakas 1971; Oehmichen 1994). At the same time, necrotic brain tissue extends into the subarachnoid space of the cord and is associated with morphological signs of secondary inflammation and secondary vascular lesions in the cord.

10.2.4.4 Iatrogenic Cord Injury

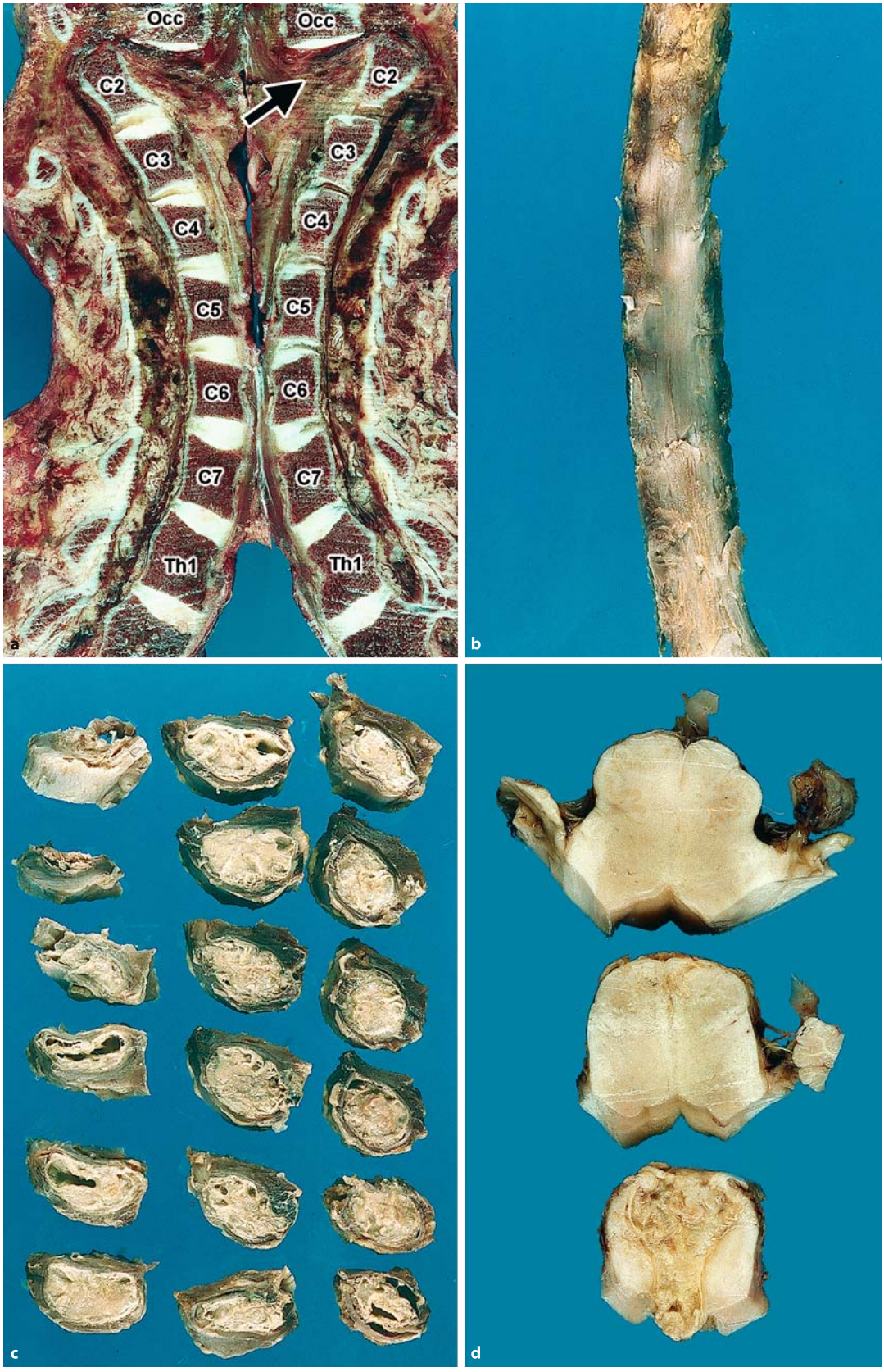
Complications may be due to *diagnostic spinal tap*, injection of contrast agents or drugs into the spinal subarachnoid space, or spinal anesthesia. Cases such as these are sometimes encountered in medicolegal practice. The clinical sequelae may result from mechanical irritation or chemical intoxication.

Spinal taps are usually performed at the level of the segments L5/S1, where only the cauda equina is located; spinal anesthesia is commonly administered at the level of the segments L2/L3, the tip of the conus medullaris usually lying at L1/L2 although it may extend further (Saifuddin et al. 1998). Access is achieved in most cases with an atraumatic needle and is checked by free flow of cerebrospinal fluid. Access at the level of L5/S1 causes a merely transient mechanical irritation of a single nerve root. Bleeding is often observed, but remains clinically inconsequential.

Access at the level of L2/L3 using spinal anesthesia sometimes induces persistent unilateral sensory loss (and sometimes pain) at the levels of L4/S1, a foot drop, and urinary symptoms (Reynolds 2001). Anesthesiologists therefore should avoid insertion of spinal needles above L3.

Injection of contrast agents or drugs may lead to fatal events if the guidelines of the pharmaceutical companies are not adhered to or if the medications are not meant for injection into the subarachnoidal space, e.g., vincristine (p. 359).

(For chiropractic manipulations of the cervical spine – see pp. 235 f).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C3
C4
C4
C5
C5
C6
C6
C7
C7
Th1
Th1
a
b
c
d

10.3 Injury of the Cervical Spine

Combined wounding of the head and spine, a type of injury termed "trauma in continuity," is very common. So-called "craniospinal injury" is seen in about 60% of cases with MBI (Davis et al. 1971). In cases involving significant brain trauma, therefore, it is imperative that a complete pathological examination is performed on the neck, vertebral vessels, and paraspinal muscles, partly even on the spine and the spinal cord, with special emphasis on the craniocervical junction. The utility of such detailed observations has been described by Saternus (Saternus 1979, 1993).

This type of examination is important, especially in regard to the diagnosis of neck vessel injuries as demonstrated by Rommel et al. (1999). His team determined the frequency of injury of vessels of the neck by Doppler studies performed on 60 patients following either severe MBI (n=29), mechanical cervical spine injury (n=26), or combined head and cervical spine injury (n=5). Clinically, three patients sustained severe cerebral ischemia due to neck vessel trauma. In 57 patients without clinical signs raising suspicion of neck vessel trauma, an ultrasound revealed abnormalities in three patients (=11%) with severe head injury, and in six patients (=20%) with cervical spine or combined head and spine injury, mainly related to the vertebrobasilar system in both groups.

The following morphological changes are associated with acceleration loading of the cervical spine:

- Hemorrhaging into the surrounding soft tissue; i.e., muscle and fat tissue hemorrhages
- Ligamentous tears in the spinal column
- Disc lesions
- Dislocations and subluxations of the vertebral bodies and small joints
- Bone fractures
- Injuries of the vertebral arteries (intramural dissection, laceration and/or thrombosis)
- Dural hemorrhages (epidural and subdural hemorrhages)
- Compression or laceration of the spinal cord, sometimes associated with spinal hemorrhage, axonal injury, and demyelination
- Edema and ischemic necrosis

The biomechanical forces and processes that can be physically explained are to be distinguished from the medically defined injuries they cause. The former include acceleration, bending, impact, compression, shearing, and tension; the latter, distortion injury, luxation, fracture, hemorrhage, and tearing injury.

Direct and indirect injuries of the upper cervical spine are partly determined by the *anatomy* of the craniocervical junction including the atlanto-occipital joint, the atlas (C1) and the axis (C2) with the odontoid process. The bony ring of the atlas provides a "bridge" between the occiput and the axis (Glasser and Fessler 1995). The occipital condyles, resting on the lateral masses of C1, allow much greater anteroposterior than lateral movement at the atlanto-occipital articulation. The dens of the axis extends rostral, posterior to the anterior arch of C1, and is embryologically the body of C1 that is missing. Ligaments connect these vertebrae to one another and to the occiput.

10.3.1 Biomechanical Features

10.3.1.1 Direct Injury

The following types of direct craniocervical injuries are encountered:

- *Dislocation injury* of the cervical spine (Figs. 10.5, 10.9) produced by forces acting in an anterior–posterior direction or, less often, in a lateral direction (Sances et al. 1986a, b).
- *Compression fractures* feature compression of the intervertebral discs or bursting of vertebral bodies. *Bending loads* create both tensile and compressive stresses, the former being much more likely than the latter to cause severe, often visible primary tearing of tissue and blood vessels as well as hemorrhage.
- *Hyperextension and/or hyperflexion fractures* are characterized by rupture of the rim of the vertebral body plates and/or by tearing and bleeding of the dorsal (= hyperflexion) and/or anterior parts (= hyperextension) of intervertebral discs. Lateral loads create similar injuries due primarily to tensile stress and are located on the right or left side of the vertebral body and/or intervertebral disc.

Fig. 10.9a–d. Compression-induced softening of the spinal cord as result of chronic spinal subdural hemorrhage after vehicular accident (luxation injury of the atlanto-occipital joint – *arrow* in **a**) with a survival time of 42 days. **a** Minor but disseminated hemorrhages within the intervertebral discs; **b, c** dural thickening as a consequence of an organized subdural hemorrhage as well as secondary necrosis of the spinal tissue; **d** ascending necrosis of the lower part of the medulla oblongata

Table 10.1. Range of motion (representative angles) of the cervical spine. Source: White and Panjabi 1990

	Lateral bending around the *x*-axis (°)	Flexion around the *y*-axis (°)	Rotation around the *z*-axis (°)
Occ–C1	±5	±25	±5
C1–C2	±5	±20	±40
C2–C3	±10	±10	±3
C3–C4	±11	±15	±7
C4–C5	±11	±20	±7
C5–C6	±8	±20	±7
C6–C7	±7	±17	±6
C7–T1	±4	±9	±2

10.3.1.2 Indirect Injury

The cervical anatomy allows rotational movements of the head in a three-axial system: lateral bending around the *x*-axis (= dorso–ventral axis), flexion around the *y*-axis (= right–left axis), and rotation around the *z*-axis (= cranio–caudal axis). The range of motion of the cervical spine is shown in Table 10.1 (White and Panjabi 1990). The spine is subject to the following forces, which lead to different injuries:

- *Rotational forces*, i.e., torque around the longitudinal *z*-axis, can disrupt the ligaments and displace the vertebral body, injuries that are sometimes associated with fracture of the odontoid, but usually not associated with neurological deficits. The main causes of such injuries are traffic accidents, blows, and chiropractic manipulation.
- *Vertical forces* (along the *z*-axis), e.g., created by an impact on the top of the head, can lead to compressed fracture of the atlas with bursting and separation of the ring of the atlas often into four parts (Jefferson's fracture).
- *Hyperextension forces* (retroflexion) can cause fracturing of the dens, the force being transmitted via the anterior ring of the atlas with consequent failure of the dens.
- A *force conveyed anterior to posterior* through the skull to the anterior ring of the atlas is transmitted to the dens where it can cause shear failure. Factures can also be produced by *hyperflexion force* (anteroflexion) and result in displacement of the vertebral body.

Flexion around the *y-axis* can produce abnormal anterior translation and dislocation. Posterior fracture dislocation is a possible consequence of translation associated with rotational movement from the opposite direction. A force vector not running directly along the *z*-axis, but generating torque around the *y*-axis, will cause rotary dislocation or subluxation.

The so-called *broken neck* (Figs. 10.5, 10.9), i.e., *fracture* of the *dens axis*, is comparatively rare. In most instances, it is caused by hyperflexion forward with retroversion of the dens fragments toward the medulla that leads to respiratory failure and may lead to rapid death (Unterharnscheidt 1992).

Injuries of the middle and lower cervical spine are caused by axial compression, or by translational hyperextension, or hyperflexion, sometimes associated with rotational components (Fig. 10.4). Among the results are disruption of the anterior (hyperextension) or posterior (hyperflexion) portions of the annulus fibrosus, or even – if the extension is extreme – traction fracture and displacement of the anteroinferior triangular portion of the vertebral body.

10.3.2 Indirect ("Whiplash") Injury

The head's relatively large mass of 4.5 kg makes it susceptible, upon *acceleration*, to acute *hyperflexion/hyperdistension* at the craniocervical and/or cervical vertebral column commissures. Injury is usually the result of *retroflexion*, in most instances combined with *rotational*, *compression or stretching loads*. Depending on the magnitude of the force, the morphological and clinical sequelae begin with *tearing of the musculature and tendons* and range from *luxation* to *fracture*. The strain is greatest on the *4th and 5th cervical vertebrae*, which are likely to dislo-

cate and fracture. The possible sequelae are partial or complete destruction of the spinal cord inducing partial or complete paraplegia. Morphologically the spinal cord exhibits local necrosis with histolysis.

One possible consequence of indirect injury of the neck is the clinical syndrome known as "whiplash injury." Walz (1993) correctly points out that the term is inappropriate since it connects an injury with the mechanism causing it. However, because it is so common in clinical usage, it will be used here. Because an organic cause for the described complaints cannot be found in most cases, whiplash trauma is a common subject of orthopedic, neurological or neurosurgical investigations and forensic opinions. It is even debated today whether whiplash injury is indeed an organic process (Bogduk and Teasell 2000) or rather a functional syndrome (Berry 2000).

The term "whiplash injury" designates a *complex of clinical symptoms* caused by minor or moderate acceleration of the head against the trunk (Barnsley et al. 1998). It is mainly seen in victims of frontal, lateral or rear-end traffic collisions. Frontal collision produces forward flexion, rear-end collision retroflexion of the cervical spine, lateral collision and lateral-rotational flexion. The risk of retroflexion can be reduced by headrests. The most important biomechanical effect of frontal collisions is anteflexion, which is usually associated with a rotation component around the *y*-axis. Head-neck kinematics could demonstrate the dynamics. Patients complain of neck pain with muscle spasm, limited motion, and/or loss of the normal cervical lordosis. Side-collisions cause more complicated injuries, especially fractures of the vertebrae.

In whiplash cases, X-rays of the cervical spine may appear normal. Patients complain of headache, numbness or weakness in one or both arms, tinnitus, vertigo. The symptoms are subjective and non-specific, i.e., unsupported by objective findings. They can arise immediately following the accident or after a symptom-free interval lasting several days and may disappear in a few days or persist for years in the form of chronic headache.

Experiments on human cadavers, healthy volunteers, and animals have shown a variety of soft tissue injuries ranging from muscle tears or sprains, ligament tears, especially of the anterior annulus fibrosus, and small or large fractures of the cervical vertebrae (Hoffman et al. 1992), and fractures or contusions of the zygapophysial joints (Kaneoka et al. 1992). Bogduk and Teasell (2000) pointed out that the zygapophysial joint injury is the only basis of chronic neck pain after whiplash. The same authors assumed that whiplash has an organic etiology and recommend diagnostic block of the cervical zygapophysial joints (Bogduk and Lord 1998). Berry (2000) listed several functional criteria for differentiating between simulated and real (functional) symptoms of chronic pain following acceleration of the cervical spine.

In another study, healthy volunteers were subjected to a load of Δv=10 km/h without suffering complaints of any kind (Schuller and Eisenmenger 1993; see also Fürbeth et al. 1999; Meyer et al. 1999; for further literature: Unterharnscheidt 2004). Despite the theoretical reservations associated with such a study, most German experts think that a load to the cervical spine of Δv=10 km/h or less cannot cause demonstrable neurological alterations or long-term injury with chronic symptoms. No predictions are possible concerning the sequelae of a load of Δv=>15 km/h. These results have been accepted by the German legal system (Griess 2000; Kieserling 2000; Wagner 2000). In contrast, Brault et al. (1998) reported that they had produced acute whiplash syndrome after a collision with Δv=4 km/h.

Patients may have a psychological motivation for trying to obtain compensation for pain and suffering from their insurance companies. A recent epidemiological analysis carried out in Canada found that the tort-compensation system's elimination of compensation for traffic injuries resulted in a lower incidence and better prognosis for whiplash injury (Cassidy et al. 2000). This finding is supported by recent experiments (Castro et al. 2001) in which 15–20% of 51 volunteers indicated symptoms within 3 days of placebo rear-end collision. Four weeks after placebo collision, nearly 10% had symptoms. Psychological examination revealed higher scores on the psychological scale of psychosomatic disorders in volunteers reporting symptoms. This study reveals that one need not be exposed to any significant biomechanical stress such as whiplash and can still behave as a whiplash patient. The criteria for being a whiplash patient after low-velocity collisions have long been assumed to include being injured. However, this assumption seems to be false, at least in some patients. The virtual elimination of whiplash in Lithuania, after compensation was eliminated, underscores these points.

10.3.3 Chiropractic Manipulation

Chiropractic manipulations of the cervical area are often cited in malpractice suits (Lee et al. 1995; Eckardt et al. 1997). The frequency of therapeutic neck manipulation remains unknown. A study of medical insurance claims in Ontario/Canada revealed that in 1998 there were at least 10.5 million chiropractic visits in a population of 11.5 million (Rothwell et al. 2001). Injuries usually occur at the vertebrobasilar system of the brain vessels causing strokes, most frequently due to arterial dissection – occasionally of the carotid artery, but most commonly of the verte-

bral artery (Rothwell and Norris 2002). The vascular injury is, as a result of forceful and vigorous movement, produced by extreme rotation and hyperextension of the head and neck. The most dangerous maneuvers seem to involve twisting movements (rotation in combination with extension and traction – see Schmitt 1991). However, systematic efforts to identify the risk factors of dissection, or to determine which manipulation techniques are most likely to cause problems have been unsuccessful (Hurwitz et al. 1996). The apparent unpredictability of stroke due to therapeutic neck manipulation is highlighted by the findings of a detailed review of 64 medicolegal cases by Haldeman et al. (2002). The strokes, which were mainly due to documented vertebral artery dissection, occurred at any point in the course of treatment, often after multiple uneventful manipulation sessions. Tragically, the majority of the strokes occurred in young adults due to the greater mobility of the young cervical spine before the desired "crack" is attained in the chiropractic adjustment. The mean age was 36 years, with 90% <45 years.

Spontaneous arterial dissections account for only 1–2% of all ischemic strokes. The *incidence* of complications, i.e., the risk of therapeutic neck manipulations, was estimated by different authors and varied widely, ranging from less than 1 in several million manipulations to as high as one in 20,000 (Vickers and Zollman 1999).

Death has been known to result from acute brain stem stroke secondary to occlusion of a vertebral artery during therapeutic manipulation of the neck (Daneshmend et al. 1984; Phillips et al. 1989) or dissection of a vertebral artery (Krieger et al. 1990).

Complications of other types of spinal manipulation are summed up by Assendelft et al. (1996) who stated that it is difficult to estimate the incidence of spinal manipulative therapy complications, as they are probably underreported in the literature. Most non-vertebrobasilar accident complications can be prevented by excluding patients with contraindications for spinal manipulative therapy. Patients who develop complications such as cauda equina syndromes should be treated as soon as possible. Vertebrobasilar accidents, however, are difficult to prevent and treat. Referral for spinal manipulative therapy should not be made to practitioners applying rotatory cervical manipulation. Information about the risk of vertebrobasilar accidents should be included in an informed consent procedure for cervical manipulation with thrust techniques.

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Injuries of Peripheral Nerves 11

Peripheral nerve pathology is of minor importance in forensic pathology since lesions of the peripheral nerves rarely cause death. Patients with peripheral nerve symptoms generally consult neurologists and neurosurgeons. Diagnosis following biopsy commonly will be performed by the clinical neuropathologist. However, because forensic neuropathologists are sometimes asked to give their opinion in cases involving physical injury of the peripheral nerves, we will deal with this topic briefly. For information regarding specific questions, the reader is referred to the Bibliography.

11.1 Anatomy

Peripheral nerves contain myelinated and unmyelinated axons from different types of neurons, subserving various motor effector functions or acting in a sensory function. The peripheral nerves include all except the first two pairs of cranial nerves, as these are more properly considered tracts, containing oligodendrocytes rather than Schwann cells. The neural components of the anterior spinal roots are motor fibers, those of the dorsal roots are sensory. The sensory fibers of the dorsal roots possess cell bodies that reside in the posterior root ganglia. The spinal roots fuse to form mixed nerve trunks. The lower cervical and lumbosacral regions contain plexuses of nerves, while the thoracic region is where preganglionic myelinated fibers from neurons in the lateral horns of spinal cord gray matter leave the anterior roots en route to the paravertebral chain of sympathetic ganglia or the splanchnic nerves. The preganglionic parasympathetic fibers pass out of the anterior spinal roots in the pelvic region and in the third, ninth, and tenth cranial nerves. The parasympathetic ganglia are located in or near their effector organs.

An outer connective tissue sheath, the *epineurium*, which binds the nerve fascicles together, is evident in transverse histological sections of the nerve (see Bischoff and Thomas 1975). Most moderate-sized nerves possess a single main muscular artery that runs longitudinally along the nerve within the epineurium. A perineural *sheath* with concentric layers of flattened cells separated by layers of collagen surrounds each nerve fascicle. The endoneurial compartment of nerve fibers is enclosed by a *perineurial sheath*. In addition to the nerve fibers, it contains blood vessels, Schwann cells, and bundles of endoneurial collagen fibers oriented longitudinally along the nerve fascicle. Cylindrical hyaline Renaut bodies are normal features of nerve, and are located in the endoneurial compartment (Asbury 1973; Dyck 1975).

Myelinated fibers are best demonstrated in paraffin sections stained for myelin with Luxol fast blue, Loyez or Heidenhain's hematoxylin techniques. Although it is difficult to satisfactorily visualize nonmyelinated axons in paraffin transverse sections of nerve, they can be stained by silver techniques (Bodian technique) and followed in longitudinal sections.

Transverse sections show the myelin sheath to be a tube surrounding the axon that extends along the nerve fiber from a position near the cell body and ceases 1–2 μm from the peripheral axon terminals.

Myelinated nerve fibers are divided into segments, each the length of a single Schwann cell and its respective myelin sheath. The axon is continuous from segment to segment, nodes of Ranvier marking the junctions between segments and the small gap between Schwann cells.

The thickness of the myelin sheath of normal peripheral nerves is proportional to the axonal diameter. Measured in transverse sections, this feature can help in detecting axons that are remyelinating following segmental demyelination if they possess disproportionately thin myelin sheaths.

A surface membrane, the axolemma, bounds the axon and is its cell membrane. Both neurofilaments and microtubules can be detected by electron microscopy. The axoplasm contains mitochondria and vesicles or elongated profiles of smooth endoplasmic reticulum.

11.2 Types of Morphological Reactions

Two general types of peripheral nerve degeneration are known, axonal and demyelinating. The processes of nerve fiber repair differ according to the type of lesion. Although peripheral nerve fibers have a striking capacity to regenerate and Schwann cells to remyelinate demyelinated or regenerated nerve fibers, it appears that the structural restoration is not complete. The degeneration and regeneration processes involve endoneurial connective tissue and myelin sheaths as well as axons, Schwann cells, and macrophages (for details, see Chap. 4.3, pp. 56 ff). The basic principles should be concisely repeated.

11.2.1 Wallerian Degeneration

The process of Wallerian degeneration (p. 66) refers to degeneration of the axon isolated distal to a cut of the axon from the nerve cell body. It includes axonal and myelin sheath changes as well as the reactions of local and hematogenous cells. Nerve fibers of the distal stump of transected nerves degenerate, while fibers of the proximal stump survive and are capable of regenerative outgrowth. If the nerve is completely transected, Wallerian degeneration in its most developed form occurs distal to the lesion. The axonal changes, however, are closely associated with Schwann cell changes that are much more complicated in myelinated than in unmyelinated nerve fibers. The degenerating myelinated nerve fibers vary considerably in their morphology depending on the interval after the traumatic event, distance from the lesion, and the part of the internode studied.

The first changes appear to involve an accumulation of organelles near the proximal and distal stumps of the transected fibers. As the distal part of the axon degenerates, a series of structural changes occur that ultimately lead to axonal fragmentation and dissolution. Then, 36–96 h after nerve crush, numerous discontinuities can be noted in the axolemma together with focal swelling or condensation of axons, dilatation of the axoplasm, zones of increased density and granularity, and dissolution of neurofilaments and microtubules (Webster 1962). Emigrating macrophages accumulate (Dyck et al. 2003).

Axonal changes are closely associated with secondary myelin or Schwann cell alterations. Fragmentation at the Schmidt–Lanterman incisures coincides with retraction of the myelin loops at the node of Ranvier and folding, contraction, and extension of myelin sheaths.

11.2.2 Retrograde Reaction (Axonal Degeneration)

Retrograde reactions involve (p. 66) sequences of events in myelinated fibers that are associated with complete degeneration of the affected neurons (neuronal degeneration) or of their distal processes (distal axonal degeneration or dying back). In distal axonal degeneration (Dyck 1975), there is a slight decrease in axon caliber with loss of neurofilaments, but relatively good retention of microtubules. More pronounced changes are associated with intoxication, characterized by a so-called dying back phenomenon involving nerve fiber degeneration. Neurons are preserved, but the distal ends of the nerves degenerate. „Dying back“ neuropathy is encountered in a number of toxic neuropathies, such as acrylamide and organophosphorus poisoning (Cavanagh 1979).

11.2.3 Remote Effects

Remote effects of peripheral nerve injury include proximal neuronal alterations (chromatolysis) and neurogenic muscle atrophy. An axon injured near the neuronal perikaryon undergoes *chromatolysis* (Fig. 3.1c). The earliest change is a proliferation of microglia around the neurons (Prineas and Spencer 1975). The neuronal cell body starts to swell, neurons lose most of their synapses, the Nissl substance (ultrastructurally, stacked granular endoplasmic reticulum and polyribosomes) migrates to the cell periphery, and the center of the cell is deprived of much of its staining by a regenerative process. *Muscle atrophy* can be caused by a motor nerve lesion. Soon

after axonal degeneration, the muscle fibers atrophy, groups of atrophic muscle fibers lying between groups of normal muscle fibers. The atrophic fibers are greatly reduced in diameter.

11.2.4 Edema

Wallerian degeneration after nerve crushing or curving is associated with increasing permeability of the blood–nerve barrier. The breakdown peaks in the distal parts about 8 days after wounding (Olsson 1975), when regeneration begins. Blood–nerve function is fully restored within about 30 days (Seitz et al. 1989).

11.2.5 Regeneration

The peripheral nervous system is surprisingly resilient, although there are certain limitations to nerve regeneration. The degree of recovery is determined by the type of lesion, its site in relation to the perikaryon, the patient's age, and whether and to what extent function can be restored (Schröder 1999). Regeneration is only possible if the nerve's endoneurial and perineurial connective tissue is largely intact and if optimal pathways to guide the regenerating axons to their original destination are provided by the bands of Büngner.

The reactive sprouting as a reaction of axonal injury appears to reflect an intrinsic neuronal response pattern (Hall 1989). The subsequent organization of the sprouting, in particular the orderly growth of mini fascicles toward the distant distal stump, does not occur in the absence of Schwann cells, which respond to axonal stimulation by temporary upregulation and re-expression of molecules to form a suitable substratum for axonal growth.

11.3 Types of Injury

Mechanical violence or other types of physical and chemical insult can damage the peripheral nerves: compression, transection, laceration, stretch, cold, heat, electricity, irradiation, and poisoning. Physical lesions usually result from an accident or are induced iatrogenically (Stöhr 1980) by injections, operations, bedding or irradiation. Clinically paresthesias predominate initially, followed by hypoesthesias and still later by anesthesias and motor paralysis. Characteristic types of peripheral nerve injury as portrayed by Schröder (1999) and others are described in the following.

11.3.1 Injuries by Compression and Percussion

Their long and superficial course makes the peripheral nerves especially susceptible to mechanical violence. Compression of sufficient magnitude and duration can injure axons (Aguayo 1975). Peripheral nerves subjected to forceful percussion, e.g., by a blow from a blunt object or by vibrating instruments, and compression against underlying bony structures can suffer axonal damage resulting in Wallerian degeneration distal to the site of injury.

The clinical feature is characterized by parasthesias within 1–2 min. Within 1 or 2 min of compression also morphological changes are to be seen: the border fibers of fascicles are edematous and more affected than centrally located fibers. Usually there is no or little transection of nerve tubes (basement membrane), perineurium, blood vessels, and epineurium. Therefore, transected axons can regrow to previous targets (Dyck et al. 2003). The primary injury is followed by marked periaxonal and intramyelinic edema with segmental demyelination leading ultimately to axonal discontinuity (Krivickas and Wilbourne 1998). Chronic nerve compression and strangulation induces swelling of proximal axons and nerves with slight thickening of the perineurium (Mackinnon et al. 1986). The superficial nerve fibers appear to protect deeper fibers. Early reactions include segmental demyelination (with remyelination) and axonal degeneration (with regeneration) as well as paranodal myelin sheath intussusception (Ochoa et al. 1972).

11.3.2 Injuries by Traction and Elongation

Stretching of the nerve trunk, nerve plexus, and spinal nerve roots can irreparably tear the nerve roots away from the spinal cord, with consequent degeneration of peripheral nerve motor axons. Because the lesion is located centrally to the spinal ganglia, the afferent (centripetal) and presumably also peripheral (centrifugal) sensory axons and their cell bodies remain intact despite a loss of sensation (Schröder 1985).

Peripheral nerve injury is the most common injury incurred by infants during childbirth. Overstretching of the nerves, usually because of extreme lateral traction, can damage the brachial plexus.

This may occur in breech delivery when the head is delivered or during cephalic deliveries as the shoulder is luxated free. The upper roots are the part of the plexus most vulnerable to stretching. Brachial plexus lesions mainly affect large infants with fetal depression who are subjected to abnormal labor and delivery. Proximal upper limb involvement, known as Erb's palsy, accounts for about 90% of brachial plexus lesions.

Klumpke's palsy is associated with injury of the brachial plexus and can lead to Horner's syndrome; i.e., combined ptosis, anhidrosis and miosis, because it affects the sympathetic branches originating at T1. Sympathetic injury can also disturb pigment formation in the iris, affected eyes remaining blue for months or years.

Slight elongation of nerves can cause temporary stimulus conduction block (Seddon 1975) lasting several hours. If the elongation is more severe, it can disrupt axonal continuity and possibly lead to tearing of the neural connective tissue and intraneural bleeding. Regeneration is hindered by the attendant intraneural fibrosis.

11.3.3 Injuries by Transection

The total separation of all constituents of the nerve, i.e., epineurium, blood vessels, perineurium, columns of Schwann cells and nerve tubes, results in a severe misalignment of nerve tubes. Either the regeneration process is totally frustrated, or the regenerating neurites grow into the nerve tube of a different functional fiber, and, assuming that such a fiber regrows to the target, it may not be able to make a functional innervation and so presumably dies back. The regeneration may be misdirected. From the clinical point of view, in spite of the misdirected regeneration often a delayed functional adaptation is possible.

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Special Physical Trauma 12

The »Special Physical Traumas« dealt with in this chapter differ from those listed under »Mechanical Trauma« (Chaps. 2–6) in their causes, even though their effects may sometimes be mechanical in nature (cf. pressure injury). This chapter will discuss a representative selection of such traumas, providing a description of the most common neuropathological findings for each.

12.1 Thermal Trauma

For metabolism and enzymes to function properly, the human body must maintain a state of homeothermy, which is controlled by paired anterior (heat dissipation) and posterior (heat retention) autonomic regulatory centers in the hypothalamus. Under physiological conditions, body temperature rarely varies more than ±1°C from the baseline throughout most of an individual's life time. Thermoregulation

is highly efficient, employing components of several regulatory systems (Boulant 1991). Temperature extremes of 25°C or 42°C are still compatible with life, but they can cause major functional loss and are potentially lethal. Temperatures below or above these extremes nearly always result in death.

Uniformity of core body temperature is maintained, e.g., by alterations in the rate of blood flow through the vascular beds of the deep organs dependent upon the rate of heat production of the perfused tissues themselves. Even if an organ receives just the minimum amount of blood flow sufficient to cover its need for oxygen, the heat produced by its aerobic metabolism can be removed by venous blood warmed by less than 1°C above the temperature of the arterial blood flowing into the organ.

The principal targets of the central thermoregulatory mechanisms are the cardiovascular system, the body's water content and blood osmolarity, the respiratory system, the rate of metabolic heat production, and the circulation to the skin. The release of heat via conduction, convection, radiation, and evaporation is regulated in particular via the cutaneous circulation. The metabolic activity of the body – and thus its O_2 and glucose consumption – is dependent upon body temperature. The brain, i.e., the hypothalamus, limbic system, lower brain stem, and reticular formation, is not just the main regulatory organ – it is also one of the organs most liable to thermal regulatory dysfunction (Oehmichen 2000a, b).

12.1.1 Hypothermia

Hypothermia is defined as the lowering of the core body temperature from its normal level of 36.5°C to <35°C (Petersdorf 1991). A core body temperature of 33–35°C is usually classified as *mild hypothermia*, of 30–33°C as *moderate hypothermia*, and <30°C as *severe hypothermia* (Lønning et al. 1986).

12.1.1.1 Incidence

Generalized hypothermia is most frequently encountered during the winter months and in extremely cold regions such as Eastern Siberia (Donaldson et al. 1998). In the cities of the industrialized West, it most often strikes the homeless. In the period of 1979 to 1998, 13,970 persons died of hypothermia in the USA, an average of 699 deaths per year; of all hypothermia-related deaths, 6,857 (=49%) occurred among persons aged >65 years (Compressed Mortality File of the CDC's National Center for Health Statistics). Interestingly, no apparent relationship has been established between cold stress in winter and the mortality rate due to influenza (Donaldson and Keatinge 2002). Hypothermia occurs in mountains, especially in victims of avalanche, in survivors of shipwreck who are pulled from frigid waters, and unfortunate recreational swimmers and boaters.

Surgical procedures entailing a likelihood of prolonged hypoxia of the brain (e.g., the neuroprotection in heart transplantation) are often performed after induction of artificial hypothermia (lowering the body temperature to 33°C or 30°C) to decrease brain metabolism, thus extending the period of ischemic tolerance. Cooling the body has been proven to protect the brain from ischemic injury. Moreover, two independent research groups found that lowering of the body temperature to 33°C for 12 or 24 h in comatose survivors of cardiac arrest resulted in an impressive improvement in the neurological outcome (Bernard et al. 2002; Holzer et al. 2002, see also Curfman 2002). In contrast, based on the results of recent multi-center clinical trials, hypothermia has evidently proven to be ineffective as a specific treatment in cases of non-penetrating mechanically induced brain injury (Narayan 2001; Clifton et al. 2001 – in contrast to Clifton et al. 1993; Dixon et al. 1998; Soukup et al. 2002).

The mechanisms of hypothermic neuroprotection during cerebral ischemia have recently been reviewed by Colbourne et al. (1997). The notable benefit of a state of mild hypothermia is probably due to a combination of variables which make it the ultimate neuroprotective cocktail (Corbett and Thornhill 2000). The results of isolated experiments providing evidence of a neuroprotective effect of hypothermia include, e.g., an observed decrease in the number of axons taking up labeling for β-amyloid precursor protein, which is a marker of disruption of fast axonal transport. Hypothermia has also been shown to lead to a reduction in the loss of microtubules and the compactness of neurofilaments occurring in animals returned to normothermia after experimentally induced hypothermia (Maxwell et al. 1999). Otherwise, pathophysiologically lowered metabolism and secondary angiospasm are known to induce tissue necrosis, chiefly of the skin in the distal extremities, with simultaneous release of potassium (Schaller et al. 1990) and an increase in blood acetone levels. Artificially induced local hypothermia of the brain – cold trauma – has been applied in experimental neurotraumatology to produce a bloodless sterile necrosis for observation of the brain's wound healing processes.

12.1.1.2 Pathophysiology

The following basic information is important in the understanding of hypothermia, its causes and its sequelae (Helm et al. 1995):

- The very young and the very old are most susceptible to hypothermia.
- Body fat acts as insulation; thus, the thinner the person, the faster body heat is lost.
- Alcohol consumption (Weyman et al. 1974) and drug ingestion (Reuler 1978) increase the risk of hypothermia.
- Voluntary muscle activity may increase energy production by as much as 25 times the basal metabolic rate (Astrand and Rodahl 1977).
- Exposure of the head, including the face and neck, accelerates the cooling process (Reuler 1978).
- Injuries, especially head injuries, appear to increase the risk of hypothermia (Luna et al. 1987).
- The thermal cooling capacity of a moving medium (air, water) is greater than that of a medium that is not moving.
- The thermal conductivity of still water is 32 times greater than that of still air; therefore, water accelerates the cooling process.

As mentioned above, hypothermia increases the *brain's tolerance* to *ischemia*, as it slows metabolic processes and decreases oxygen consumption. At a core temperature of 20°C, cardiac arrest can be tolerated for up to 30 min and - in very rare cases - up to 4 h (Walpoth 2004) without clinically significant neurological or neuropsychological deficits (Barratt-Boyes et al. 1976; Messmer et al. 1976; Walpoth et al. 1997). Hypothermia appears to inhibit the ischemia-induced efflux of amino acids and thus to lessen neuronal damage (Ooboshi et al. 2000). Another possible mechanism of hypothermic neuroprotection has been the recently discovered upregulation of the pentose shunt, which normally diverts 2–6% of glucose from Embden–Meyerhof glycolysis (Kaibara et al. 1999). It is unusual for hypothermia to upregulate a system, but the relative upregulation of the pentose phosphate pathway may yield a number of metabolic products that are beneficial: UDP-glucose for DNA repair, NADPH for maintenance of damaged lipid molecules, etc.

During hypothermia the energy level will be maintained slightly better than under normothermic conditions, i.e., ATP breakdown is reduced more than its synthesis (Erecinska et al. 2003). Intracellular alkalinization stimulates glycolysis and independently enhances energy generation. Lowering of temperature during hypoxia-ischemia slows the rate of glucose, phosphocreatine, and ATP breakdown and lactate and inorganic phosphate formation, and improves the recovery of energetic parameters during reperfusion.

The benefit of artificially induced hypothermia of 26°C in coronary artery bypass operations is thought to result from a 60% reduction in the cerebral O_2 consumption as well as a 45% reduction in the consumption of glucose (Stephan 1991). However, since mild hypothermia, which does not lower O_2 uptake, may also be beneficial, it seems likely that hypothermia provides protection against numerous deleterious biochemical mechanisms including calcium shifts, excitotoxicity, lipid peroxidation and other free radical reactions, DNA damage, and inflammation (Safar 1997; Safar and Kochanek 2002). At the same time, there is an increase in cerebral blood flow (to about 200% of normal) secondary to alterations in the acid–base balance, which is related to temperature. This balance is necessary for maintaining homeostasis of the temperature-adapted 40 mmHg pCO_2 needed for proper brain functioning.

12.1.1.3 Clinical Features

The conscious hypothermic patient will exhibit slurred speech, slowed mental reactions, and uncoordinated and clumsy muscular movements (Paton 1983). Shivering may or may not occur. Depending on the degree of peripheral vasoconstriction, the patient may be cadaver-like, pale, pink or cyanotic. If core body temperature drops to between 32°C and 30°C, the victim becomes increasingly somnolent and may sink into unconsciousness; vasodilatation occurs and the skin turns to a bright pink. The reaction of pupils to light is sluggish. Below 26°C, victims appear cadaver-like, with cyanotic skin, barely discernible breathing, stiffness of the musculature and dilated pupils that may not react to light. In this state, victims may be mistaken for dead.

There is generalized edema, the *skin* is often puffy and cold, not only on the extremities, but over the trunk in areas protected by clothing. The face may present an appearance of severe myxedema. The subcutaneous tissues have an unnatural, doughy feel. The *pulse* may not be palpable, the heart rate is slowed in proportion to the decrease in temperature. *Arrhythmias are common*, especially *atrial fibrillation*. Blood pressure, if obtainable, is lower than normal.

Blood viscosity increases with cold, which leads to a decrease in peripheral circulation, but the diminished extraction of oxygen results in very little hemoglobin desaturation and a bright pink periphery. *Gastrointestinal function* ceases. *Neuromuscular reflexes* are diminished or lacking entirely at lower temperatures.

The *hematocrit* rises in part due to hemoconcentration secondary to cold diuresis and in part due to loss of fluid to subcutaneous edema. An intrinsic defect of clotting can occur, the *coagulation cascade* being retarded and bleeding time increased (Fisher et al. 1958). *Petechial hemorrhages* have been reported (comp p. 548).

At core temperatures below 35°C other factors beside the decrease in metabolism can play a role in the

changes caused by hypothermia (Tipton et al. 1999). In water, for example, uncontrollable hyperventilation can impede coordination between swim stroke and respiration, thus increasing the risk of aspiration and an inability to swim (Golden et al. 1986).

A core temperature of below 28°C causes circulatory and neurological disturbances (Danzl and Pozos 1994), which are associated with high mortality rates (Locher et al. 1991; Larach 1995; Kornberger and Mair 1996). The single most important prognostic indicator may be serum potassium, the level of which can serve as a triage tool for initiation of cardiorespiratory resuscitation in victims of profound hypothermia (Schaller et al. 1990).

Survival of controlled hypothermia without brain damage undoubtedly depends on the hypothermia-induced increased tolerance of the brain to ischemia, but successful revival depends on slow warming procedures to avoid arrhythmogenic temperature gradients in the sub-endocardium where the cardiac conduction system lies. Follow-up examinations are essential.

Death caused by hypothermia is commonly associated with high blood (and urine) levels of acetone (Fujita et al. 1998) and potassium (Muszkat et al. 2002), which may be an additional diagnostic marker at autopsy.

12.1.1.4 Neuropathology

Autopsy cannot definitively prove hypothermia as the underlying cause of death with a single exception (*Morbidity and Mortality Weekly Report* 1983, 32:46–48), i.e., demonstration of elevated acetone levels in the blood must arouse a suspicion of hypothermia (see Hanson and Johnson 1966; Fujita et al. 1998). Morphological changes secondary to angiospasm and/or vascular dilatation, such as local ischemic, hemorrhagic necroses, and/or petechial hemorrhages, can also be demonstrated in the brain (Madea and Oehmichen 1989). It is not clear whether these phenomena result directly from the cold or are iatrogenic, from therapy. Their occurrence is often delayed, possibly after unsuccessful attempts at warming the victim. Hyperemia, edema, and (petechial) hemorrhages (so called cold-induced purpura) are found, especially in the area of the third ventricle (Jacob 1955; Peters 1970; Schmitt 1983). Caplan et al. (1984) observed cold-related intracerebral hemorrhages obviously caused by a cold-associated increase of catecholamines and a secondary increase of blood pressure perhaps as a consequence of a primary contraction of the vessel walls and consequent ischemia.

Local cold trauma produces a sterile necrosis, inducing a (predominantly) local cellular reaction (granulocytes, macrophages, astrocytes, fibroblasts) as well as an increased release of cytokines. This necrosis is apparently secondary to local angiospasm (Donaldson et al. 1998). Although systemic hypothermia is reported to have no additional specific effects on blood–brain barrier permeability (Krantis 1983), local hypothermia stimulates permeability (Schindelmeiser et al. 1987). In addition to neuropathological findings, indications of hypothermia may be found at autopsy on the exterior of the body in the form of pink to brownish-pink patchy discolorations of the skin over the large joints (chilblains) or as numerous acute erosions in the gastric mucosa (Wischnewsky's spots – Ehrlich 2004).

The peripheral nerves are more vulnerable to cold than other tissues and can be injured if an individual is exposed to ambient temperatures below 10°C. Axons of myelinated nerve fibers are injured first (Kennett and Gilliatt 1991). As in heat trauma (Hoogeveen et al. 1992), cold-induced impairment of the blood–nerve barrier can induce a marked endoneurial edema with a consequent rise in intraneural pressure. In the absence of endoneurial lymph vessels, this can inflict damage on peripheral nerve fibers.

12.1.2 Hyperthermia

Hyperthermia is defined as an increase in core body temperature to >37.5°C (for review see Jelkmann 2000). The maximum core temperature compatible with life is 42°C. For every degree Celsius rise in core temperature, the metabolic rate increases by 13% (Holtzclaw 1992). Early rewarming, for example, after cardiac arrest may be detrimental to recovery of the brain. Moreover, mild cerebral hyperthermia worsens brain injury (Dietrich et al. 1990). The increased metabolic demand is especially harmful to ischemic neurons.

Heat-related illness includes sunburn, heat cramps, heat rash, heat exhaustion, and heatstroke. The most serious types of these heat-related illnesses are heat exhaustion, sunstroke, and heatstroke.

12.1.2.1 Incidence

Hyperthermia-induced disease arises secondary to generalized overheating of the body during physical exertion at high environmental temperatures, in crowded meeting rooms with poor ventilation, during heat waves and in the desert (environmental hyperthermia). In the United States each year approximately 400 deaths are attributed to excessive natural heat (Semenza et al. 1996). During 1979–1999 in the United States, 8,015 deaths were associated with excessive heat exposure. Of these, 3,829 deaths (48%) were due to weather conditions (National Center for Health Statistics 2002). In July of 1995, at least 700

heat-related deaths were recorded in Chicago (Semenza et al. 1996). In Missouri, New Mexico, Oklahoma, and Texas during July–August 2001, 95 deaths were attributed to excessive natural heat (*Morbidity and Mortality Weekly Report* 2002; 51:567–570).

Infants, the elderly, socially isolated people, those who are bedridden, and those with mental and chronic illnesses are at high risk (Kaiser et al. 2001). The elderly are susceptible to heat-related illness because they are less able to adjust to physiologic changes, e.g., vasodilation that occurs with exposure to excessive heat, and are more likely to take medications for chronic illnesses that increase the risk of heat-related illness (Kilbourne 1997). Infants are known to be sensitive to heat. For example, mild fever can progress quickly to heatstroke if heat stress occurs. Heatstroke can occur in young healthy persons who are exercising (Vassallo and Delaney 1998).

Infant and early childhood death caused by environmental hyperthermia (fatal heatstroke) is rare, but typically occurs in vehicles or beds. Ten cases ranging in age from 53 days to 9 years have recently been reported (Krous et al. 2001; see also Wadlington et al. 1976; Bacon and Bellman 1983). Infants and young children left unattended in motor vehicles are at high risk of heatstroke and death because intra-vehicular temperatures can increase quickly to lethal levels, especially when the vehicles are parked in direct sunlight.

Hyperthermia is frequently seen in patients following mechanical brain injury which may be due to posttraumatic cerebral inflammation, direct hypothalamic damage, or secondary infection resulting in fever (Thompson et al. 2003). Regardless of the underlying cause, hyperthermia increases metabolic expenditure, glutamate release, and neutrophil activity to levels higher than those occurring in the normothermic brain-injured patient. This synergism may further compromise the injured brain, enhancing the vulnerability to secondary pathogenic events, thereby exacerbating neuronal damage.

Moreover, brain hyperthermia is also a symptom of methamphetamine (METH) intoxication and a factor implicated in neurotoxicity during chronic METH use (Käferstein and Sticht 2000). METH produced dose-dependent hyperthermia, with brain structures showing a more rapid and pronounced temperature increase than the muscle. At the highest dose, brain and body temperatures increased 3.5°C to 4.0°C above basal levels and remained elevated for 3–5 h. Stressful and other high activity situations such as interaction with a conspecific female are also known to induce a significant hyperthermic response in the rat. METH administration during social interaction produced stronger and longer-lasting increases in brain and body temperature than induced by the drug alone, heating the brain in some animals to near its biological limit (41°C) (Brown et al. 2003).

12.1.2.2 Pathophysiology

In normothermia, heated venous blood from the deep organ vasculature and cooled venous blood from the periphery mix to result in a stable arterial blood temperature (Brengelmann 2002). Hyperthermia develops when the venous streams from the periphery (from heated skin or active skeletal muscle) supply heat to the mix. Then arterial temperatures rise, followed with little lag by an increase in temperatures of the well-perfused tissues since their blood flow rate is high relative to their mass.

Because splanchnic and renal blood flow rates drop drastically in hyperthermic humans (Rowell et al. 1970), the temperature increment of the venous blood draining from these organs will approach the 1°C limit consistent with steady-state aerobic metabolism. Temperatures of the organ parenchyma, therefore, rise relative to arterial temperature. As far as we know, brain blood flow is unaffected in the readjustment of distribution of cardiac output that occurs in hyperthermia (Rowell 1986). The heat that is being delivered to the body arrives via heated blood.

At the cellular level, it is known that cells within the CNS exhibit an altered pattern of gene expression and elevated synthesis of heat shock proteins (HSP – Tytell et al. 1993). The 70-kDa protein HSP 70 is one of the major proteins induced by thermal stress. The HSP 70 gene is activated in glial cells within 1 h, in neurons within 5 h.

The harmful effect of hyperthermia is caused by several additional factors (Corbett and Thornhill 2000):

- High body temperatures escalate the rate of glutamate release (Sternau et al. 1992).
- High body temperatures stimulate the production of oxygen radicals following recirculation after global ischemia (Globus et al. 1995).
- Hyperthermia compromises the blood–brain barrier, leading to edema (Kil et al. 1996).
- Hyperthermia increases cytoskeletal protein degradation, e.g., spectrin, microtubule-associated protein 2 (MAP2), and calpain activity (Morimoto et al. 1997).

12.1.2.3 Clinical Features and Neuropathology

In addition to the factors named above, the victim's age and preliminary state of health, especially of the cardiovascular system, also play a role, as does the degree of dehydration (Visser and Gallagher 1998). Recent experimental data (pigtail monkeys, cerebral temperature: 42°C) provide evidence that the CNS exhibits functional disturbances, although the brains were found to be macroscopically and microscopically normal in six of eight monkeys (Eshel and

Safar 2002). The authors concluded that the acute cerebral derangements during and after lethal hyperthermia are reversible. The cause of death is not structural CNS damage but systemic hemodynamic deterioration.

Moreover, febrile seizures are known, especially in infants and children, but the mechanisms underlying the generation of febrile seizures are poorly understood. By animal experiments it could be stated (Liebregts et al. 2002) that hyperthermia contributes to seizures in the immature hippocampus by decreasing CA1 inhibition while in adults a decrease in CA1 inhibition requires a high degree of hyperthermia, and hippocampal seizure generation is opposed by an increase in dentate gyrus inhibition.

The following clinical and morphological syndromes are to be distinguished.

12.1.2.4 Heat Exhaustion

The clinical features are characterized by heavy sweating, muscle cramps, fatigue, weakness, cold or clammy skin, dizziness, headache, nausea or vomiting, and fainting. Untreated heat exhaustion can progress to heatstroke (Knochel 1974). Even with prompt medical care, 15% of heatstroke cases are fatal (Kilbourne 1997).

Heat exhaustion can be caused by high ambient temperatures as well as by excessive endogenous heat generation due to, for example, fever or physical exertion. It is characterized by dilatation of the peripheral vessels and a drop in circulating blood volume (hypovolemia). Heat prostration is almost always survived, making acute morphological findings rare. The functional changes are attributable mainly to the state of the victim's hemodynamics.

12.1.2.5 Sunstroke (Insolation)

So-called sunstroke is heatstroke caused by prolonged exposure of the uncovered head to the sun. It is apparently triggered by a 1.5°C to 2.5°C increase in brain temperature (Koslowski and Krause 1970). The brain is within the head, which comprises 9% of the body surface area, and is subjected to selective heating and cooling. Brain temperature is affected by local cooling (e.g., nasal ventilation) and heating (e.g., the helmeted head) factors (Cabanac 1993). Symptoms in sunstroke develop suddenly on exposure without prodrome and include headache, visual disturbances, nausea, delirium, confusion, and coma. Like heat prostration, sunstroke is usually survived; persistence of symptoms is an indication of brain edema. In cases resulting in death, which are virtually indistinguishable clinically from heatstroke, the morphological picture is dominated by edema and congestion.

12.1.2.6 Heatstroke

Clinical Features. Heatstroke is characterized by high body temperature (core temperature: >41.1°C), red, hot, dry skin, and no sweating; rapid pulse, headache, dizziness, nausea, confusion, disorientation, delirium, and coma. The clinical picture of heatstroke must be regarded as extremely life threatening, ending in death in about 50% of cases (Shibolet et al. 1967; Sherman et al. 1989; Hiss et al. 1994).

Pathogenesis. The true pathogenetic process remains unknown (Brengelmann 2002) in spite of recent experimental data (Eshel and Safar 2002). Heatstroke is caused by a failure of the diencephalic temperature regulation centers. Heat exhaustion also results from dehydration combined with salt deficiency. Only a few experimental studies have dealt specifically with heatstroke. Sharma and Westman (2000) could show that the effects of heat can disrupt the blood–brain barrier, leading to cerebral edema which, combined with secondary ischemic changes, can lead to cerebral functional disturbances. According to these authors, there is a simultaneous upregulation of GFAP and vimentin in astrocytes as well as an increased expression of heat shock proteins, nitric oxide synthase, and heme oxygenase.

Neuropathology. The morphology of heatstroke is characterized by hemodynamically induced injury (shock and blood–brain barrier disturbances with plasma and cellular extravasation – see Jacob 1955; Sohal et al. 1968). There is a conspicuous preponderance of neuronal loss in the cerebellar cortex (Shibolet et al. 1967). Petechial hemorrhages (Lahl 1974) and purpura (Schwab 1925), sometimes in the form of hemorrhagic encephalitis (Büchner 1962), are seen; neuronal swelling has been described in a few cases (Schwab 1925). But the signal neuropathologic finding is the brain edema described by several authors (Sharma and Westman 2000; Krous et al. 2001) and explained by a heat-induced disturbance of the blood–brain barrier (Sharma and Westman 2000). Other postmortem findings vary and depend on the duration of survival and hyperthermic exposure (Hiss et al. 1994) and include petechiae, pulmonary edema, visceral cellular degeneration and necrosis as well as disseminated intravascular coagulation (DIC) (Di Maio and Di Maio 2001).

Heatstroke results in a wide variety of neurological complications, which are secondary to cerebellar, basal ganglia, anterior horn cell, and peripheral nerve involvement (Kalita and Misra 2001). In a review comprising 29 patients from 13 published re-

ports, a cerebellar syndrome was the most common (12 patients). The pancerebellar syndrome following heatstroke is attributed to a direct thermal effect on the cerebellum resulting in degeneration of Purkinje cells (Yaqub 1987). Computed tomography and magnetic resonance imaging (MRI) studies have also revealed cerebellar atrophy and white matter involvement (Mehta and Baker 1970). However, in various cases, the cerebellar atrophy was noted on MRI after 10 weeks, being progressive for 1 year (Albukrek et al. 1997), or appeared 1 year later and became more marked at 2 years (Biary et al. 1995).

12.1.3 Trauma by Fire and Burns

12.1.3.1 Incidence

Death from fire that results directly or indirectly from the effects of flames and/or heat on the brain is extremely rare. In most cases, acute death is primarily caused by shock or inhalation of poisonous fumes, especially of carbon monoxide, before the brain can be affected by flames or heat. A delayed death, on the other hand, is caused by protein loss, edema, renal failure, and/or secondary infection.

The mortality rate from burns depends in large part on three factors: the age of the victim, the severity and extent of the burns, and the intensity and composition of the fumes. Mortality can be depicted by scatter diagrams showing survivors and fatalities plotted against age and the percentage of full-thickness burn. Elderly victims may die of chronic organic diseases in combination with burns, e.g., from stroke.

If the victim suffers only burning of the skin of the head, which comprises 9% of the body surface, the aforementioned correlation between age and percentage of full thickness burn would indicate that such an injury is compatible with survival almost regardless of age, provided other aggravating factors are excluded.

12.1.3.2 Clinical Features

As mentioned above, injury and acute death result primarily from *asphyxia* or *inhalation of poisonous fumes* rather than from the effect of flames on the brain. The relationship between the duration of exposure to noxious gases or oxygen depletion and their effects was summed up by Davies (1991, Table 14.2). The fumes, especially carbon monoxide (CO-intoxication, see pp. 347 ff), induce coma. In most cases, the intoxication itself proves fatal or the coma-induced immobility leads to death from the flames and heat. If more than 40% of hemoglobin (carboxyhemoglobin level) is bound to CO, the victim may fall into a coma and if more than 60% is bound, the victim will die.

In survivors, the heat as well as inhaled poisons can cause *inhalation injury* of the upper respiratory tract and lungs, with loss of surfactant-associated proteins and injury of type II pneumocytes. A *shock phase* develops if the victim survives the primary injury of heat, fire, fumes, and inhalation injury. The severity of shock symptoms depends on the extent of skin burned, not the depth of burning. The factors underlying the grave circulatory and metabolic disorders as a result of burn injury are gradually being identified. Distant effects of thermal injury of the skin include intravascular hemolysis, vascular permeability, acute lung injury, renal failure, and impaired liver function. Both primary fume-induced CNS intoxication and indirect sequelae such as hypoxia due to inhalation injury or shock can lead to changes in the brain.

12.1.3.3 Neuropathology

In cases of acute death as a consequence of CO intoxication, signs of CO poisoning predominate, with macroscopically evident bright red coloration in formalin-fixed brain sections (Fig. 17.3). Postmortem alterations, such as coagulation of the brain surface or of the entire brain, are also visible (Fig. 12.1c, d), especially if the cranium has lost all of its soft tissue or has burst from the heat (Fig. 12.1a, b). The brain may be shrunken, although the structures of the gray and white matter can still be differentiated. The brain is partially or wholly dehydrated (Dotzauer and Jacob 1952; Klein 1975) and coagulated. These changes, like the accumulation of blood in the epidural space (burn hematoma – Fig. 12.1e, f), occur postmortem (see below). The almost invariably demonstrable high carboxyhemoglobin levels of >50% indicate that the victim had already died of CO poisoning before heat affected the brain (Gerling et al. 2000; Oehmichen 2000a).

The morphological differentiation between intravital and postmortem injuries may be difficult as demonstrated in Fig. 12.2. Similarly, proof of epidural and subdural accumulation of blood as well as the demonstration of herniation, of cortical hemorrhages in the frontal base of the brain and the pons give evidence of a vital mechanism, while burn hematoma and brain surface coagulation are postmortem alterations.

If burns are survived, secondary phenomena will result from the fire-induced burn wounds and/or the wound healing process. Survival depends on the severity of the burns, i.e., on the extent of skin surface

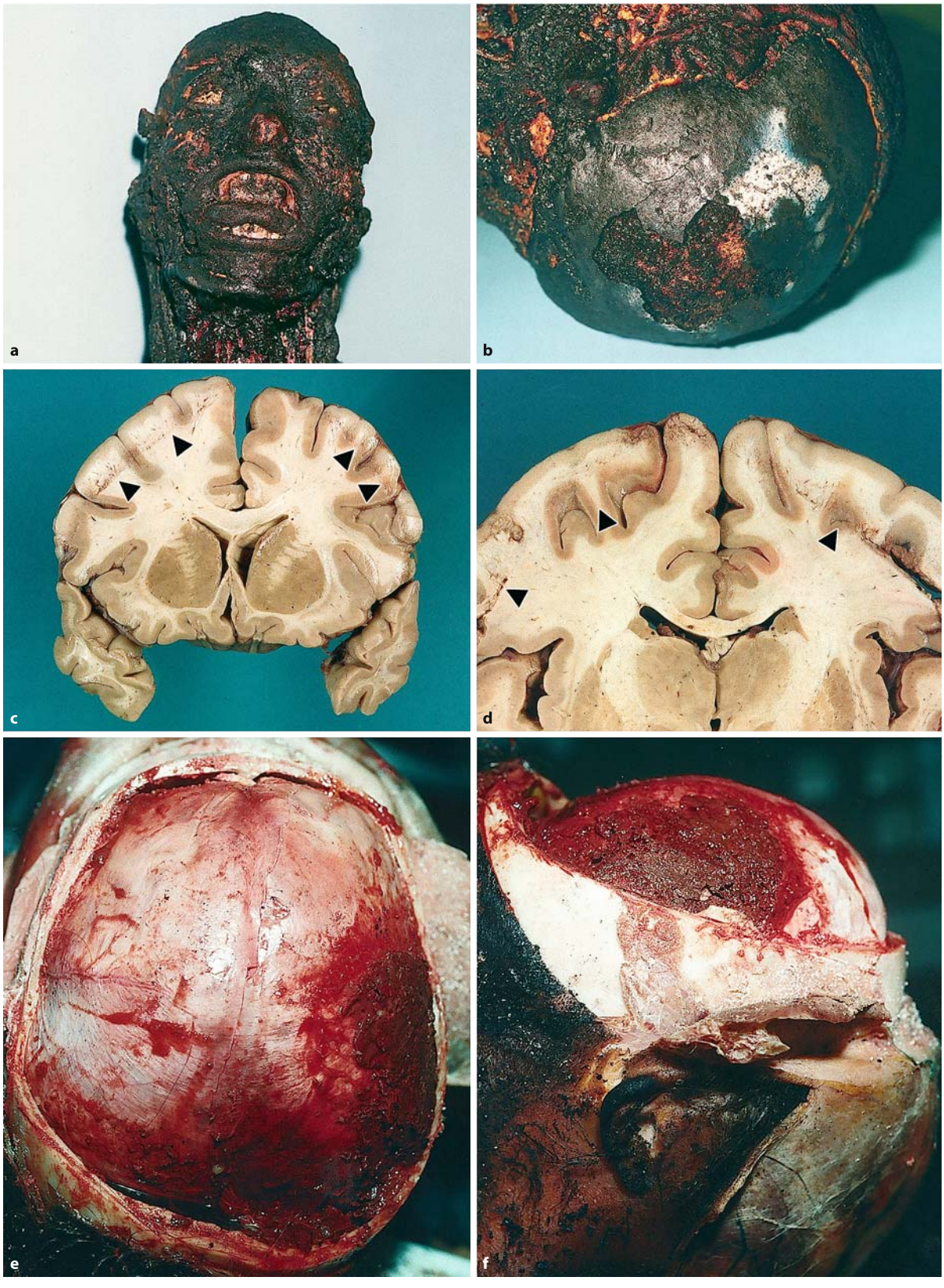

Fig. 12.1a–f. Postmortem alterations as a result of fire and burning on scalp, skull and brain. **a**, **b** Loss of hairs, cutis, and soft tissue, i.e., loss of total the scalp, as well as fracture and loss of parts of the external table of the skull; **c**, **d** coagulation of the brain surface (arrowheads) **e**, **f** accumulation of blood in the epidural space = burn hematoma

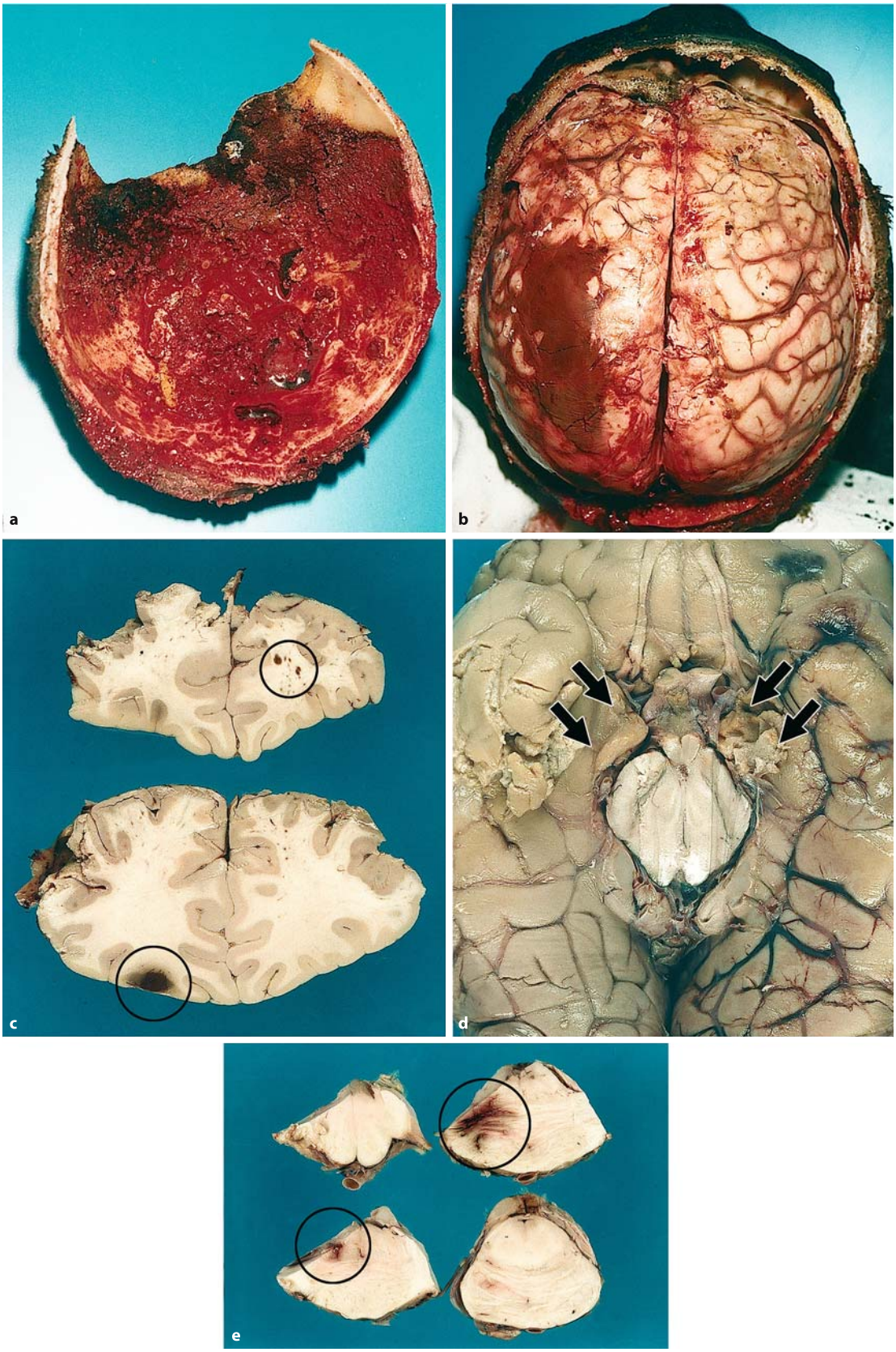

Fig. 12.2a–e. Differentiation between intravital and postmortal alterations. **a** Postmortem (extradural) burn hematoma; **b** intravital "subdural" hemorrhage; **c** intravital white matter and cortical hemorrhages (*circles*); **d** intravital herniation (*arrows*); **e** intravital pontine hemorrhage (*circles*)

and soft tissue destruction, and on the severity of the CO-induced brain damage.

Clinically, burn victims who survive only briefly (*early death*) develop a clouding of consciousness, often lapsing into coma. The morphological picture is characterized by hyperemia and edema secondary to the altered hemodynamics and toxic vessel damage (Hagedorn et al. 1975). The simultaneous increase in the permeability of the blood–brain barrier to plasma proteins causes inflammation with intravascular thromboses and sometimes also gives rise to intravascular fibrin bodies secondary to shock (Hagedorn et al. 1975). Perivascular spongiform disintegration of myelin, perivascular aggregation of lipid-containing and hemosiderin-containing macrophages, cerebral hemorrhages, nerve cell shrinkage, pallor and astroglial swelling and proliferation have all been described (Jacob 1955).

Delayed death from burn injuries is caused mainly by infections of burned skin areas and airways. Extravascular water retention increases throughout the body (including the brain) secondary to a pathologic increase in the permeability of vessel walls and enhanced loss of plasma proteins. The result is both generalized edema and brain edema, which may be potentiated by systemic hypoxia. Common delayed complications of burn injury include CNS infection with sepsis (15% of cases), secondary changes (septic arterial occlusion or DIC), which induce infarction (18% of cases), and intracerebral hemorrhage (Winkelmann and Galloway 1992). In cases with long survival times, the clinical picture is dominated by the ischemic injury. Internal hydrocephalus has the clinical features of an encephalopathy, which is seen mainly in children.

The Problem of Vitality. In cases of acute death, it must always be determined whether the victim was already dead or still alive at the time of the fire. This question can usually be answered at autopsy by demonstration of soot in the airways and elevated CO-Hb levels in the blood.

In some cases, signs of vital processes may be lacking, an indication that death did not result from the fire. The neuropathologist must then help to establish the exact cause of death and find signs of whether, for example, the fire was intentionally set to conceal a prior homicide (e.g., by strangulation, asphyxia, MBI, etc.). Two frequent morphological findings are of importance in this respect:

1. *Skull fractures* and/or skull destruction (Fig. 12.1a, b): biomechanical analysis of the type of fracture can help to establish whether the dome of the skull burst as the result of a heat-induced increase in intracranial gas pressure (bursting fractures) or has broken as a consequence of a blow (bending fractures).
2. *Epidural hematoma* (Fig. 12.1e, f): a so-called burn hematoma must be differentiated from primary mechanically caused hemorrhage. If there are no signs of external mechanical violence to the head, and no secondary (vital) effects such as shifting of the brain, brain edema, or cell reactivity, then primary mechanically induced hematoma can be ruled out. There are, however, difficulties in the interpretation of findings in cases in which blow and fire injure the head at the same time or at only very brief consecutive intervals. In cases of burn hematomas the head has usually already undergone skeletonization, with incineration of the overlying soft tissues as well as heat-induced deformation of the inner table of the skull.

Local thermal changes in the brain are caused almost exclusively by electrically induced burn injuries. The effects of heat can cause considerable destruction of the scalp and skull at the point of contact, which is typical of electrical burns. Heat-induced local tissue necrosis is also seen in the underlying dura mater and brain tissue, especially in high voltage industrial accidents or as induced by lightning.

12.2 Electrical Trauma

12.2.1 Incidence

Deaths from electric violence are usually accidental, although occasionally they are associated with suicide or homicide. In the USA, about 1,000 deaths from electrical shock are reported annually (Lee 1997), another 100,000 injuries from electrical shock are survived (Mellen et al. 1992). In 1967, global rates of fatal electrical accidents per 100,000 inhabitants ranged from 0.13 in Northern Ireland to 0.76 in Italy (Wyzga and Lindroos 1999).

12.2.2 Clinical Features

The symptoms are determined by the type and the quantity of electrical current, its path through the body as well as its density, frequency, and duration. Even relatively weak intensity can cause acute symptoms such as paresthesias, muscular spasms and muscular pain, numbness of the limbs, somnolence, convulsions, and loss of consciousness (Panse 1955; Posner 1973; IEC 1987, 1994). The latter symptoms in particular, as well as persistent headache, nausea, and

vomiting, may be associated with cerebral edema and increased intracranial pressure. If the current passing through the heart is strong enough, asystole-induced ventricular fibrillation will occur, resulting in respiratory arrest. Delayed effects of electrical shock include *phantom sensations* in limbs amputated due to electrical injury, *spinal atrophy* and *spastic spinal paralysis*, as well as *seizures*, which sometimes occur at intervals and usually disappear again (Levine et al. 1975; Petty and Parkin 1986). Long-term cognitive and emotional deficits, apparently the result of post-traumatic stress disorder (Kelley et al. 1999), are also described, as well as total or partial loss of memory, sometimes in the form of retrograde amnesia.

12.2.3 Pathogenesis

Electrical violence can cause *thermal injuries* (cf. "Hyperthermia") that must be distinguished from electrical shock-induced functional injuries. Thermal injuries from electrical shock can range in severity from local necrosis to complete carbonization. The degree of *functional injury* depends on the extent of the electrolyte shift at the molecular level (IEC 1987, 1994; Chen et al. 1999; Tsong and Su 1999). Exposure of cells in suspension to direct intense electrical pulses has been shown to damage cell membranes and the supramolecular organization of cells and cause denaturation of macromolecules, producing injuries and tears much like those seen in victims of electrical violence (Tsong and Su 1999).

The severity of the injury depends on the *source of voltage and* the *type of electrical current* [direct current (DC), alternating current (AC), impulse current (IC)], on the *type* and *medium of conduction* (broad surface contact, point contact, spark gap in air, water, etc.), on the *anatomic location of the contact site*, and on the *current path* through the body (hand-hand, right hand-left foot, etc.). The severity also depends on quantitative factors such as the touch voltage, skin impedance, internal body impedance, and the resulting effective intensity of the current (root-mean-square value), duration of current flow, current density, frequency (IEC 1994, 1987) and – of course – on the victim's primary state of health (cf. Barnes et al. 1996). Tensions as low as 25 V can be dangerous (Jaffe 1928), and tensions of 46 V can be lethal (Stevenson 1942) if the total body impedance and the contact resistances are very small and if the heart lies in the current path.

The brain appears to be relatively resistant to long-term functional disturbances and morphological changes secondary to electrical shock, as evidenced for example by the lack of secondary injuries following *electroconvulsive therapy* for depressive disorders (stimulus load: 25–50 mC, stimulus frequency: 30–70 Hz, impulse duration: 0.5–2.0 ms, stimulus duration: 0.5–8 s) (cf. Abrams 1992; Devanand et al. 1994; Folkerts 1995, 2000). The effect on the systems of transmitters as well as the ion shift in the nervous system disturb *conduction*, *impulse formation*, and *stimulus transport* and may cause *permeability changes* in the vessels due to angiospasm (American Psychiatric Association 2001). Secondary mechanical and toxic injury may also occur, but will not be dealt with here in detail.

12.2.4 Neuropathology

Venous hyperemia is observed, sometimes accompanied by hemorrhage in the third ventricle of the brain, the floor of the fourth ventricle, and in the cerebral cortex at the border between the gray and white matter; the hemorrhaging is sometimes massive (Somogyi and Tedeschi 1977; Stanley and Suss 1985). The hemorrhages are caused by angiospasm and by an electric shock-induced rise in blood pressure (Koeppen 1953). Demyelination, fragmentation of axons, degeneration of neurons, and perivascular necrosis are caused by hypoxia (Stevenson 1942) and have been described in persons temporarily surviving an execution in the electric chair (Hassin 1933; Silversides 1964). Cerebral venous thrombi have been described in a few cases (Patel and Lo 1993; Sure and Kleihues 1997).

A *delayed disease* caused by electrical shock is *electrotraumatic spinal atrophy* (Farrell and Starr 1968; Levine et al. 1975; Panse 1975; Petty and Parkin 1986), which can occur weeks or months after the traumatic event. This is especially common after hand-to-hand contacts, which cause lesions between the fifth and seventh cervical segments (mainly softening with myelin degeneration, slight hemorrhaging, and cavitating lesions) (Alexander 1938). *Spastic spinal paralysis* with atrophy of the posterior white column and lateral white column has also been described (Koeppen and Panse 1955; Panse 1955; Osypka 1963), in each case with attendant demyelination. A few cases of internal hydrocephalus have been reported (Bach 1950). Recent intense study has failed to explain cases of delayed psychopathological reactions resembling post-traumatic stress syndrome without morphological equivalents (Pliskin et al. 1998, 1999; Kelley et al. 1999).

Peripheral nerve injuries are associated with severe burning of adjacent tissues, overextension of the limbs, muscle rupture, and fracture-dislocation of bones and joints, all of which can be caused by electroshock therapy of psychotic patients. Myelin degeneration and axon cylinder injury may result from impaired blood flow (Alexander 1938).

Eickhorn et al. (1988) studied the effect on the isolated frog nerve of high voltage condenser discharges with a field strength of up to 1,000 V/cm applied for 0.24–8 ms. They noted impaired propagation of action potentials, including a transient total block of conduction. Such conduction disturbances usually disappear within minutes. Electric shock-induced injury of peripheral nerves is often manifested morphologically – in the form of axonal injury and demyelination – only after a long latency period.

12.2.5 Electric Shock Devices

The use of electric shock devices has increased in recent decades. Their effect depends largely on the type and magnitude of the electric current they deliver to the body (Osypka 1963). The individual pulses of its high-frequent oscillating impulse current can attain peak values of several amperes with durations of less than a tenth or even a hundredth of 1 ms. Weak devices can deliver impulse energies of several mJ, powerful devices of up to about 1 J. The effective current strengths (root-mean-square current) range from 10 to 100 mA with impulse repetition rates of 10–30 Hz. For the more powerful devices with an impulse repetition rate of 10 Hz or more a shock duration of only a few seconds is sufficient to block the whole motor nervous system completely.

The electric current spreads throughout the whole body, following the routes of least resistance such as blood vessels, lymph channels, tissue fluid, muscle, and nerve paths (Robinson et al. 1990). The resulting block of the motor nervous system is due to the intervals between the applied impulses being shorter than the refractory period of the muscle fibers following contraction (~100 ms), but longer than the interval for the relative recovery of the nerve cells after stimulation (~5 ms).

12.2.6 Electromagnetic Radiation

In recent years, a number of authors have hypothesized that the electromagnetic radiation of mobile phones (cellular phones) can induce brain tumors (Rothman et al. 1996; Maier et al. 2000). Cellular phones transmit and receive electromagnetic radiation at frequencies of about 1,000 MHz, just above the ultrahigh frequencies of television transmissions and just below the microwave portion of the electromagnetic spectrum. Recent studies were able to allay most of these fears (Inskip et al. 2001; Utteridge et al. 2002).

12.3 Lightning Trauma

12.3.1 Incidence

Lightning can strike humans under a variety of circumstances and is certainly life threatening, but not always fatal (only 20–30% of victims die) (König and Pedal 1983; Blount 1990; Mackerras 1992). In the United States, the National Oceanic and Atmospheric Administration evaluated the years 1959–1994 (Curran et al. 1997): lightning was responsible for more than 3,000 deaths and nearly 10,000 casualties. Injury and death are due to the effects of electric, thermal, and mechanical violence. Cardiac arrest is the principal cause of death from lightning strikes, but for survivors the most devastating complications are neurologic. Lightning injuries differ significantly from other high voltage electrical injuries because of the high current flow, but extremely short duration of the lightning bolt. Also, mechanical injury from the blast effects of lightning is unlike injury due to common human-generated currents. This includes fractures of the skeleton and the skull (Skan 1949).

12.3.2 Clinical Features

Slight clinical symptoms are intact consciousness and reversible neurological deficits with a distribution pattern that cannot be explained based on anatomical structures. Coma can last up to several days and "secondary changes," especially hypoxia, dominate the clinical picture and may lead to death. If the victim survives, there is the potential for disturbances of cardiac function and peripheral neurovascular complications. Successful resuscitation is common, even among victims with conventional signs of brain death (Lifschultz et al. 1993).

According to the review of Cherington (2003; see also Cherington et al. 1992; Muehlberger et al. 2001) we have to differentiate four groups of neurologic complications, which vary from transient benign symptoms to permanent disabilities:

1. *Immediate and transient symptoms*, i.e., brief loss of consciousness, amnesia, confusion, headache, paresthesia, and weakness.
2. *Immediate and prolonged or permanent symptoms*, i.e., patients will have structural lesions, for example post-hypoxic/ischemic encephalopathy, intracranial hemorrhages, cerebral infarction or cerebellar syndromes.
3. *Possible delayed neurologic syndromes*, i.e., motor neuron disease and movement disorders which

have followed lightning strikes by days, months or years.
4. Lightning-linked secondary injury from falls or blast.

Burn-induced necrosis (punctate burns) is usually visible at the sites of entry and exit; only a few cases of lightning injury without burns have been reported (Wetli 1996). Death is apparently caused by a very powerful and rapidly increasing magnetic field in the immediate vicinity of the lightning bolt, which produces brief high voltage currents in the human body. If this happens in the vulnerable period of atrial conduction, it can trigger asystole and produce ventricular fibrillation (Cherington et al. 1998).

12.3.3 Neuropathology

A lightning strike to the head causes local burns on the epidermis and subcutaneous connective tissue; it can also produce subarachnoid or even parenchymal cerebral hemorrhages (Andrews et al. 1992; Lifschultz et al. 1993; Wetli 1996). Hypoxia-related changes are also observed. A few reported cases have found hemorrhagic foci beneath the point of lightning strike, with tearing of the white matter of the brain thought to be a direct result of the electrical violence itself. Moreover, some authors attribute basal ganglionic hemorrhage (Andrews et al. 1992; Wetli 1996) as well as skull fracture (Morgan et al. 1958) directly to the lightning stroke with the obvious difficulty of differentiating fracture due to a fall. Lightning has induced fractures in a recumbent, sleeping individual (Skan 1949) and an epidural hemorrhage was described in one case (Morgan et al. 1958). But even fatal lightning injury with severe blasting mechanical injuries and skull fractures leaves the brain intact (Skan 1949).

12.4 Irradiation Trauma

Ionizing radiation has become an increasingly important therapeutic tool in medicine. Widely accepted radiation standards have been developed for the protection of patients and clinicians; their implementation has resulted in a dramatic decline in the number of injuries due to manmade sources of radiation (X-ray, nuclear pharmaceutical agents, therapeutic radiation apparatus). The genetically relevant annual dose from medical and dental sources is about 1 mGy (radiation dose 1 Gy=1 J radiation energy per kg body mass).

12.4.1 Pathogenesis

The effect of X-ray irradiation to the adult CNS is dose-dependent (Zeman 1963, 1964):
- 100 Gy: whole body irradiation causes immediate death.
- 70 Gy: local irradiation causes acute necrosis of white and gray matter.
- 50–70 Gy: local irradiation causes partial tissue necrosis.
- 20–25 Gy: local irradiation causes delayed white matter necrosis because X-rays induce the functional impairment of oligodendrocytes (Blakemore 1978) and endothelial cells (Blakemore and Palmer 1982).

According to Schmitt (1983) local application of ionizing radiation to the CNS can have the following effects:
- *Inactivation of enzymes*, generation of free radicals, and/or loss of binding sites on molecules and atoms.
- Oxygen free radical damage to DNA (Ravanat et al. 2001) with *loss of the ability of DNA to replicate*; it can damage chromosomes and cause mutations and abnormal cell growth.
- *Reduction of brain metabolism*, especially cerebral consumption of glucose (d'Avella et al. 1994).
- *Death of cells* (Chan et al. 1999) and *organelles* ensuing from destruction of the organic molecular structure.
- *Changes in the cerebral arterial wall* due to the sensitivity of endothelial cells and smooth muscle cells to irradiation (O'Connor and Mayberg 2000).
- The *developing brain* is highly sensitive to X-ray and CNS malformation may be the consequence of X-ray exposure during pregnancy (Sundaresan et al. 1978).

Cell division is blocked by X-rays by three different pathways:
1. Mitosis is irreversibly interrupted and the cell will die by apoptosis when exposed during the G1- and S-phases (Ferrer et al. 1993).
2. X-irradiation induces the production of free radicals and inhibits DNA repair enzymes with the result of cell death by necrotic mechanisms.
3. There are indications of an increase in apoptosis as well as active caspase-3 expression following exposure to radiation (Marshman et al. 2001). These investigations are based on irradiated intestine, but may reflect basic principles of radiation injury.

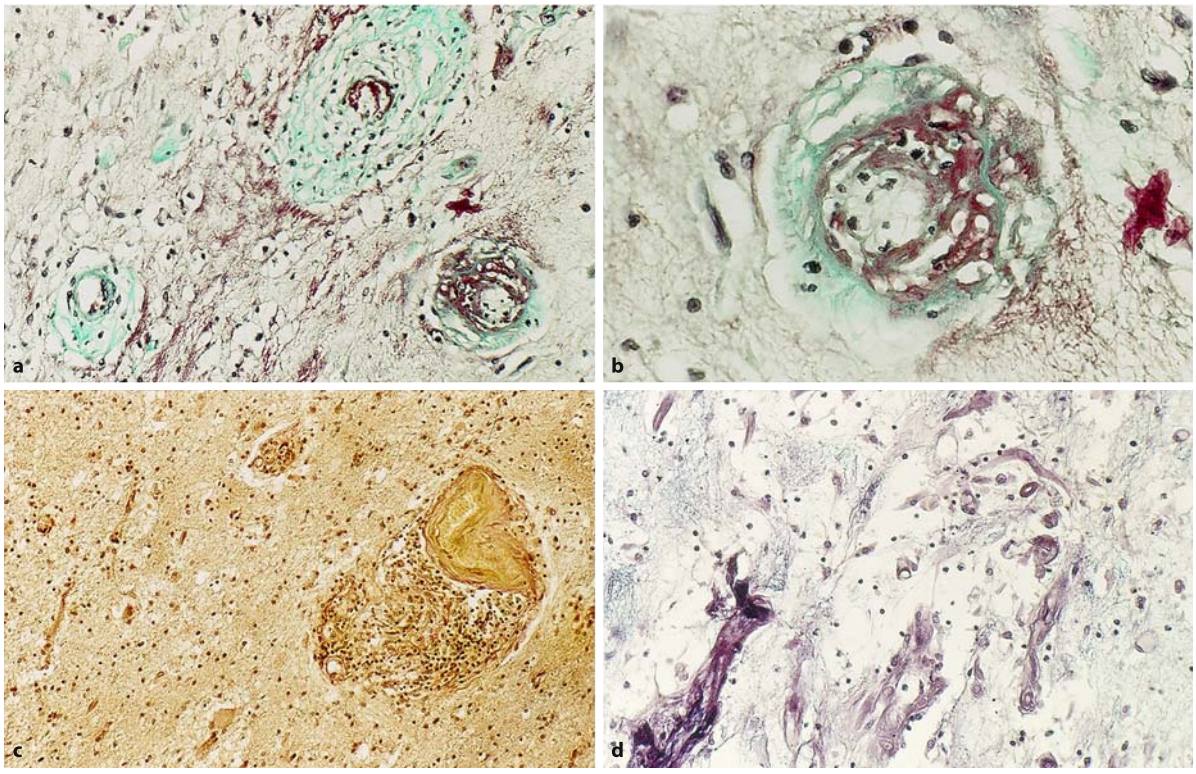

Fig. 12.3a–d. Radiation injury. **a–c** Vasculopathy marked by hyalinization of the vascular wall without fibrinoid necrosis; **d** extreme gliosis; (**a, b** trichrome stain; **c** van Gieson stain; **d** Holzer stain; magnification **a, c, d** ×300; **b** ×1,000)

Radiation energy acts through *radiolysis of water molecules* to trigger the release of OH and H radicals, which react with amino acids and SH groups on the membranes of cells and organelles. With regard to complex molecules, radiation can alter the activity of enzymes, giving rise to an accumulation of enzyme-dependent substances. The decisive pathogenetic factor is *damage to the capacity of cells to reproduce*, resulting in acute radiation necrosis and mutations. The most vulnerable cells are those capable of mitosis within the CNS, i.e., glial cells as well as endothelial and muscle cells of vessel walls (Hopewell 1979; Schmitt 1983).

The histopathological findings in vessels following irradiation include thickening of vessel walls, thrombosis, luminal occlusion, and occasional telangiectasis (O'Connor and Mayberg 2000). In the early stages, the combined effect of irradiation on vascular walls and parenchyma causes damage to the oligodendroglia and the remaining parenchyma; in later stages, injury of vascular walls predominates (O'Connor and Mayberg 2000). The injury is thought to be mediated by cytokines and growth factors (Kureshi et al. 1994) released from hematopoietic and local cells.

12.4.2 Types of CNS Reaction

The following types of CNS reaction may be distinguished:

- Acute reaction: impaired blood–brain barrier leads to edema (Rubin et al. 1994).
- Early delayed reaction: within weeks, myelin and axons are involved as well as the vessels; hyalinization without fibrinoid necrosis (Jellinger and Sturm 1971).
- Late delayed reaction: coagulative tissue necrosis with hyaline and fibrinoid alterations of the vessels, activation of astrocytes and microglia (Chiang et al. 1993).

12.4.3 Acute Radiation Injury

12.4.3.1 Radiation Necrosis

In the early phase after irradiation, the first morphological change is vasculopathy (Fig. 12.3a–c), which may be an initiating factor and the cause for subsequent changes. Reactive astrocytes appear later at

both the target site and in the surrounding regions (Yang et al. 2000). A gliosis develops in addition to tissue necrosis (Fig. 12.3d). Calcium deposits, inflammatory reactions, vessel proliferation, and hyalinization are seen. There is infiltration by T-cells (CD4, CD8) and a proliferation of macrophages; TNF-α and interleukin-6 (Kureshi et al. 1994) are released. Irradiation causes increased vulnerability of myelin sheaths comparable to that found in radiation injury to nerve cells. The nerve cells exhibit central chromatolysis.

The irradiation-induced blood–brain barrier disturbance causes a *brain edema*, which largely accounts for the morphological sequelae. *Oligodendroglia* are more sensitive to radiation than astroglia, which in turn are more sensitive than nerve cells (Blakemore and Palmer 1982).

12.4.3.2 Transitory Radiation Myelopathy

The spinal cord is generally *more sensitive* than the cerebrum to ionizing radiation (Scholz et al. 1959), apparently due to comparatively less bone absorption (Fröscher 1976). The cervical area is especially susceptible to irradiation of tumors in the oral cavity, pharynx, and larynx. The doses tolerated in these areas range 10–60 Gy (Fröscher 1976). Today, normal therapeutic regimens (55–60 Gy, administered over 5–6 weeks) entail a 1–5% risk of radiation-induced myelopathy. The vulnerability of the oligodendroglia leads in most cases to demyelination, mainly in the posterior white columns, which may induce clinical symptoms, i.e., an unpleasant electric shock-like paresthesia upon tilting of the head.

12.4.3.3 Radiation Neuropathy

Delayed X-ray injury to the peripheral nerves (Fritzemeier 1985) is rare. It is mainly seen in the area of the plexus brachialis in patients undergoing, for example, irradiation of breast carcinoma; in most cases it develops 3–4 years after the irradiation. Fibrosis dominates the microscopic picture.

12.4.4 Early Delayed Reaction

Development of clinical symptoms occurring weeks after X-irradiation is termed "delayed reaction." Neuropathologically this type of injury is characterized by distinct hyalinization of the vascular wall without fibrinoid necrosis (Fig. 12.3b) as well as by demyelination and axonal injury (Jellinger and Sturm 1971).

12.4.5 Chronic Radiation Injury

The latent period between irradiation and onset of clinical symptoms ranges from a few months to 13 years (an average of 16.4 months) (Fröscher 1976). An acute onset is distinguished from a chronic-progressive form.

12.4.5.1 Acute Onset

Symptoms of delayed injury of both the brain and, especially, the spinal cord can appear in an acute form after a period of latency. Partial or complete paraplegia and other central nervous symptoms can develop within days. Morphologically, vascular changes do not predominate, but, in contrast, *injury of the glia*, with *demyelination* and *white matter necrosis* are most apparent. During the latency period, the mitotically damaged glial cells develop functional disturbances after several mitotic cycles similar to those seen in endothelial cells (Hopewell 1979), e.g., edema.

12.4.5.2 Chronic Progressive Injury

Clinically, the picture in spinal cord damage is predominated by marked *sensory disturbances* (54%); less common are combined motor and sensory deficits (21%) and paresis (22%) (Fröscher 1976). In this prognostically unfavorable form of delayed injury, the vascular component predominates, with simultaneous partial or complete demyelination and slight spongiform structural disintegration.

12.5 Special Mechanical Trauma

12.5.1 Ultrasound Injury

Occurrence. Accidental exposure to high-dose ultrasound is rare. At frequencies of up to 10 MHz ultrasound is used today in *diagnostic sonography*. All available evidence suggests that, when properly applied, this modality is safe (Lele 1972).

Ultrasound has a mechanical effect on tissue dependent upon its the wavelength or frequency, intensity, and the duration of exposure (Lizzi and Ostromogilsky 1987). Accidental application of high-energy ultrasound has been known to cause thermal injuries. Exposure of brain tissue to 2.7 MHz for 2 s

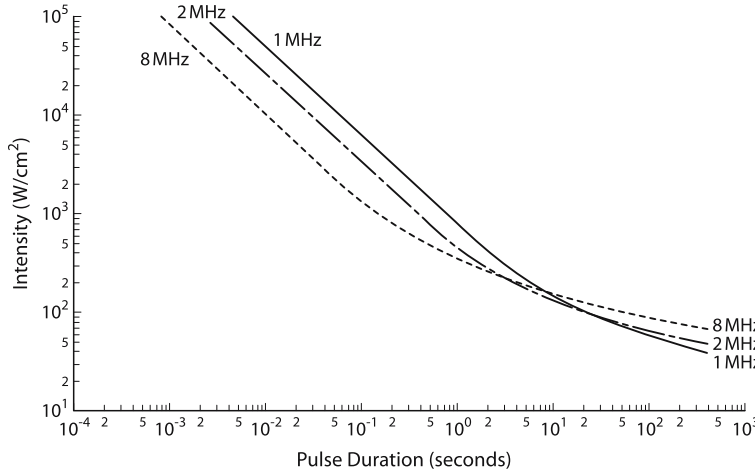

Fig. 12.4. Ultrasound: time-intensity thresholds for production of necrosis in cat brain by focused ultrasound (source: Carstensen et al. 1974, modified)

at an intensity of 600 W/cm^2 can induce brain tissue temperatures as high as 55°C in anaesthetized animals (Davies 1997).

Focused high-energy ultrasound applied to the CNS can cause local coagulation necrosis (Fig. 12.4), the extent of which is a function of dosage (Heyck and Höpker 1952; Nelson et al. 1959; Aström et al. 1961), as well as chromosomal damage (Brown and Gordon 1967). Focused high-dose ultrasound has been used to destroy lesions such as Schwannomas and to destroy brain tissue in patients with Parkinson's disease (Myers et al. 1959; Nelson et al. 1959; Ballantine and Bell 1960); as the increase in heat at interfaces between different types of tissue can result in cell destruction.

12.5.2 Pressure Injury

Natural changes in pressure conditions, e.g., decreased atmospheric pressure at high altitudes, most frequently associated with changes in oxygen tension caused by a reduction in O_2 partial pressure (pO_2) or under water, with increased environmental and increased partial pressure of the breathing gases acting on divers can injure the human organism. Pressure equipment allowing a controlled release of gases and liquids is frequently used today in various therapeutic and non-therapeutic situations. The use of such equipment can be hazardous and produce injuries with a unique pathophysiology and morphology (for review see Török 1997).

12.5.2.1 Barotrauma

Pathophysiology. As the environmental pressure to which humans are exposed decreases or increases, so does the pressure in the intrathoracic space. The adult lung has a total lung volume of about 6 l. At increasing depths, associated for example with apnoe diving, external pressure increases on the diver's chest and the volume of air in the lungs decreases as the pressure increases. Air breathed at 50 m under the water surface is at a pressure of about 600 kPa (6 atm) and is 6 times denser than at the surface. The gases dissolve in the body fluids and tissues in direct proportion to their environmental pressure. The increase in pressure against the atmospheric conditions at the water surface together with the added resistance of breathing apparatus increase the effort of breathing.

The most hazardous period, however, is that of returning to the water surface, as the relative pressure–volume changes are greatest at this time and gas loses its solubility in liquid. When a diver ascends toward the surface, the environmental pressure decreases and gas will be released by the tissues. Furthermore gas in the air-filled body cavities expands according to Boyle's law. Lung damage is thus caused by over-distention and stretching rather than by any direct effect of increased pressure. Pulmonary barotrauma manifests itself in pneumothorax, interstitial emphysema, and air embolism, whereby a tearing of tissue may occur.

Neuropathology. In instances of barotrauma, changes in brain tissue are characterized by those of systemic hypoxia and extreme edema. In cases of the additional influence of decompression sickness a combination of hypoxia, edema, and extravascular bubbles within the cerebral parenchyma and spinal cord can be observed in histological sections (see below). Obviously, the air bubbles do not cause a breakdown of the blood–brain barrier (Hjelde et al. 2002). The brain edemas may be the result of the hypoxic–ischemic process.

12.5.3 Toxicity of Hyperbaric Gases

Pathophysiology. Increases in external pressure lead to nitrogen build-up and carbon dioxide retention. Increased arterial nitrogen partial pressures of more than 8 kPa lead to nitrogen narcosis. Hypercapnia also leads to an increase in the level of circulating catecholamines, which, in turn, alter tissue blood flow so that, under special circumstances, decompression sickness (and possibly hypothermia) becomes more likely (see below). Increased pO_2 in diving (eubaric hyperoxemia) as well as the process of reperfusion (Aronowski et al. 1997) may be associated with tissue damage due to increased oxygen free radical production (oxygen intoxication, see Bacon et al. 1996). In contrast to this concept are recent experimental findings by Flynn and Auer (2002) showing that hyperoxia isolated to the reperfusion period reduces cortical necrosis.

In diving, effects of O_2 on the lungs and CNS are paramount, although a systemic fatigue syndrome has also been described (Sterk and Schrier 1985). At depths exceeding 100 m the diver experiences a state of rapture with euphoria, and impairment of thought processes and coordination caused by N_2 intoxication (Strauss and Prockop 1973). However, significant impairment of safe diving due to N_2 narcosis may be present from depths of 40 m. There is also a risk of oxygen intoxication – as described below – with seizures and loss of consciousness. CNS toxicity usually presents first at pO_2 values of 300 kPa and above while the pulmonary effects predominate at pressures of 200 kPa or less. The CNS manifestation of oxygen poisoning is a grand mal seizure occurring with no predictable warning signs or symptoms.

The phenomenon of oxygen toxicity of the brain has been systematically investigated by Donald, and susceptibility to it was found to vary markedly from day to day and between individuals (Donald 1947; see also Flynn and Auer 2002). Donald found that breathing pure oxygen at pressures as low as 190 kPa (1.9 atm, 9 m depth) while working in the water produced convulsions, but exposure to 176 kPa (1.7 atm) did not. Susceptibility to oxygen toxicity is increased by immersion and underwater activity. Hypercapnia also increases susceptibility to oxygen-toxic seizures, which are, therefore, most likely when dense gas is being inhaled under pressure and while a diver is working. The subject of CNS oxygen toxicity has been reviewed (Mayevsky 1984).

The incidence of oxygen-toxic seizures associated with routine hyperbaric oxygen therapy was evaluated by Hampson and Atik (2003). Among 20,328 total patient treatments performed from 1992 to 2001, 6 patients experienced an oxygen-toxic seizure for an overall incidence of 1 in 3,388 treatments (0.03%).

Neuropathology. The morphological features of exposure to hyperbaric gases are characterized by the phenomenon of decompression sickness (see below) as well as by generalized hypoxic alterations.

12.5.4 Decompression Sickness (DCS)

Synonyms for DCS are "Caisson" disease, or "the bends" (Bühlmann 1993; Oehmichen et al. 1994; van Laak 1999).

12.5.4.1 Incidence

DCS occurs in professional divers engaged in tasks such as bridge building or construction of drilling platforms at sea, as well as in recreational divers. Two types of DCS are differentiated. Type I is characterized by pain in the joints and muscles and lymph node swelling. Its most common symptom is joint pain. Type II DCS is serious and life threatening. It most commonly includes peripheral nerve and/or CNS compromise; 90% of serious DCS injuries involve the CNS. Most cases of DCS can be successfully treated in a hyperbaric chamber. Permanent injury is uncommon and death extremely rare, usually resulting from drowning due to decompensation.

12.5.4.2 Pathophysiology

The clinical findings result from a change in atmospheric pressure from above normal to normal. The *hydrostatic pressure* on the body increases proportionally to the water depth, producing a proportionally greater *capacity for dissolution* of *inhaled gases*, especially nitrogen, *in blood and tissues*, creating excess saturation.

12.5.4.3 Clinical Features

A whole range of changes from bradycardia, muscle, and bone pain to shock, loss of consciousness, and paralysis of disseminated type are encountered (Petropoulos and Timiras 1974). If a diver surfaces too quickly (Hock et al. 1994), decompression results in the release of the excess gas into soft tissues, vessels, and parenchymatous tissue such as that of the brain. It forms embolic gas bubbles that cannot be released into the atmosphere, i.e., expired by the lungs. The number of bubbles is a function of the correlation between the water depth and the speed of ascent to the surface.

Permanent neuropsychological changes such as memory disturbances and depression occur even

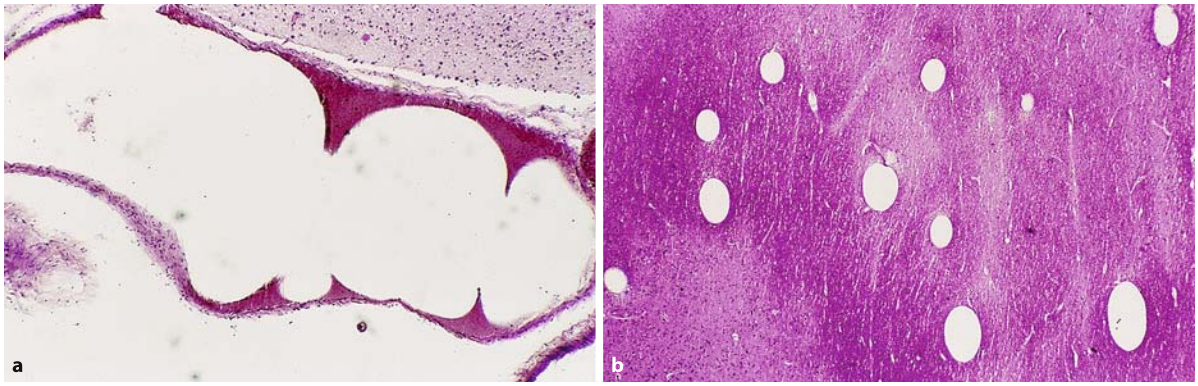

Fig. 12.5a, b. Pressure injury. **a** Venous gas embolism; **b** gas bubbles and edema within the brain parenchyma as a result of reduced hydrostatic pressure seen after a diving accident caused by a fast return to the water surface (**a, b** H&E; magnification ×100)

in professional divers who have never experienced clinical decompression sickness. The spinal cord is also damaged histologically in divers who have never had overt symptoms, showing Marchi-positive myelin degeneration in the white matter (Palmer 1990). The changes are probably the result of intravascular microbubbles insufficient to cause primary clinical symptoms. Recent investigations have found evidence of CNS lesions in amateur divers as well (Reul et al. 1995).

12.5.4.4 Neuropathology

The released gases can be demonstrated in tissues and intravascularly (Novomeský 1994). Gas bubble embolism (bubbles within the vessels – Fig. 12.5a) and local generation of gas bubbles within the tissue (Fig. 12.5b) are seen, together with disturbed microcirculation (Wolf et al. 1990), disseminated intravascular coagulation, lipid embolism, and fat embolism (Pedal 1994). The brain exhibits foci of spongiform structural disintegration as well as signs of a breakdown of the blood–brain barrier (Fig. 12.5b). A cohort study of multiple brain lesions in recreational divers showed that all victims had a patent foramen ovale (Knauth et al. 1997).

It must be noted that demonstration of the release of gas bubbles in the corpse is not in itself proof of a vital process, and thus cannot be established as the cause of death. The same phenomenon also occurs when a body is recovered from great depths (Oehmichen and van Laak 1994). The demonstration of extravascular and intravascular bubbles in combination with brain edema and in the absence of putrefaction, however, is generally regarded as a marker of air embolism. Demonstration of thrombocytes on the surface of bubbles does not confirm the intra-vital release of the intravascular bubbles either (Ritz-Timme et al. 1998). Since the gas bubbles themselves cannot be interpreted as a vital phenomenon, the only valid criterion of vitality is brain edema.

In professional divers, the repeated release of gas bubbles has been shown to produce focal injury and scarring of the CNS (cortex, white matter, ependyma), the spinal cord being especially affected (Palmer 1990; Morild and Mørk 1994; Mørk et al. 1994; Tetzlaff et al. 1999). Chronic vascular disease can also develop (Palmer et al. 1992), with hyalinization of vessels walls, necrotic foci in gray matter, and perivascular vacuolization in white matter. The pathological process seems to be that of endothelial injury. Some authors assume that endothelial changes arise from intravascular gas bubble formation (Nossum et al. 1999).

12.5.5 Gas Embolism

12.5.5.1 Pathophysiology and Clinical Features

Gas embolism may be produced by bubbles forming in the circulatory system in DCS. Arterial gas embolism is the most dangerous manifestation of type II DCS. Gas emboli can also occur (for differential diagnosis – see Muth and Shank 2000) during diving as a result of barotrauma secondary to changes in gas volume within gas-filled body cavities during compression or, particularly, decompression. There are two categories of gas embolism, venous and arterial, which are distinguished by the mechanism of gas entry and the site at which the emboli ultimately lodge: the pulmonary tissue can be injured if gas flow is impeded (see above: Barotrauma). The resultant gas emboli can lodge in coronary, cerebral, and other systemic arteries and capillaries.

In instances of *venous gas embolism* the gas is transported to the lungs through the pulmonary ar-

teries, causing interference with gas exchange and cardiac arrhythmias. Rapid entry of large volumes of gas produces pulmonary hypertension by gas bubble obstruction of the pulmonary circulation, resulting in a strain on the right ventricle and eventually cardiac failure.

Arterial gas embolism is caused by entry of gas into the pulmonary veins or directly into the arteries of the systemic circulation. As mentioned above, gas may enter the arteries as a result of over-expansion of the lungs by decompression. Besides this type of gas embolism we have to consider iatrogenic cerebral arterial gas embolism (Peirce 1980), which may occur as a complication of central venous catheterization (Heckman et al. 2000), of cardiac operations (Ziser et al. 1999), and other invasive medical procedures (Murphy et al. 1985). Even if only small amounts of gas enter the arterial system, the flow of gas bubbles into functional end arteries occludes these vessels. Obstruction of the nutrient arteries of the brain is especially serious and may be fatal.

Bubbles obstructing end-arterial flow cause distal ischemia and development of cytotoxic edema. The surface of the bubble generates a foreign-body response of the cellular and humoral immune mechanisms. The bubble also causes mechanical irritation of the arterial endothelium. Both processes result in vasogenic edema and impairment of perfusion in the adjacent vicinity, so the neuronal injury extends beyond the area of obstruction (Moon 1996; Muth and Shank 2000).

The *clinical features are* dependent on the body region involved. Commonly it is characterized by cramps, headache, anxiety, extremity weakness, syncope, impaired vision, speech disturbances, confusion, dizziness, somnolence, focal neurological deficit, and unresponsiveness, paresis, paraesthesia, hemi- or tetraplegia or generalized seizures (Tovar et al. 1995). Benson et al. (2003) describe the clinical features of 19 patients with iatrogenic cerebral arterial gas embolism after hyperbaric O_2 therapy. Immediately after treatment, 5 patients completely resolved all signs and symptoms, 11 had improvements, 1 had no change, and 2 were not assessable. Within 2 months of treatment, 3 additional patients completely resolved and 6 had further improvements. Patients with a venous source all experienced pulmonary signs or symptoms, with 8 of 9 chest radiographs demonstrating pulmonary edema. Patients with an arterial source had no pulmonary edema.

12.5.5.2 Neuropathology

The morphologic features of gas embolism are distinguished by ischemic encephalomalacia, ischemic neuronal cell changes (tigrolysis), air-induced vacuolization of vessels and capillaries, as well as *microcirculatory disturbances*. Small areas of *hemorrhage* are often found in the cortex, the meninges and – less often – in the medulla oblongata (Janssen 1967); these hemorrhages lie in the topographical vicinity of the vessels occluded by the air embolism (Rössle 1948). There is a pericapillary and periarterial accumulation of air or air-plasma mixtures in the perivascular spaces [*emphysema around the perivascular sheaths* according to Rössle (1944)].

12.5.6 High-Altitude Illness

12.5.6.1 Incidence

At roughly 5,500 m (18,000 feet), the atmospheric pressure is half that at sea level, which means that the partial pressure of all atmospheric gases, including O_2, is half that at sea level (Arias-Stella 1977; Auer and Sutherland 2002). Altitude sickness can occur at even lower levels, at elevations beginning at 2,500–3,000 m (Sonna 2002), and is characterized by impaired cell function due to reduced oxygen supply (Austin and Sleigh 1995). As reported by Maggiorini et al. (1990), 34% of trekkers develop "acute mountain sickness" when ascending to 3650 m. Klocke et al. (1998) reported that altitude sickness is experienced by approximately 20% of tourists to Colorado ski resorts at an altitude of about 3000 m. A review of the frequency of clinical relevant symptoms in adults on ascent to moderately high altitudes (3600–4600 m) has been presented by Sonna (2002). The symptoms are due to the decrease in pO_2 that occurs with the reduction in atmospheric pressure accompanying altitude increase.

12.5.6.2 Clinical Features and Pathophysiology

Three manifestations of acute altitude sickness are differentiated (Houston 1976; Hackett and Roach 2001; Sonna 2002; Basnyat and Murdoch 2003):

- Acute mountain sickness (AMS) is characterized by headache accompanied by symptoms such as fatigue, dyspnea, gastrointestinal symptoms (anorexia, nausea, even vomiting), dizziness, or sleep disturbance.
- High-altitude pulmonary edema (HAPE) is characterized by a non-cardiogenic form of pulmonary infiltrates of patchy distribution as demonstrable on chest radiograph.
- High-altitude cerebral edema (HACE) is a potentially fatal encephalopathy, and is a dreaded condition that begins with headache, ataxia, altered mental status (confusion) and may progress to

stupor, coma, and death from cerebral herniation.

As supposed by Roach and Hackett (2001), the symptoms of AMS and HACE are largely neurological in origin and HACE is considered the end-stage of severe AMS, which has recently been identified as a vasogenic edema (Hackett et al. 1998) opening the possibility of blood–brain barrier permeability playing a role in the etiology of AMS. The likely source of the edema is fluid leakage from new microvessels stimulated by hypobaric hypoxia (Mironov et al. 1994), in the face of a hyperdynamic cerebral circulation. Chronic acclimatization does, however, double the tissue pO_2 (Dunn et al. 2000).

The incidence and severity of the various altitude illnesses are dependent upon factors such as the rapidity of ascent, the final altitude achieved, residence at a low altitude prior to ascent, sleeping at altitude, and a host of individual physiological variables (for further information, see Chap. 13, pp. 277 f). Untreated, HAPE has a reported mortality of 44%, compared with 6% among those who receive supplementary oxygen, descend to a lower altitude, or both; evidence of pulmonary edema has been demonstrated in 40 (15%) of 262 people climbing up to 4559 m (Sonna 2002).

The *clinical picture* of HAPE is dominated by dyspnea, generalized malaise, and a cough that is at first dry and later produces foamy pink sputum. The patient feels anxious, the lips and limbs are cyanotic, and disseminated rales can be heard throughout the lungs. Hemodynamically, there is a marked increase in arterial pressure in the pulmonary circulation with normal left atrial pressure.

The risk of HAPE obviously is not confined to a small group of genetically susceptible people but likely exists for most climbers if the rate of ascent and degree of physical effort is great enough, especially if the lung size is normal or low (Cremona et al. 2002).

12.5.6.3 Pathology and Neuropathology

Patho-anatomically there is an alveolar edema of the lung, accompanied by hyaline membranes and fresh thrombosis in pulmonary capillaries and arterioles, and marked capillary congestion and dilatation of lung arterioles. Cerebral involvement is clinically characterized by impaired concentration and memory, visual disturbances, apathy, and slurring of speech.

The neuropathological findings are non-specific. As mentioned elsewhere (pp. 277 f), high altitude mountaineering as an example of hypoxia, i.e., reduction of pO_2 in external atmosphere, commonly does not lead to permanent alterations of mental functioning or permanent morphological alterations of the CNS. In delayed death due to HACE associated with severe pulmonary injury, the neuropathology is characterized by extensive (vasogenic) edema of the brain.

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Ischemia and Asphyxia III

Hypoxia, Ischemia(Hypoglycemia) 13

The following three chapters describe the neuropathological features caused by a reduction of energy supply to the total brain. The morphological phenomena of a metabolic disturbance of single cells and tissue compartments are described in Chap. 4, while the focal disturbances of cerebral blood flow are discussed in Chap. 28. The present chapter describes the global oxygen depletion of the brain and its functional and neuropathological consequences.

13.1 Basic Principles

The terms "ischemia" and "asphyxia" describe the failure of cells to receive or to utilize oxygen (DiMaio and DiMaio 2001). While ischemia is characterized by an isolated interruption of the oxygen supply, the physiologic definition of asphyxia is associated with carbon dioxide retention, i.e., asphyxia will be associated with acidosis, hypotension, and occasionally hypoglycemia and coagulopathy (Taensch et al. 1991). Each of these additional insults – isolated – may have a deleterious effect on the brain. The combined effect will become the worst case and the neuropathological features will be characterized by mixed morphological alterations. Hypoxia is characterized by a reduction of the partial pressure of oxygen (pO_2) below the normal level, i.e., a lack of molecular oxygen.

The target organ of ischemia, hypoxia, and asphyxia will be the brain and within the brain the target cells are the neurons which exhibit a different susceptibility to oxygen deficiency. The susceptibility is dependent on the vasculature and the vulnerability of different types of neurons. According to Fig. 13.1 ischemic necrosis of neurons will first be seen in the cleft between the first and second frontal gyrus (watershed zone), in the globus pallidus, in the cornu Ammonis and the cerebellar cortex (Purkinje cells). In the cornu Ammonis (Fig. 13.2) the very early ischemic alterations are seen in the CA1 sector and in the CA4 sector, the hilus.

Neurons of the CA1 sector and hilar region of the hippocampus and layers III, V, and VI of the cerebral cortex have been deemed "selectively vulnerable" because of their inordinate sensitivity to transient ischemia. Furthermore, biochemical studies of protein synthesis during reperfusion (Kleihues and Hossmann 1973; Grosse Ophoff et al. 1984; Bodsch et al. 1985; DeGracia et al. 1996) support the contention that its suppression is an early event (Araki et al. 1990) and its restoration may play an important role in neuronal survival after transient ischemia (Thilmann et al. 1986). It is now generally accepted that this suppression of protein synthesis is a result of inhibition of translation initiation (Krause and Tiffany 1993).

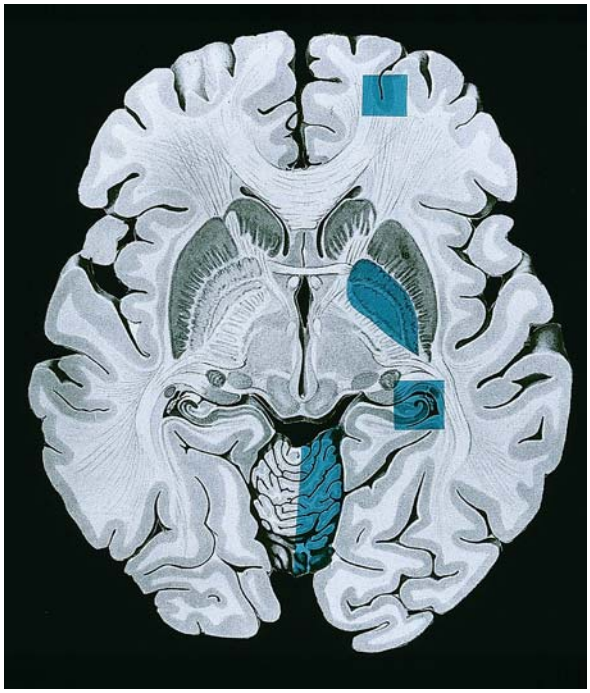

Fig. 13.1. Topography of ischemia-susceptible areas in the cerebrum and cerebellum (*blue areas*)

Though the target organ of ischemia will be the cerebrum, including the cerebellum and brain stem, we should also point out the sequelae for the spinal cord (see p. 285). On the basis of alterations of reflex activity and morphology, van Harreveld and Schadé (1962) examined the results of asphyxia on spinal cord neurons of cats for periods of 30–50 min, which allowed them to recover within 2 weeks. If the asphyxiation lasted for 30 min reflexes were present, whereas prolongation to 50 min led to a loss of tone and reflex. After asphyxiation for 28 min, marked neuronal destruction – with the total loss of nerve cells in the central cord around the spinal canal – had taken place.

Because the brain stores neither glucose nor oxygen, severely reduced or completely blocked cerebral blood flow can lead, within minutes, to irreversible cerebral damage and long-lasting neurological disorders, including memory, motor, and sensory losses. The outcome of the ischemic impact is mainly determined by post-ischemic factors (Hossmann et al. 1973), but it cannot be excluded that differences in the metabolic response of the brain during ischemia are of equal importance (Hossmann et al. 1993). In particular, the roles of the residual level of energy-rich substrates, of the degree of acidosis developing during ischemia as well as the factors responsible for the speed of removal of metabolic waste products from the brain to the blood have not been established.

The normal cerebral blood flow (CBF) to the brain in adults is 50-60 ml/100 g per min which is autonomously regulated, dependent on the consumption (for neonates, see p. 436). In the hypoxic state CBF will increase while the O_2 utilization will become normal.

The ischemic damage of the CNS involves a cascade of molecular and biochemical mechanisms which are discussed in part in Chap. 4 (pp. 56 ff) and which are reviewed in detail by Siesjö (1992), Pulsinelli (1992), and Choi (1998). Focal cerebral ischemia is associated with the total loss of neurons in the region supplied by the arteries, while transient global ischemia yields progressive damage to selectively vulnerable populations of neurons (Smith et al. 1984). As described by Berger and Garnier (1999), oxidative phosphorylation in the brain comes to a standstill owing to the acute reduction in oxygen supply. The Na^+/K^+ pump of the cell membrane has no more energy to maintain the ionic gradients. In the absence of a membrane potential, large amounts of calcium ions flow through voltage-dependent channels, down an extreme extra-/intracellular concentration gradient, into the cell. Current research suggests that the excessive increase in levels of intracellular calcium, so-called calcium overload, leads to cell damage through the activation of proteases, lipases, and endonucleases. During ischemia, as well as the influx of calcium ions into the cells via voltage-dependent calcium channels, yet more calcium enters the cells through glutamate-regulated ion channels.

Glutamate, an excitatory neurotransmitter, is released from presynaptic vesicles during ischemia following anoxic cell depolarization. The acute lack of cellular energy arising during ischemia induces almost complete inhibition of cerebral protein biosynthesis. Once the ischemic period is over, protein biosynthesis returns to pre-ischemic levels in non-vulnerable regions of the brain, while in more vulnerable areas it remains inhibited. The inhibition of protein syntheses, therefore, appears to be an early indicator of subsequent neuronal death. A second wave of neuronal cell damage occurs during the reperfusion phase. This cell damage is thought to be caused by the post-ischemic release of oxygen radicals, synthesis of nitric oxide (NO), inflammatory reactions, and an imbalance between the excitatory and inhibitory neurotransmitter systems.

A selection of diseases associated with asphyxia are summed up in Table 13.1. The pathophysiological principles and the neuropathological findings are put together in Table 13.2. The pathophysiologic and neuropathologic principles and sequelae in infants and children are discussed elswhere (see Chap. 22, pp. 435 ff).

We can distinguish different stages of severity of neuronal loss, which depend on the duration of global brain ischemia, brain temperature, the effects of drugs, etc. According to the morphological sequelae the following neuropathological features are known:

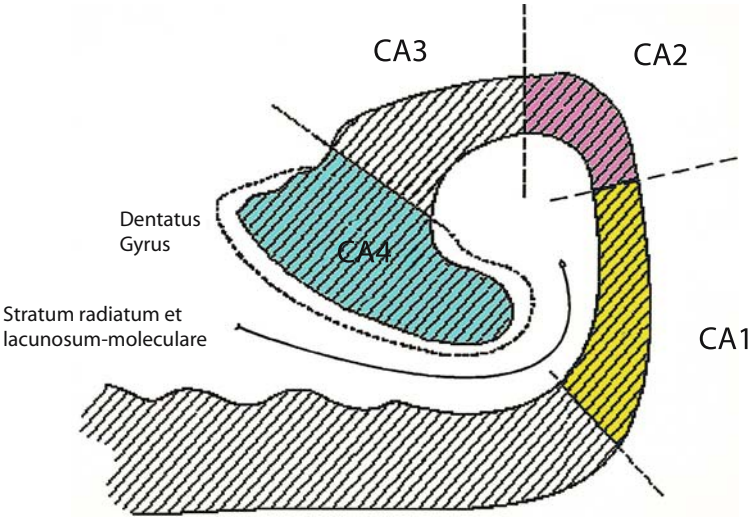

Fig. 13.2. The anatomical structure of the cornu ammonis demonstrating the different segments

Table 13.1. Diseases associated with asphyxia

Pathophysiology	Causes
Reduction of pO_2 in external atmosphere	High-altitude illness
Blockage of the external respiratory openings	Plastic bag, pillow on the mouth/nose
Stenosis/blockage of internal respiratory passages	Asthma bronchiale, aspiration, bolus, external compression of the trachea
Restriction of respiratory movements of the chest	Thorax compression, curare-like drugs, brain-induced respiratory arrest
Lung diseases	Pneumonia, pulmonary edema, adult respiratory distress syndrome
Reduction of cerebral blood flow	Cardiac arrest, arterial hypotension
Reduction of O_2-blood transport capacity	Severe anemia, carbon monoxide
Blockage of the cellular O_2 metabolism	HCN – intoxication

1. *Selective neuronal necrosis* associated with disseminated damage of single neurons.
2. Transient ischemia with a *distinct focal loss of neurons* in vulnerable regions of the brain and their glial and/or cystic replacement.
3. Transient ischemia with *pan-necrosis* including neurons, glial cells and neuropil of cortical and subcortical brain structures.
4. Persistent vegetative state or *apallic syndrome* associated with a total loss of cortical neurons and an intact – but reduced – cerebral blood flow.
5. *Respirator brain* (brain death) characterized by a global brain necrosis as a result of the complete cessation of the intracranial circulation.

To start with, we will evaluate the morphological sequelae of isolated types of metabolic failures within the CNS, i.e., hypoxia, ischemia as well as hypoglycemia; in Chap. 14 we sum up forensic types of asphyxia; in Chap. 15 we describe the characteristics of the global permanent ischemia (or respirator brain).

13.2 Metabolic Disturbances

The energy metabolism of the brain depends on the oxygen and glucose supply. The absence or reduction of one of these energetic elements in blood unquestioningly leads to a breakdown of the metabolism in

Table 13.2. Pathophysiological principles and neuropathological findings in different types of asphyxia

Term	Meaning	Disease/trauma	Neuropathology
Anemic hypoxia	Low blood hemoglobin	Hemorrhagic shock	No alterations
Hypoxemia	Low oxygen in blood	Asthma, pneumonia	Reversible synaptic alterations
Hypobaric hypoxia	Hypoxemia + pO_2 athmosphere ↓	High-altitude disease	
Transient ischemia	pO_2 tissue ↓	Cardiac arrhythmia, heat stroke	Ischemia (neuronal necrosis)
Stagnant hypoxia	pO_2 tissue ↓	Cardiac arrest	
Ischemia	No oxygen in blood	Respiratory arrest	Edema

brain cells. As interruptions of the oxygen and glucose supplies lead to the same metabolic disaster, we will describe both their pathologies together in one chapter, though – from the systematic aspect – hypoglycemia is additionally discussed elsewhere (Chap. 30, pp. 607 ff).

The normal oxygen consumption of the brain will be 46 ml O_2/min associated with a cerebral blood flow of about 750 ml/min. Under normal conditions of hemoglobin concentration, cerebral blood perfusion and pH, the critical O_2 saturation will be 68% and the critical arterial concentration 13.8 ml O_2/100 ml blood while the critical pO_2 will be 36 mmHg (Nunn 1993). Under anoxic conditions consciousness will be lost within 15–20 s and irreversible brain lesions will be seen within 2–3 min.

Ischemia is associated with a marked elevation in extracellular glutamate concentrations. Hypoxia, without ischemia, is not associated with extracellular glutamate and there are no neuropathologic changes even with pO_2 maintained below 20 mmHg for 20 min in rats (Pearigen et al. 1996). Thus, although the terms hypoxia and ischemia are often used interchangeably, the pathophysiologic sequelae are different (see Pappert et al. 1999; Simon 1999). The commonly used term "hypoxic brain damage" has been loosely applied to a number of conditions ranging from global ischemia (cardiac arrest), to high-altitude hypoxia, air embolism after deep sea diving ("the bends"), and even epileptic brain damage or hypoglycemic brain damage.

It is one of the purposes of this chapter to clearly distinguish and define each of these influencing entities, their basic pathophysiology, and their potential for producing brain damage. We will outline the regional brain predilections for each of these insults to produce neuronal necrosis, and only then will combinations of these insults be dealt with, as seen in the various forms of asphyxial deaths in the field of forensic pathology. The aim is to provide clarity with respect to mechanism and pathogenesis, which in turn will provide a practical guide for the medicolegal neuropathologist in assessing brains that have been referred for delineation of the degree and nature of a cerebral insult which could comprise ischemia, hypoxia, hypoglycemia, in reference to carbon monoxide poisoning, epilepsy or any of these insults with superimposed hypoxia. These subthemes will partly be dealt with in the present chapter as they are representative of different types of metabolic disturbance. Additional information will be given elsewhere [Chaps. 4 (pp. 56 ff, Cell and Tissue Reactions), 27 (pp. 529 ff, Seizures and Epilepsy), 28 (pp. 542 ff, Vascular Diseases), 30 (pp. 606 ff, Nutritional and Metabolic Insults)].

To start, it would be useful to add some more definitions. Table 13.3 implicitly presents the terms "hypoxia" and "ischemia" and also outlines the changes in cerebral energy state, blood flow, extracellular amino acids, lactate, and the potential of the insult to produce neuronal necrosis. We define ischemia as a reduction of cerebral blood flow, and hypoxemia as a reduction in blood oxygen concentration. We note that arterial hypoxemia immediately leads to an *increase* in cerebral blood flow (CBF) whereas ischemia, by definition, decreases CBF. Thus, at least one aspect of these two conditions (hypoxia and ischemia) contrasts sharply. We will consider these episodes singly and combine them only later when the pathophysiology of each condition has been given consideration. The various traditional forms of hypoxia will be discussed first.

13.3 Hypoxia

Hypoxia is often divided into decreased supply of oxygen to the body, decreased transport of oxygen (anemia), and decreased utilization of oxygen (histotoxic

Table 13.3. The different pathophysiologic principles of hypoxia and ischemia. (*CMRgl* cerebral metabolic rate of glucose, *0* no consistent change, ± change in both directions reported at different time points, locations in relation to ischemia, + increased, – decreased)

	Hypoxemia	Anemia	Ischemia	Hypoglycemia	Epilepsy	Histotoxic Hypoxia (CN^-, S^{-2})	CO poisoning
Energy failure	0	0					
Cerebral blood flow	++	++	0	+	+	+	+
CMRgl		0	±				
Lactate		0					
pH of brain	0	0					
Extracellular excitatory amino acid overflow	0	0	Glutamate	Aspartate	0	0	0
Clinical coma	+	–	+	+	+	+	+
Brain necrosis (without hypotension)	0	0	++++	++	+	0	+

hypoxia). In its pure form hypoxia differs from ischemia (or stagnant anoxia) in as far as the blood flow is maintained: consequently the oxygen-deficient tissue continues to be supplied with glucose and blood substances other than oxygen, while waste products, such as lactic acid, continue to be removed. Classic reports have suggested that this type of hypoxia preferentially leads to damage of the neostriatum, globus pallidus, and subthalamic nuclei (Scholz 1953).

We will first consider exemplary arterial hypoxemia due to a decrease in the fractional inspiratory concentration of oxygen (fiO_2) due to hypobaria, a decrease in the general atmospheric pressure without decreasing the actual percentage of oxygen in the air, and then respiratory obstructive disease. Both have equivalent pathophysiologic results in that the effective oxygen concentration in the alveoli is reduced.

13.3.1 High-Altitude Mountaineering

(See also Chap. 12, pp. 263 f) We note that halving the atmospheric pressure from sea level to 5,486 m (=18,000 ft) of altitude is tantamount to cutting the normobaric fiO_2 in half – from normal air which has 20.96% O_2 to 10.48% O_2. Both produce a pO_2 in the inspired air of 80 mmHg or approximately half the normal of 160 mmHg. It is now clear that, in an intact animal, pure hypoxia without a decrease in CBF does not by itself cause necrotizing brain damage. The first arena to reveal this startling fact is human high-altitude mountaineering.

Beginning with Edmund Hillary and Tenzing Norgay, who ascended to the 8,848 m summit of Mt. Everest in 1953, individuals have returned from the summit with no neurologic deficit (Jason et al. 1989). Articles claiming to find differences from normal in high-altitude mountaineers (Townes et al. 1984) show "abnormalities" in only 2 out of 22 tests, no higher than by chance. Examination of the raw data of the tests that are claimed to show group differences (finger tapping and short-term recall) in fact reveals that there are no significant differences between the controls and the individuals exposed to high altitude.

Further attesting to the high level of mental functioning of individuals who have climbed Mt. Everest is the authorship of good literature by individuals who have summited, arguing against high-altitude brain

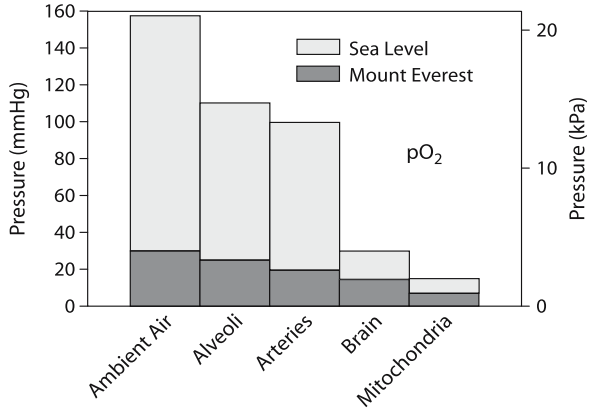

Fig. 13.3. Oxygen cascade demonstrating a step-wise decrease in pO_2 levels and flattening of the cascade

damage. The book detailing the 1996 Mt. Everest disaster (Krakauer 1997) which killed nine people, entitled *Into Thin Air*, was written by Jon Krakauer after summiting Mt. Everest, and won a literary award. Such high-level literary composition, performed after protracted periods spent at high altitude, has for years been a tacit element against the very existence of brain damage due to high-altitude mountaineering. One individual who was left for dead and nearly succumbed at high altitude and without oxygen was a pathologist, Dr. S. Beck Weathers. The title of his book, *Left for Dead* (Weathers 2000) gives another personal account of the Everest tragedy of 1996 and was written after exposure to prolonged hypoxia at altitude including a 16-h coma. Noteworthy with respect to the question of hypoxic brain damage is the fact that Dr. Weathers has returned (after initial hesitation fostered by the widespread belief in hypoxic brain damage) to practicing pathology. Like literary composition, practicing pathology is a high-level mental function. Dr. Weathers (personal communication) relates that an initial skepticism, critical self-examination, and examination by colleagues of high-level mental functioning eventually gave way over months to the realization that no alteration in pathologic diagnostic competency had taken place according to professional colleagues.

The sum of the entire high-altitude mountaineering experience attests to the ability of altitude to cause freezing necrosis of limbs, but there is no good evidence of permanent alteration of mental functioning. There is in fact ample evidence of intact preservation of brain function long after return from high altitude.

While on the mountain, several mechanisms account for long-term tolerance to high-altitude hypoxia. These maintain the pO_2 even at altitude, and include an increase in the circulating hemoglobin and a proliferation of brain capillaries. The adaptive increase in brain capillary density at altitude reduces the average distance from capillary to brain mitochondrion, and maintains the tissue pO_2 in the range of 16–18 mmHg, similar to that at low altitudes. Unfortunately, one consequence of this new capillarization of the brain at altitude may be high-altitude cerebral edema (HACE), since new capillaries are more leaky. This, combined with the hyperdynamic cerebral circulation caused by the increased CBF at altitude, leads to a propensity to HACE. We note that HACE occurs independently of the level of previous mountaineering expertise, being related to physiological, not psychological, factors. Unless there is a rapid return to lower altitude to reverse the hyperdynamic cerebral circulation leaking through the brain capillaries, death due to progressive and fatal cerebral edema rapidly results.

13.3.2 Respiratory Disease

Anesthetists have long known that short periods of hypoxia, unaccompanied by significant hypotension or cardiac arrest, are innocuous. But additional documentation that hypoxia does not cause brain damage comes from the arena of bronchopulmonary and ventilatory diseases, including asthma, anaphylaxis, occlusive bronchitis and bronchiolitis, pneumonia, croup, and epiglottidis.

One of the most amazing well-documented cases was that of a two-and-a-half-year-old boy, who had a respiratory arrest due to bronchitis. Rapid clinical action led to tracheotomy and removal of pus with forceps – pus which had formed virtual casts of the bronchi. Although the boy remained in a coma for 14–16 days, subsequent recovery was without neurologic impairment, including school performance (Sadove et al. 1961). Another paper on pure hypoxia (Gray and Horner 1970) presents a collection of profoundly hypoxic patients without vascular disease, with arterial pO_2 levels under 20 mmHg and ranging to a low of 8 mmHg (with survival). The outcome of these patients showed that pure hypoxia, without global ischemia, causes no permanent brain damage. The venous pO_2 corresponding to the lowest recorded arterial pO_2 of 8 mmHg was 2 mmHg! Noticing that hypoxia could not cause brain damage, Rie and Bernad (1980) reported three neuropathologic autopsies of profoundly low arterial pO_2 levels which all failed to show necrotizing brain damage. All patients died subsequently of other causes after having had 28–192 h of exposure to profoundly low arterial pO_2 levels in the range of 24–38 mmHg that were commonly assumed to cause necrotizing brain damage.

That such profound arterial hypoxemia is even survivable is made possible by a flattening of the staircase of the "oxygen cascade" (Fig. 13.3) where

there is a progressive, step-wise decrease in pO_2 levels. In the case of respiratory obstructive disease, pulmonary venous pO_2 levels are greatly reduced in the blood. The principle of flattening of the staircase of the oxygen cascade also applies to high-altitude mountaineering.

13.3.3 Anemic Hypoxia

Anemia does not cause brain damage. The high white blood cell (WBC) counts associated with various forms of leukemia give rise to leukostasis with WBC counts >300,000 per mm^3 (Freireich et al. 1960), with accompanying ischemia and hemorrhage as seen in leukemia. But anemia itself is not the mechanism of brain damage in leukemia. Anemia actually has a protective effect in cerebral ischemia (Kannel et al. 1972; Tohgi et al. 1978) via the increase in CBF, and the hyperdynamic circulation generally that accompanies anemia, upholding the cerebral metabolic rate for O_2 (Borgström et al. 1975). In contrast to pure anemia or isolated hypoxic events the combination of anemia or hypoxia and hypotension will lead to brain damage as described below in the case of CO poisoning (pp. 347 ff) as well as in Chap. 14 (pp. 294 ff).

As might be suspected, polycythemia and high hematocrit are a risk factor for cerebral ischemia (Pearson and Wetherley-Mein 1978), even in normal individuals, with stroke risk in the general population increasing with the hemoglobin (Tohgi et al. 1978). When ischemia occurs, the consequences are worse in the face of high hemoglobin. There thus seems to be a linear association between the hemoglobin level and ischemic risk. There also seems to be a negative correlation between ischemic brain damage when it occurs, and the hematocrit, spanning the low, medium and high range of hematocrit, although smoking and high blood pressure may be the underlying causes (Kannel et al. 1972). It is important to remember, however, that although the hemoglobin level influences ischemic brain damage, hypoxic brain damage due to anemia does not exist.

13.3.4 Histotoxic Hypoxia

By this it is meant the inability of tissue to utilize oxygen. This may occur due to poisoning of the mitochondrial cytochromes, or it may be due to intrinsic mitochondrial disease as in the MERRF (mitochondrial encephalopathy with ragged red fibers) and MELAS (mitochondrial encephalopathy with lactic acidosis and stroke) syndromes. In such poisonings or in such diseases impairing mitochondrial function, inadequate energy production leads to a stimulation of glycolysis. Lactate and proton production is increased, but without ischemia brain necrosis should not occur. "Non-vascular infarcts" and parenchymal gliosis have been noted, however, in mitochondrial disease (Ohno et al. 1997; Prayson and Wang 1998; Ohshita et al. 2000; Oppenheim et al. 2000), Leigh's disease (Detre et al. 1991), and in the vulnerable brain tissue areas in Wernicke's encephalopathy (Hakim 1984, 1986), the likely mechanism being profound focal acidosis in brain tissue causing pan-necrosis (Kraig et al. 1987).

We focus here, however, on the exogenous or environmental toxins azide, sulfide, and cyanide. Since azide (pp. 359 f) is no longer used as a cleaning or fumigating agent, the most common agents causing histotoxic hypoxia at present are cyanide and sulfide. Cyanide (pp. 351 f) is encountered as an agent used in accidental and intentional poisoning (MacMillan 1989), while sulfide (pp. 352) is most commonly seen in workers of the sour gas industry, where gas wells contain not only aliphatic and cyclic hydrocarbons but also hydrogen sulfide or H_2S (Baldelli et al. 1993). Although cyanide is usually considered the ultimate histotoxic poison in discussions such as this, it is interesting to note that the sulfide anion has a potency to inhibit mitochondrial cytochrome respiration that exceeds even that of cyanide (Smith et al. 1977). Sour gas exposure is the most common occupational setting of histotoxic hypoxia, due to the sulfide anion in the blood, formed in an equilibrium between H_2S, NaHS, and Na_2S. Unless the heart stops due to the cardiotoxic effects of sulfide (or cyanide), brain damage in the form of necrosis does not occur (Baldelli et al. 1993).

The practical implications in histotoxic hypoxia for the patient are, similar to the situation in hypoxemia, that ventilation and maintenance of cardiac function are of paramount importance in order to obviate brain necrosis. These pure hypoxic insults can only generate brain necrosis through heart stoppage or hypotension (MacMillan 1989; Baldelli et al. 1993).

13.3.5 Neuropathology

Recognition of the fact that hypoxia alone does not cause necrotizing brain damage is especially important in view of the fact that acute-onset hypoxia may cause prolonged coma. A pure hypoxic coma of this kind is caused by synaptic alterations, not neuronal cell body necrosis. Such a patient may be mistaken as being brain dead as they would be in the truly hopeless situation of ischemic decortication consequent to cortical necrosis in transient global ischemia. If there has been no ischemia, however, because cardiac function was preserved, patients with purely hypoxic coma invariably wake up after ~2 weeks. Hypoxia,

while not causing cell body necrosis, clearly causes synaptic alterations. In this regard, it is important to clearly think about the relationship of the pathology to the clinical state: ischemia causes cell body necrosis of neurons (perikaryal necrosis, evident by pathologic examination), whereas hypoxia does not. Synaptic function is tested by clinical neurologic examination (whereas pathology examines cell bodies, not synapses) and synaptic function is profoundly deranged in hypoxic coma without cell body necrosis.

The distinction between hypoxia and ischemia is thus of paramount importance in determining the prognosis of coma. If the heart has not stopped, and blood pressure has been well maintained, or if the heart has stopped for only a brief period, and ventilation has been adequate, then widespread pan-cortical necrosis and brain death is unlikely to have occurred. If such patients eventually die, autopsy will reveal no significant necrosis in the brain, whereas brain death will reveal the classical changes in neocortex and pituitary gland (Auer and Sutherland 2002).

13.4 Ischemia

13.4.1 Pathophysiology

Ischemia can be divided into focal and global, transient and permanent. Permanent global ischemia constitutes brain death, and is dealt with in Chap. 15 (p. 319). *Transient global ischemia* constitutes the typical clinical situation of cardiac arrest, where a duration of 2–4 min is known to be critical in the development of irreversible necrotizing cerebral damage (Smith et al. 1984). Of course, the actual duration in any clinical situation will depend on the temperature (Busto et al. 1987), the blood glucose level (Voll and Auer 1988), and any accompanying epileptic activity (Voll and Auer 1991), in addition to the duration of cerebral ischemia. The extreme importance of the temperature is attested to by the fact that 40 min of immersion drowning can be survived without permanent neurologic sequelae if the temperature is very low (Siebke et al. 1975). Or – according to Walpoth (2004) – a 25-year-old man fell into a crevasse to a depth of 42 m where he became wedged in the ice. He was found to have a rectal temperature of 17.5°C and a total arrest time of nearly 4 h. He was immediately re-warmed by cardiopulmonary bypass and regained a sinus heart rate at a temperature of 29°C. After being discharged from the intensive care unit after 11 days he was transferred to a rehabilitation centre which led him to complete normalization of all his functions at late follow-up 5 years later.

Transient global ischemia renders the entire brain ischemic for a limited period of time and because the commonest cause of this entity is heart stoppage, it is virtually synonymous with "cardiac arrest encephalopathy." It is to be delineated from the condition of the brain after extracorporal circulation, i.e., cardiopulmonary bypass (Nussmeier et al. 1986; Moody et al. 1990; Kol et al. 1993), and is to be distinguished even more clearly from the brain and spinal cord changes after nitrogen embolism following diving ("the bends") (Palmer et al. 1981, 1987; Palmer 1990). It is important to remember that ischemia is centrally involved in the pathophysiology of these conditions, and is also part of the pathophysiology and morphology of MBI (Graham et al. 1978).

Transient focal and permanent focal ischemia constitute a continuum: if the duration of transient focal ischemia is long enough, irreversible necrosis takes place and it becomes irrelevant whether reperfusion takes place at later times, since only dead tissue is perfused and the infarct maturation is completed (Persson et al. 1989). As in transient global ischemia, the duration of ischemia necessary to cause necrosis in transient focal ischemia is variable, depending again on the depth and duration of ischemia, as well as the other factors of temperature, glucose, and epileptiform activity mentioned above. It is clear, however, that transient focal ischemia has a much longer tolerable duration (at least half an hour, depending on temperature, glucose levels, etc.) before necrosis develops than the 2–4 min of transient global ischemia. The implication is that focal ischemic brain damage has a deleterious effect on other parts of the brain. As progressively more of the brain is rendered ischemic, the tolerable duration decreases.

Despite the immediate event of ischemia, specific cellular signal transduction pathways in the CNS ultimately influence the extent of cellular injury (White et al. 2000). It is a cascade of mechanisms, rather than a single cellular pathway, which determines cellular survival during toxic insults. These include the pathways of free radical injury, the independent mechanisms of programmed cell death (Chan 2001; Graham and Chen 2001), the role of the complement cascade (D'Ambrosio et al. 2001), and the downstream signal transduction pathways of endonuclease activation, intracellular pH, cysteine proteases, the cell cycle, and tyrosine phosphatase activity (Malese 2001). Moreover, we have to mention the term "penumbra" again (pp. 63 ff). Ischemic penumbra has been documented as severely hypoperfused, non-functional, but still viable brain tissue surrounding the irreversibly damaged ischemic core (Schaller and Graf 2004). This region is of interest as a potential area for the rescue of neurons from cell death and will provide evidence of the therapeutic window.

Table 13.4. Cytopathological features of ischemic neuronal damage

Loss of Nissl bodies
Basophilia
Shrinking of the perikaryon and developing of triangular neurons, containing microvacuoles in the cytoplasm, swelling of dentrites aggregation of Ca^{2+} in the mitochondria
Eosinophilia (Johansen et al. 1986)
Acidophila (acid fuchsin – Auer et al. 1984a, b)
Argentophilia (Yamamoto et al. 1986)

Early edema, i.e., blood–brain barrier disruption was found in 47 of 144 (33%) patients as demonstrated by MRI (Latour et al. 2004), having a median time from stroke onset to observation of 10.1 h. Reperfusion was found to be the most powerful independent predictor of early blood–brain barrier disruption which may lead to a hemorrhagic transformation and poor outcome in 22 of 47 patients.

13.4.2 Neuropathology

The general neuropathological features are summarized in Table 13.4. Moreover, there are topographical differences that are described below.

13.4.2.1 Cerebral Cortex

The usual picture of global ischemia is neuronal necrosis in the cerebral cortex, hippocampus, and cerebellar Purkinje cells (Mandel and Berry 1959). Exceptions will be discussed below.

The cerebral cortex is the structure most highly sensitive to cardiac arrest, and at the gross level damage usually begins in the triple watershed zone, at the intersection of the territories of the anterior, middle, and posterior cerebral arteries (Fig. 13.1, 13.4a). The microscopic features of cortical ischemia show involvement generally of the middle cortical laminae. Although a specific laminar predilection has been described, most severe cortical damage involves the middle layers (layer III > V, VI).

The cytologic features are those of acidophilic neuronal necrosis (Fig. 13.4b), initially consisting of eosinophilic transformation of neuronal cell cytoplasm and nucleus in H&E stains. These "pink neurons" (as opposed to pre-lethal "dark neurons") are definitively known to be necrotic for two reasons: first, they disappear with uniform regularity from tissue sections in experiments studying differing survival times (Auer et al. 1985a; Lee 1989), and second they show cell membrane breaks and mitochondrial flocculent densities on electron microscopy (Auer et al. 1985b).

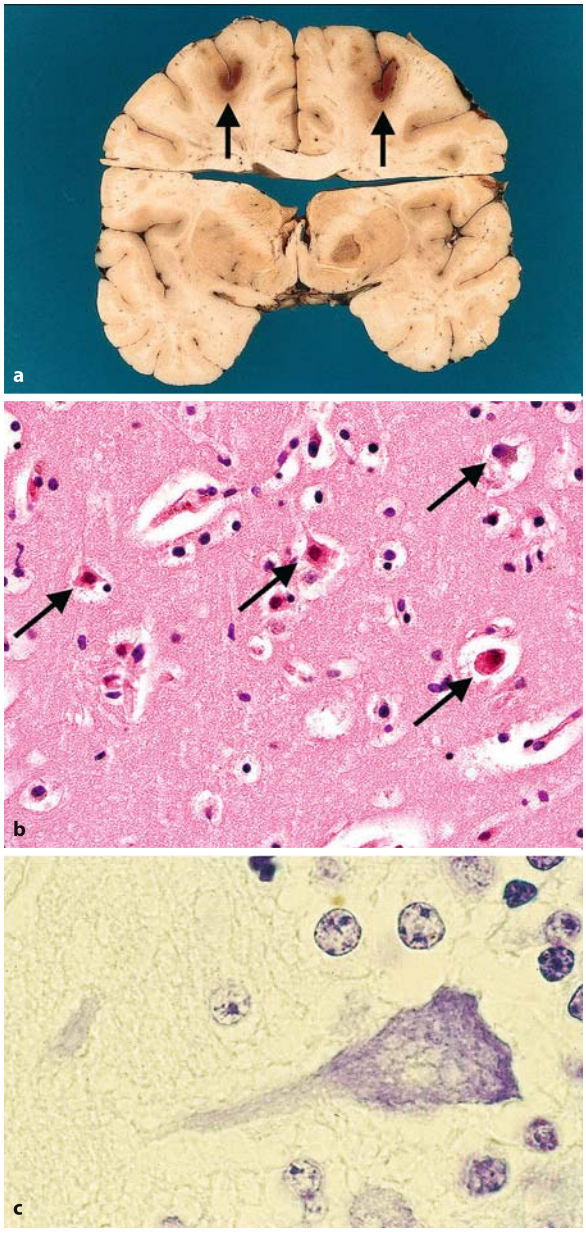

Fig. 13.4a–c. Cortical ischemic lesions. **a** Ischemic lesions in the watershed zone between the 1st and 2nd frontal gyri (*arrows*); **b** distinct acidophilic alterations of cytoplasm and nucleus in H&E stain of neurons (*arrows*) (magnification ×300); **c** neuronal microvacuolar degeneration in Nissl stain as a very early indication of ischemic neuronal lesion (magnification ×1,000)

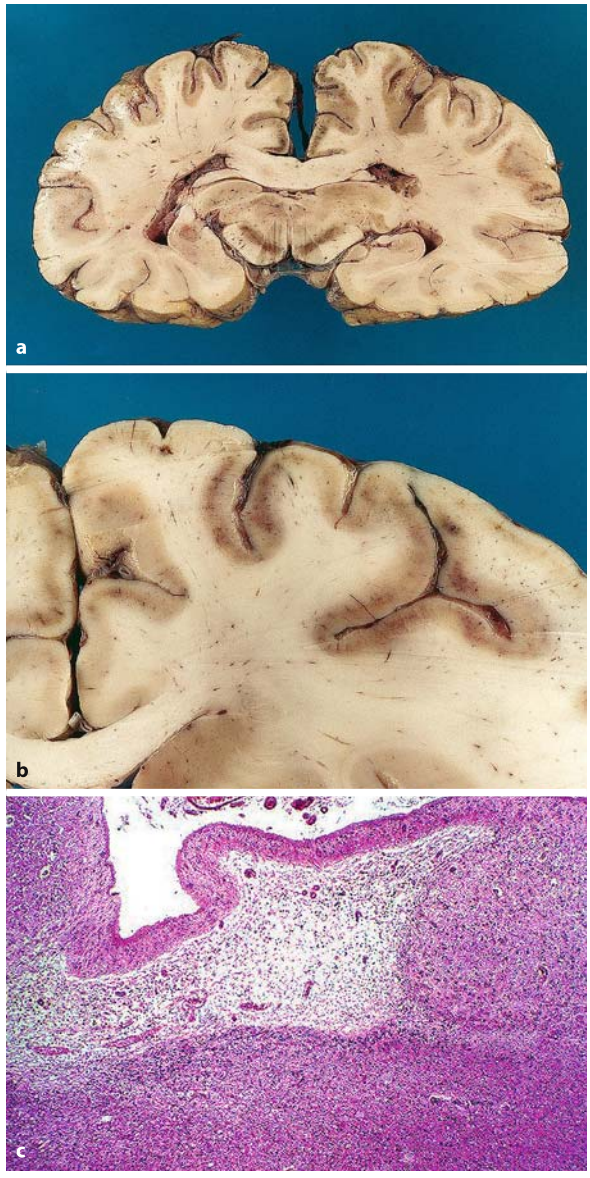

Fig. 13.5a–c. Pan-necrosis of the cortex. **a, b** Involvement of the middle cortical layers as seen on macroscopic sections as well as – after a longer survival time – **c** in histologic sections with a characteristic sparing of layer I of the cortex (H&E stain; magnification **c** ×50)

If the degree and/or duration of ischemia is severe enough, possibly with exacerbating factors, then pan-necrosis rather than selective neuronal necrosis will result (see p. 312). Especially high glucose levels in the blood are prone to produce cerebral pan-necrosis, the mechanism being enhanced by lactate and proton (H^+) production. Pan-necrosis sweeps away the neuropil and glial cell nuclei, as well as neuronal cell bodies, and likely has a different pathogenesis from selective neuronal necrosis. The morphologic features distinguishing selective neuronal necrosis from pan-necrosis apply in every brain region. Acidosis is implicated in the pathogenesis of pan-necrosis (Kraig et al. 1987) whereas excitatory amino acid release, neuronal cell surface receptors, and intrinsic neuronal properties are implicated in selective neuronal necrosis. The histologic features of selective neuronal necrosis and pan-necrosis are contrasted in Fig. 13.5. When both these alterations occur in the brain, these two entities are pathophysiologically as well as morphologically distinct.

13.4.2.2 Hippocampus

The hippocampus is extremely sensitive to cardiac arrest, in general, slightly more than even the cerebral cortex, so that changes are often limited to the hippocampus in global ischemia in humans (DeJong et al. 1969; Zola-Morgan et al. 1986) or animals (Auer et al. 1989). It is important to remember, however, that sometimes the hippocampus can be selectively spared (Adams et al. 1966) in global ischemia. In animals, physiologically controlled experiments demonstrate that ischemic periods as short as 2 min are capable of causing hippocampal CA1 pyramidal cell neuronal necrosis (Smith et al. 1984). Like the cerebral cortex, the hippocampus in global ischemic damage can show asymmetric damage, probably due to asymmetries in the human vasculature. These include the size of the carotid arteries and, more importantly, asymmetries in the circle of Willis (Riggs and Rupp 1963; Stehbens 1963).

Of all the brain regions, the hippocampus demonstrates within it a most heuristic selective vulnerability, and an order of vulnerability which is quite specific. Whereas some diseases, such as neurolipidoses, affect the CA3 pyramidal cells first, most diseases such as Alzheimer's disease and ischemia first affect the smaller CA1 pyramidal cells within the hippocampus, which are less rich in RNA and protein synthetic capability.

Ischemic CA1 necrosis (Figs. 13.2, 14.9, 14.14) can occur after only 2 min of global ischemia. After 2–4 min of global cerebral ischemia, the CA1 pyramidal cells regularly undergo neuronal necrosis (Smith et al. 1984). However, this does not occur at the time of ischemia or shortly thereafter as was once believed. The seminal experiments of Kirino in the 1980s have conclusively shown that, in gerbils (Kirino 1982) and rats (Kirino et al. 1984), neuronal necrosis after global cerebral ischemia takes place between the second and fourth days. Delayed neuronal death may occur earlier with greater degrees of insult, and even later with insults that are mitigated by hypothermia, or insults that are shorter. But the basic principle in global ischemia is that there is delayed neuronal death, especially in the hippocampus.

The phenomenon of delayed neuronal death has also been demonstrated in humans, with roughly the same time course of 2–4 days in the hippocampus (Petito et al. 1987; Horn and Schlote 1992). The principles outlined are thus especially important for medicolegal timing of an ischemic insult in relation to the death. In other brain regions such as neocortex and especially striatum, neuronal death occurs more quickly than in hippocampus (Pulsinelli et al. 1982).

The hilus cells of the dentate, also known as CA4 (Fig. 13.6a), is phylogenetically the oldest, reticular nervous tissue of the hippocampus. In CA4, cells die after only small global ischemic insults, as they do in CA1, and calcium accumulates there early (Benveniste and Diemer 1988). This is of importance because of the large number of cell types in CA4 (Amaral 1978), many of which are inhibitory (Ribak and Anderson 1980). Loss of such inhibitory cells in the dentate hilus might worsen ischemic damage by removing inhibition through the trisynaptic chain from the dentate granule cells to the CA3 cells, in turn to the CA1 pyramidal cells. The pathologist should examine the dentate hilus if there is suspicion of short periods of global cerebral ischemia, especially in children where microglial activation may be the only change seen (Del Bigio and Becker 1994).

After CA1 cells are affected, progressively longer or more severe ischemic insults will cause recruitment of CA3 cells into the necrotic process. Lastly, the dentate gyrus, very resistant to cerebral ischemia, is recruited in the most severe cases of insults. This contrasts with the often seen vulnerability of the dentate gyrus to hypoglycemia, but the latter is based on the massive release of aspartate into the extracellular fluid of the brain (see Sect. 13.5). The above pattern of damage in the hippocampus can be seen unilaterally or bilaterally. This asymmetry has been alluded to above, and its basis may be either vascular or in an asymmetric timing of onset of spreading depression and other prerequisite events which precede and lead to neuronal necrosis in the ischemic process later.

In addition to sampling both hemispheres, the hippocampus should ideally be sampled at several points along its septo-temporal axis. The classic section of the hippocampus is seen when a coronal section is taken from the temporal lobe at the level of the lateral geniculate body. This produces a microscope section including the dentate gyrus in its classic C-shape, the hilus or CA4, the CA3 pyramidal cell band, and CA1 cells. CA2, the zone generally ignored, is theoretically a very narrow zone where the zinc-containing mossy fibers do not terminate from dentate granule cells on CA3 cells, yet they have the morphology of CA3 cells.

The order of vulnerability within the hippocampus deserves further discussion. CA1 cells are exquisitely sensitive to ischemic insults (as well as hypoglycemic and epileptic insults). This may be related to a combination of cellular features leading to selective vulnerability: small amounts of Nissl substance relative to neuronal size, and high concentration of NMDA receptors (Greenamyre et al. 1985) leading to long-term changes in neuronal excitability that can run down ion gradients of the neuron, without the protein synthetic machinery necessary to ensure a robust cellular response (Bodsch et al. 1986).

Since memory formation in the human brain depends on the hippocampus, and the hippocampus can be selectively involved in global brain ischemia or bilateral posterior cerebral artery occlusion (Victor et al. 1961), it is not surprising that selective

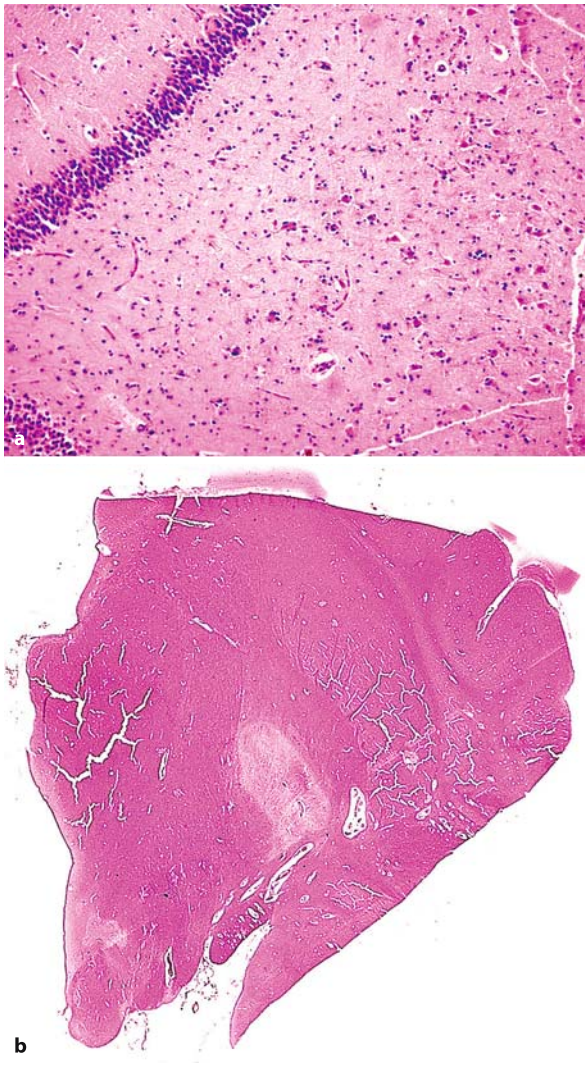

Fig. 13.6a, b. Neuronal necrosis in the cornu ammonis and pallidum. **a** CA4 segment of the cornu ammonis with ischemic neuronal lesion and microglial reaction; **b** sparing of the lateral pallidal nucleus in a case of generalized ischemia after cardiac arrest (H&E stain; magnification **a** ×200, **b** ×5)

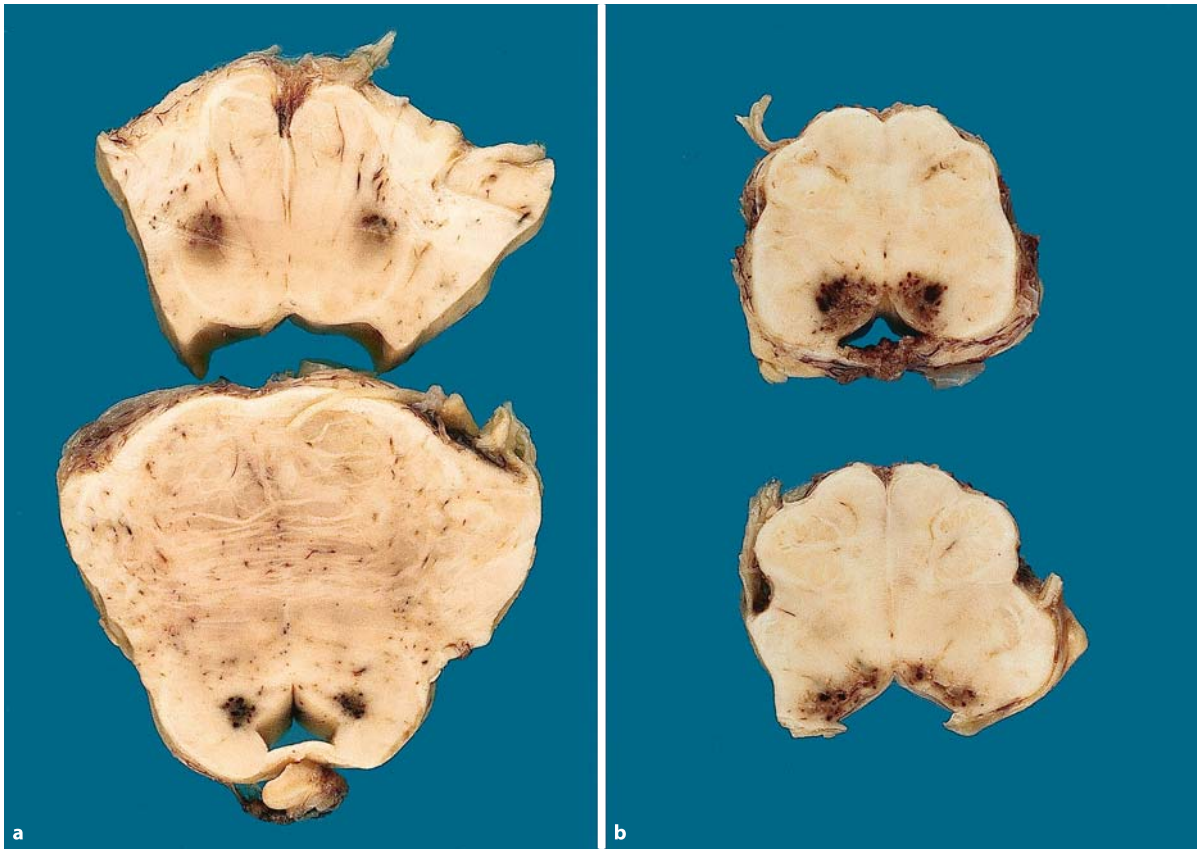

Fig. 13.7a, b. Ischemic lesions in brain stem and medulla oblongata. The lesions are dark-stained as a consequence of focal hemorrhagic infarction symmetrically involving distinct nuclei in pons (**a**) and medulla oblongata (**b**) as a result of hypotension and transient ischemia

amnesia occurs after global ischemia (Woods et al. 1982; Zola-Morgan et al. 1986). However, amnesia of events prior to 15 years before the insult are preserved, as storage and retrieval of distant memories slowly migrate out of the hippocampus into the temporal lobe (Squire et al. 1989).

13.4.2.3 Basal Ganglia

Basal ganglia changes in global ischemia (Fig. 13.6b) are interesting in that they can sometimes resemble carbon monoxide poisoning (see below). The globus pallidus has been seen to be selectively affected in global ischemia where no exposure to carbon monoxide has taken place (Garcia 1988). This pattern resembles the true histotoxicity of carbon monoxide poisoning, but without exposure to the gas. It seems that in some cases of cardiac arrest or prolonged hypotension, necrosis of the globus pallidus and pars reticulata of the substantia nigra can occur, similar to that seen in carbon monoxide poisoning. The basis for this is poorly understood, but may relate to focal, post-ischemic hypermetabolism in those structures (Diemer and Siemkowicz 1980).

The thalamus is affected in some cases of global ischemia, and, together with other extra-hippocampal damage, can contribute to a clinical picture of dementia, rather than merely memory loss (Volpe and Petito 1985).

13.4.2.4 Brain Stem

The brain stem can show a pattern of hypotensive necrosis that is more commonly seen in younger individuals (Janzer and Friede 1980). Symmetrical necrosis of brain stem nuclei (Fig. 13.7) can affect the inferior colliculi, or various tegmental nuclei of the midbrain or pons (Révész and Geddes 1988). Sometimes, the pars reticulata of the substantia nigra is affected (Brierley et al. 1971b) as seen in rodents (Smith et al. 1984). The basis for the selective vulnerability is likely relative hypermetabolism of brain stem structures following the actual cardiac arrest, leading to lactate accumulation, acidosis, and pannecrosis.

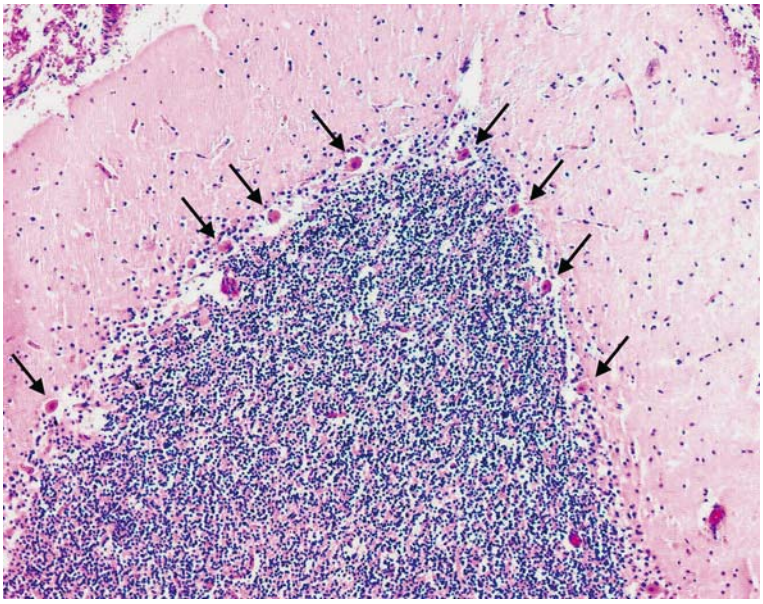

Fig. 13.8. Ischemic lesion of the cerebellar cortex including a selective necrosis of the Purkinje cell layer: eosinophilic staining of the Purkinje cells and an increase of Bergmann's glia in the granule cell layer (H&E stain, magnification ×50)

13.4.2.5 Cerebellum

The cerebellum is regularly affected (Fig. 13.8) in global cerebral ischemia, and can be devastated (Cole and Cowie 1987). Purkinje cells are the most vulnerable cell, in spite of the granule cells being laden with the NMDA subtypes of glutamate receptors (Olson et al. 1987) capable of causing long-term alteration in neuronal excitability, run down of ionic cellular transmembrane gradients and other precursors of neuronal death. Thus, the basis of Purkinje cell vulnerability in cerebellar global ischemia is poorly understood.

13.4.2.6 Spinal Cord

Spinal cord damage is often seen after global ischemia, provided the spinal cord is examined at autopsy. Two patterns of selective vulnerability at the gross level are noteworthy: a rostro-caudal change in vulnerability along the length of the spinal cord, and vulnerability of the various parts of the spinal cord in any transverse section, especially in the rostral part of the cord.

The rostro-caudal distribution of vulnerability is related to watershed zones between the descending supply via the anterior spinal artery, which derives its flow from the vertebral arteries, and the lumbo-sacral enlargement inferiorly, subserved by the artery of Adamkiewicz. The latter is really an extra large fifth lumbar artery, although other arteries can be enlarged and serve the function of the artery of Adamkiewicz. This vascular pattern leaves the low thoracic and lumbar spinal cord vulnerable (Gilles and Nag 1971; Azzarelli and Roessmann 1977; Cheshire et al. 1996).

On transverse section, the spinal cord is subserved in its posterior third (dorsal columns, nucleus proprius and substantia gelatinosa) by the paired dorsal spinal arteries, and in its anterior two-thirds by the anterior spinal artery running in the ventral median fissure (Sliwa and Maclean 1992). Thus, a given cross-section of spinal cord can show demarcated watershed or borderzone necrosis (Garland et al. 1966; Wolf et al. 1990) between the anterior two-thirds and the posterior one-third, effectively the central region of the cord (Blumbergs and Byrne 1980; Imaizumi et al. 1994). To obtain such a section, it is necessary to sample the cord at the level of maximum rostro-caudal ischemia. It is quite common for the spinal cord above and below such a section to be normal, and with reperfusion, the spinal cord ischemia, like brain ischemia, may be morphologically hemorrhagic (Burger and Vogel 1977). Like brain ischemia, spinal ischemia, and the consequent paraplegia, is sensitive to temperature (Marsala et al. 1994) and blood glucose (LeMay et al. 1988; Drummond and Moore 1989). Repeated cardiac arrest may selectively involve the spinal cord (Jennings and Newton 1969). Recovery can occur (Sandson and Friedman 1989), and is more likely with incomplete lesions characterized by spastic paraparesis than flaccid paraplegia (Kim et al. 1988). Asphyxiated infants may also show spinal cord infarction (Sladky and Rorke 1986).

13.4.2.7 White Matter Lesions (Leukoencephalopathy)

In contrast to neuronal damage in acute ischemia rare cases are published demonstrating selective injury of the white matter (Feigin et al. 1973; Ginsberg et al. 1976; Pantoni and Garcia 1997a). In forensic pathology these findings are known as a consequence of chronic drug abuse (see p. 395, Fig. 19.1c). These lesions constitute the core pathology in several dementing disorders, such as Binswanger's disease, a form of subcortical vascular dementia, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (pp. 634 f) as well as methotrexate intoxication (p. 359), sniffing of organic solvents (pp. 383 f) and granulomatous angitis (p. 554). A positive correlation between white matter lesions and cognitive dysfunction has been demonstrated (Pantoni and Garcia 1997b), although it remains controversial (Hurley et al. 2000). In humans, white matter lesions are accompanied by apoptosis of oligodendroglia and have been thought to be caused by chronic cerebral hypoperfusion, a prolonged period of hypoxemia, hypotension, metabolic imbalance, and elevated venous pressure (Ginsberg et al. 1976; Tomimoto et al. 2003).

Meanwhile white matter lesions have been shown to be induced in rats by clipping the bilateral carotid arteries (Wakita et al. 1994). These animals exhibit long-standing cerebral hypoperfusion and behavioral disturbances. A study on this system and human material implicated a dysfunction of the blood–brain barrier (BBB), perivascular edema, and microglial activation in the mechanism underlying the white matter lesion (Wakita et al. 1994). During this process, microglia may play a pivotal role because their activation and the white matter lesions occur concurrently, and both are suppressed by the administration of immunosuppressants such as ciclosporin A or FK 506 (Wakita et al. 1995, 1998). Moreover, reports have suggested that mononuclear phagocytes may play an important role in the pathogenesis of inflammatory demyelination by releasing matrix metalloproteinases (Kieseier et al. 1999). Matrix metalloproteinases influence cell-matrix interactions in the human brain and may also be involved in the disintegration of the basement membranes of microvessels during cerebral ischemia (Hamann et al. 1995). In a more recent study Ihara et al. (2001) could prove the relation between white matter lesions and the expression of matrix metalloproteinases in chronic cerebral hypoperfusion.

13.5 Hypoglycemia

For many years (for review, see Auer 1986; 2004), it was believed that hypoglycemia was a form of ischemia (Courville 1957; Brierley et al. 1971a). Part of the reason for this was the belief that low oxygen and low glucose had the same potential to cause neurons to perish. We now know (see above) that hypoxia alone is incapable of causing neuronal necrosis in organisms with an intact beating heart. Rather, ischemia is necessary, not merely hypoxia. Thus, the idea that hypoxia and hypoglycemia have identical consequences within the nervous system was flawed from the beginning.

The second flaw in this argument became apparent when the biochemistry of hypoglycemia was worked out by Siesjö and colleagues in Sweden. Salient neurochemical features of hypoglycemic brain damage contrast sharply with those of ischemia (Auer and Siesjö 1993). These include an alkalosis, caused by both increased ammonia production during hypoglycemia and the lack of production of metabolic acids such as lactate, which would normally drive the pH downward. In addition to tissue alkalosis, hypoglycemia is characterized by increased, not decreased cerebral blood flow, again contrasting sharply with ischemia.

The amino acid perturbations in the neurochemistry of hypoglycemic brain damage also contrast with ischemia. Excitatory amino acids are known to play a pathophysiologic role in neuronal death in both conditions of hypoglycemia and ischemia. However, in ischemia, the release of synaptic glutamate (Benveniste et al. 1984) has been shown to be the culprit, whereas in hypoglycemia, the predominant excitatory amino acid released seems to be aspartate (Sandberg et al. 1986). It is the lack of glycolytic flux that drives aspartate production in hypoglycemia. The paltry glycolysis in turn leads to a shortage of pyruvate and, because decarboxylation to acetate is slowed, acetate is in short supply. Since oxaloacetate lacks acetate to condense with, to form citrate in normal quantities, oxaloacetate builds up before the block. The increased tissue oxaloacetate, in turn, drives the aspartate-glutamate transaminase reaction towards aspartate and away from glutamate. Thus, tissue amino acid levels of aspartate rise, and glutamate is actually lowered in the tissue during hypoglycemia. The extracellular aspartate increases to 10–20 times the normal concentration. Aspartate is a potent activator of NDMA receptors on neurons. In this fashion, aspartate, not glutamate, kills the neurons in hyperglycemia. The chain of pathophysiologic events leading to neuronal death is thus much longer than would be expected with the cursory thought that glucose deprivation directly starves the neuron

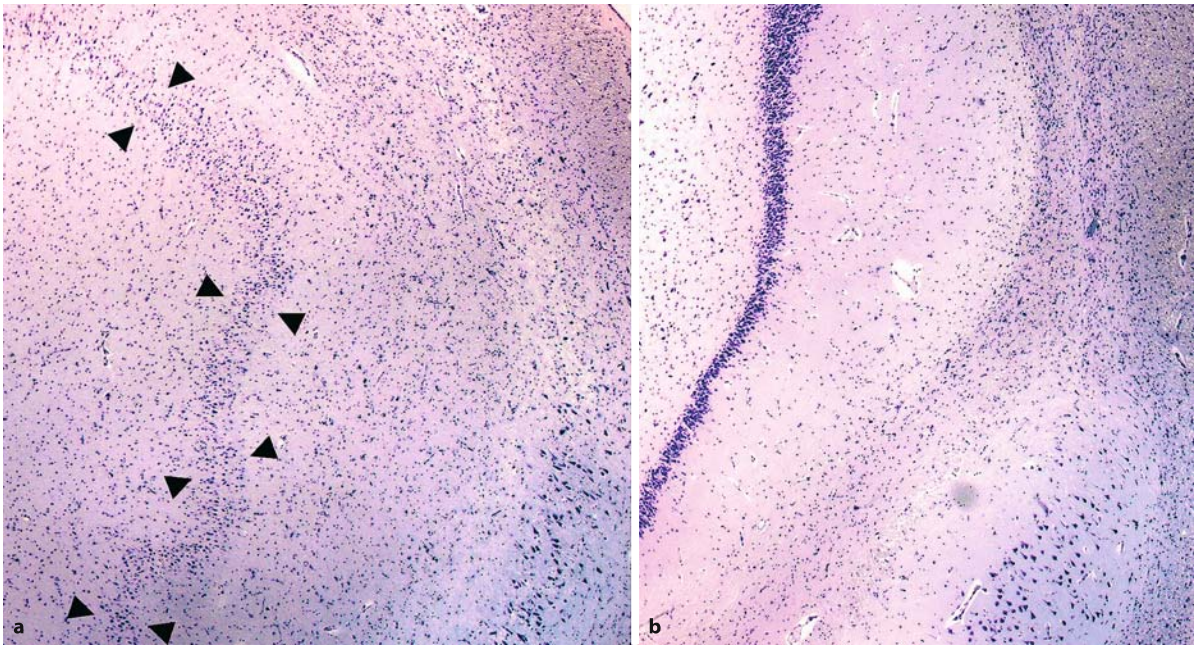

Fig. 13.9a, b. Hypoglycemic versus ischemic brain damage. **a** Hypoglycemic damage of the hippocampal dentate gyrus (*arrow heads*), while **b** in ischemia the dentate gyrus is not involved (H&E stain; magnification **a, b** ×200)

and kills it. Hypoglycemia is, rather, an excitotoxic death of hyperexcitation. This active neuronal killing contrasts sharply with the old, outmoded concept of neuronal starvation. The idea that neurons can be killed by a negative phenomenon of oxygen or glucose deprivation is an obsolete one. Indeed, even the neuropathology of hypoglycemia can, on occasion, show differences that can be clearly delineated from ischemia.

13.5.1 Neuropathology

Both ischemia and hypoglycemia affect neurons in the cerebral cortex and hippocampus. This is another basis for the previous notion that these two insults are identical. Indeed, it is common in neuropathologic material not to be able to tell the difference definitively. Nevertheless, if certain distinguishing features are seen, it is sometimes possible to distinguish hypoglycemic brain damage and rule out ischemia (Auer et al. 1984a, b).

In the cerebral cortex, hypoglycemia occasionally shows a superficial distribution of neuronal necrosis (Fig. 13.9). This can be attributed to extracellular production of aspartate which accumulates in the cerebrospinal fluid above the cerebral cortex. However, since cortical tissue itself is the source of the metabolically derived aspartate (see above), one cannot always expect a superficial distribution in hypoglycemic brain damage. Indeed, in several cases (Auer et al. 1989) there is disseminated neuronal death throughout all laminae of the cerebral cortex.

In hippocampus, hypoglycemia, like ischemia, selectively affects the CA1 pyramidal neurons. However, often a distinguishing feature from ischemia is seen: neuronal necrosis in the dentate gyrus. In ischemia, the dentate is the last structure within the hippocampus to be affected, but if dentate necrosis is prominent with relative sparing of CA3, and not all the CA1 is necrotic, hypoglycemic brain damage should be suspected. If it is ischemia causing dentate necrosis, this ischemia would have to be very severe indeed, and one should therefore expect widespread cystic necrosis of the cerebral cortex.

Hypoglycemia does not cause pan-necrosis of the cortex, due to lack of acidosis and the maintenance of cerebral blood flow in hypoglycemia. Of course, the neuropathologic findings must be seen in an integrative analysis including the circumstances of death, insulin overdose or other causes of hypoglycemic brain damage being likely or present. We must remember that in hypoglycemic brain damage, the heart continues to beat while the brain is damaged. Cardiac function can be maintained by oxidation of substrates other than glucose.

Another distinguishing feature of hypoglycemic brain damage is the absence of brain stem or cerebellar necrosis. This is made possible by the upheld energy state in these structures. In fact, protein synthesis, a high-level function that is quite sensitive to energy failure, continues unabated in the brain stem during hypoglycemic coma, while telencephalic

structures show no protein synthesis (Kiessling et al. 1986).

The cerebellum, including the Purkinje cells, is spared in hypoglycemic brain damage, contrasting sharply with ischemia. Neurochemical perturbations in the cerebellum (Agardh and Siesjö 1981) are minimal compared to the cerebrum (Agardh et al. 1978).

The above neurochemical and neuropathological contrasting features between hypoglycemic brain damage and ischemic brain damage should allow a more complete understanding of the different neurochemistry and pathophysiology of neuronal death and tissue necrosis in hypoglycemia and ischemia.

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Forensic Types of Ischemia and Asphyxia 14

In Chap. 13 we described the sequelae of disturbances of the pure primary insults of hypoxia, ischemia, and hypoglycemia. Under common pathologic conditions, a combination of different types of metabolic disturbances regularly occurs. The clinical and morphological features, therefore, may partly overlap. This overlapping of processes is especially important in surviving victims, especially in cases of ischemia (or stagnant anoxia) as well as in cases of prolonged hypoxia.

In this part we will describe the primary forensic types of ischemia and asphyxia, but we are also aware of natural types of asphyxia, i.e., diseases of the lungs (prevention/reduction of the gaseous interchange by pneumonia, edema, etc.) and the heart (prevention/reduction of the circulation of oxygenated blood).

From the forensic point of view we have to distinguish three types of ischemia/asphyxia:

- Type 1: Suffocation
- Type 2: Strangulation
- Type 3: Chemical asphyxiation

This classification is according to DiMaio and DiMaio (2001). The last type is described elsewhere, i.e., hydrogen cyanide, hydrogen sulfide (Chap. 17, pp. 351 f); types 1 and 2 are discussed in the present chapter.

However, to start with we should state that, in spite of innumerable experiments demonstrating morphological, immunohistochemical, biochemical or molecular alterations, no early neuronal changes are detected, even in experimental circumstances (Oehmichen and Meissner 2000; Oehmichen et al. 2003), if an extremely short period of ischemia leads to early death before cellular alteration can mature and appear morphologically. Especially in human autopsy material the ever-present postmortem and agonal changes will interfere with the subtle early signs of ischemic changes (Knight 1996).

Table 14.1. Types of suffocation and strangulation

Term	Meaning	Spontaneous brain perfusion or reperfusion	Ischemia/hypoxia
Suffocation	**Deprivation of oxygen**	**+**	**Hypoxia**
Environmental suffocation	Lack of oxygen in breathable environment	+	
Smothering, gagging	Blockage of the external air passage	+	
Choking	Blockage of the upper airways by foreign body (bolus, aspiration),	+	
	Manual strangulation: external compression of trachea	+	
Drowning	Immersion-induced blockade of the external air passage and upper airways (aspiration)	+	
Mechanical asphyxia	Restriction of respiratory movement of the chest by pressure outside the chest or upper abdomen	+	
Strangulation	**External pressure to the neck**	**+/–**	**Intermittent ischemia**
Ligature strangulation	The band is tightened by a force other than the body weight	+/–	
Manual strangulation	Occlusion of the vessels is produced by pressure of hands, forearm or other limb against the neck	+/–	
Mugging	Pressure to the neck by means of an arm crocked around from the rear	+/–	
Hanging	**Constricting band is tightened by the weight of the victim's body**	**–**	**Ischemia**
Garroting	Ligature strangulation (Spanish method of judicial execution)	–	

14.1 Suffocation

Death by suffocation is caused by a reduction of the oxygen concentration in the respired atmosphere. The different types of suffocation are listed in Table 14.1. The passing neurologic deficits depend on the oxygen concentrations and are described in Table 14.2, while the relationship between carbon dioxide concentration and clinical symptoms is demonstrated in Table 14.3.

14.1.1 Environmental Suffocation

The scene is partly described in Chapters 12 and 13 (altitude mountaineering), which is associated with a hypoxic state. An identical lack of atmospheric oxygen concentration may be observed by a physical displacement of oxygen, e.g., by gases such as carbon dioxide, nitrogen or methane, or by chemical changes such as combustion. Each of these will reduce the partial pressure of inspired O_2.

Table 14.2. The relationship between the time of exposure to oxygen depletion and the clinical effect. Source: Davies 1991

Atmospheric oxygen (%)	Clinical symptoms of O_2 depletion
21	Normal concentration in air
12–15	Shortness of breath, headache, dizziness, quick pulse, fatigue on exertion, loss of muscular co-ordination for skilled movements
10–12	Nausea and vomiting, exertion impossible, paralysis of motion
6–8	Collapse and unconsciousness – rapid treatment can prevent death
<6	Death in 6–8 min
2–3	Death in 45 s

Table 14.3. The relationship between atmospheric concentration of carbon dioxide and clinical effect. Source: Davies 1991

Carbon dioxide (%)	Clinical features of CO_2 narcosis
0.025–0.035	Normal concentration in air
2.5	Ventilation increases
5.0	After 30 min: headache, dizziness, sweating
12.0	Unconsciousness (immediate); death in minutes

14.1.2 Smothering, Choking, and Gagging

A mechanical occlusion of the external respiratory orifices may be caused by sand or by a plastic bag over the head, which may cling to the face by static electricity and occlude the external airways (accidental, suicidal, or homicidal). This type of asphyxia will not be associated with any specific findings, neither at autopsy nor neuropathologically.

Otherwise, smothering may be achieved by a gag obstructing the nose and mouth or by a pillow which is placed over the face and pushed down, or – in children – by a hand. Abrasion injuries of the face will occur if the victim puts up resistance. No other morphological features are to be seen.

The same negative pathological and neuropathological findings will result from choking, i.e., obstruction within the respiratory passage. This event may be observed in cases of epiglottidis under "natural" circumstances, but also in homicides in conjunction with gagging. Most often choking is accidental in manner: unintentional inhalation of food or other foreign bodies, resulting in obstruction of the respiratory passage (death by bolus – Mallach and Oehmichen 1982; Oehmichen et al. 2003).

14.1.3 Drowning

Typical drowning is characterized by an immersion-induced blockage of the external air passage as well as of the upper airways by water. The common sequelae will be a retention of carbon dioxide, an increase of catecholamines, and convulsions. At autopsy a plume of froth from the mouth and nose, an acute emphysema of the lung, water in the stomach, and brain edema are characteristic of drowning and

allow one to distinguish death by drowning from death by a primary cardiac arrest in water or from other causes. Those "other" causes may be sudden unexpected natural diseases such as stroke, etc. The following types of alternative mechanisms are to be discussed in death from immersion other than drowning (according to Knight 1996, modified):

1. Sudden immersion in cold water can cause intense stimulation of cutaneous nerve endings and induce sudden overactivity of the parasympathetic system as well as triggering of cardiac arrest via the tenth cranial nerve nucleus and its vagal outflow (Tipton 1989).
2. Sudden entry of cold water into the pharynx and larynx can stimulate the nerve endings of the mucosa and lead to a comparable breakdown of the circulatory system as described above.
3. Entry of water into the larynx causes a laryngeal spasm and leads to a hypoxic death from closure of the airway.
4. Hyperventilation before intended diving leads to a reduced pCO_2 in plasma, which results in a blockage of the natural stimulus of the respiratory center of the brain.

Under these conditions the morphological symptoms will not give any evidence of the pathophysiological background of death in water. There are no characteristic neuropathological findings in acute drowning. But there are characteristic neuropathological (and clinical) observations in cases of near drowning (see below).

14.1.4 Mechanical Asphyxia

Mechanical asphyxia is characterized by mechanical fixation of the chest (thorax compression), i.e., by prevention of respiratory movements of the chest caused by pressure on the outside of the chest or upper abdomen as well as by curare-like drugs or brain-induced primary respiratory arrest, i.e., by morphine poisoning. The autopsy findings in cases of pressure are characterized by congestion and skin petechiae in the drainage area of the superior vena cava (Oehmichen et al. 2000). Neuropathological findings are marked by congestion, but specific findings are unusual.

A special type of mechanical asphyxia is "burking," a combination of suffocation and mechanical asphyxia. By kneeling or sitting on the chest of a supine victim any chest excursion is impossible; at the same time the external airways are occluded by hand. There may be no visible injuries at autopsy or neuropathology (Knight 1996).

14.1.5 Neuropathology of Suffocation

14.1.5.1 Acute Death after Suffocation

As mentioned above, the different types of rapid death by suffocation will not be associated with any specific neuropathological alteration, though the death will be primarily caused by a metabolic breakdown of the neuronal functions. The non-specific finding will be in most cases a brain swelling or a brain edema which, however, will not be present in all victims of death by suffocation. The morphological sequelae may be extreme in cases of survived suffocation (see below).

14.1.5.2 Delayed Death after Suffocation

In cases of delayed death after suffocation the neuropathological findings may range from being totally negative, to expressing the signs of brain death, dependent on the duration of interruption of the oxygen supply and the time interval between the insult and resuscitation or blood reflow. The neuropathological findings correspond in part to the alterations summed up below under the heading "Delayed Death after Strangulation" (p. 299). But in contrast to the rare cases of survived strangulation there are several clinical, epidemiologic, and prognostic evaluations (Bierens et al. 1990; Wintemute 1990; Kemp and Sibert 1991, 1992; Schöchl et al. 1994) that provide evidence of the surprisingly good outcome in some cases of near drowning, especially in children under special conditions of hypothermia.

Modern imaging techniques provide evidence, especially of the process of brain alterations, after *near drowning* that are to be compared with neuropathological alterations, summed up below (pp. 301 ff). In the majority of comatose patients a normal, initial CT examination is seen shortly after the traumatic event (Taylor et al. 1985), but abnormal findings are evident in most cases during the first week (Fitch et al. 1985). The most frequent finding is a loss of gray–white matter differentiation. Other findings include effacement of sulci and cisterns, focal areas of edema in the cerebral cortex or basal ganglia, and hemorrhagic infarction of the basal ganglia. Subsequent CT scans obtained from 2 weeks to 5 months later show progression of cerebral tissue loss from cortical infarction with gyral hemorrhage and enhancement to global parenchymal atrophy. Apart from this ischemic brain injury, the brain may be additionally damaged by the consequence of hemorrhagic shock, which may influence the prognosis. The histological findings are additionally characterized by multiple intravascular

microthrombi, hyaline bodies, and fibrin thrombi in the brain (Ikeda et al. 1988).

14.2 Strangulation

Whenever pressure is applied to the neck, five types of mechanisms may occur in various combinations: venous obstruction, arterial occlusion, reflex mechanisms, airway collapse, and mechanical neck injury.

1. *Obstruction of the veins*. Obstruction of venous outflow from the head is most easily produced because the veins have thin walls and collapse easily. This accounts for the commonly seen conjunctival and facial skin petechial hemorrhages in victims of manual strangulation, hanging, etc. The increase in venous pressure also causes the almost ubiquitous lesions at death: congestion of the brain vessels and a minor or "smear" subarachnoid hemorrhage as well as periventricular hemorrhages. A generalized increase in venous pressure observed by thoracic compression (see above) can lead to petechiae seen in pleurae and viscera as well as in the skin of arms and legs. Though venous obstruction may be a phenomenon of all types of strangulation, their obstructions alone do not lead to death.
2. *Carotid artery compression*. If more force is used in constricting the neck, carotid artery compression can result (Reay and Holloway 1982). This is known to lead to loss of consciousness in roughly 7–10 s, from studies by Kabat et al. using an apparatus causing rapid carotid occlusion in the human (Kabat et al. 1941; see also: Rossen et al. 1943 – for details, see p. 310). In attempting to overcome a victim by choking or mugging, it is this period of carotid insufficiency that is needed by the attacker to produce unconsciousness and finally subdue the victim by obviating the possibility of further struggle and resistance. In cases of survived hanging, infarcts in the brain have been described, and are due to carotid artery injury (Pollak et al. 1987).
   The tension force in the vertical part of the ligature constricting the neck which is necessary to occlude the carotid arteries (Brouardel 1985) is approximately 50 N (corresponding to the gravitational force of 5 kg loading mass). For the vertebral arteries 300 N (corresponding loading mass: 30 kg) is necessary; for the jugular veins, 20 N (2 kg, cf. Camps and Hunt 1959). The result will be a cerebral hypoxia or anoxia. If tension force is immediately released, consciousness is regained within 10–12 s (DiMaio and DiMaio 2001).
3. *Stimulation of the carotid sinus*. Vagal cardiac arrest may be due to stimulation of the carotid sinus, which requires less pressure. Mechanical stimulation of the carotid sinus leads to an increase in blood pressure in these sinuses with resultant slowing of the heart rate (bradycardia), dilatation of blood vessels and a secondary fall of blood pressure, and can cause fatal cardiac arrest. This occurs rapidly and can be considered as a form of neurocardiac death (p. 526). This phenomenon may be comparable with a sudden cardiac arrest due to a blow to the neck or throat, the basis of the so-called commando punch which is potentially lethal.
   Mechanical irritation of the common carotid artery below the sinuses reduces the blood pressure within the sinuses by reducing the amount of blood following into it. The sequelae will be tachycardia, a constriction of the vessels, and a rise of the blood pressure. But both phenomena are commonly associated with minimal effects – with rare exceptions of extreme hypersensitivity in single individuals.
4. *Blockage of the internal airways*. If focal force is used and pressure applied to the anterior neck, then blockage of internal airways results. This usually occurs between the pharynx and the tracheal bifurcation. An identical result of hypoxia can come not only from choking, but also from suffocation, postural asphyxia, etc. as described above.
5. *Breaking and dislocation of the cervical spine*. If great force is applied, there is mechanical damage to the bony and musculo-ligamentous structures of the neck. The cervical spine will be dislocated resulting in traction on the spinal cord with consequent spinal cord or brain stem disruption. Head and neck preparation after judicial hangings has shown cervical spine ligamentous injury, vertebral artery injury, cervical vertebral subluxation, and spinal cord transition (Wallace et al. 1994). Not surprisingly with this degree of injury, subarachnoid hemorrhage was also present around the brain.

14.2.1 Hanging

Hanging is characterized by a tightening of a constricting band by the weight of the body, which may be associated with a complete or incomplete suspension of the body. Death is caused by a compression of the arterial vessels of the neck. Virtually all hangings are suicidal. The scene as well as a furrow from the noose (a noose mark) commonly will characterize the cause of death. The furrow generally does not completely encircle the neck. In *typical hanging* the face is pale while in atypical hanging, i.e., in partially suspended individuals, the arteries are not

completely occluded – while the veins are completely occluded – and produce congestion of the face (and brain) as well as petechiae in skin, conjunctivae, and mucosa (*atypical hanging*). At autopsy additional (rare) findings are fractures of the thyroid and/or hyoid cartilage and fractures of the cervical spine (C1/2, C3/4, C6/7 – Feigin 1999), which are not correlated with the height of suspension. In judicial hangings, however, the victim falls within a specific distance, the fall will be abruptly stopped, and the head is jerked suddenly backward, fracturing the spine (see below).

The neuropathology of acute death by hanging is non-specific. Congestion and edema will be the main symptoms, partly accompanied by discrete periventricular perivascular hemorrhages (Schröder and Saternus 1983).

14.2.2 Ligature Strangulation

The biomechanics of ligature strangulation will be identical to those associated with death by hanging, but the tightening force will be other than the body weight. Constricting all or parts of the circumference of the neck by a ligature leads to an attack called "garroting," a type of Spanish judicial execution. Ligature strangulation, however, is the most common method of homicidal asphyxia and rarely the result of an accident or a suicide.

Because there usually is no complete occlusion of the arterial vessels at the beginning of neck compression, the face will be congested, petechiae and scleral hemorrhages are common as well as swelling of the tissues, both from an increase of intravascular volume and from rapid transudation of fluid into tissues (edema) and cyanosis. The ligature mark usually encircles the neck in a transversal plane often overlying the larynx or upper trachea. The internal structures of neck tissue are mostly intact but often characterized by focal subcutaneous hemorrhages. The brain examination will give evidence of congestion and brain edema. Specific findings are absolutely uncommon.

14.2.3 Manual Strangulation

Manual strangulation covers pressure forces of hands, forearms, so-called arm-lock, etc. against the neck. In this case the cervical spine commonly is the butt of the pressure of the frontal neck tissues. Bruises and abrasion are characteristic of the assailant's attack. Petechiae are common. The skin of the neck is commonly characterized by marks of violence, i.e., abrasion injury, contusion injury, and fingernail marks. At autopsy often fractures of the hyoid bone or thyroid cartilage are observed.

Death will be explained by occlusion of the arterial neck vessels, which accounts for the extreme congestion of the face, the multiple petechiae, and the cyanosis of the skin. Moreover, compression (and stimulation) of the carotid sinuses may occur (DiMaio and DiMaio 2001).

14.2.4 Neuropathology of Strangulation

The dynamic development of visible neuropathology is dependent on the phenomenon of recirculation and will be time-dependent, in cases of intermittent and/or stagnant recirculation of blood. The neuropathological differences are described by Kalimo et al. (1982, 1983, see also van Reempts 1984; Lipton 1999), but this classification is not generally accepted. The authors point out that the character of ischemic nerve cell injury varies depending on whether the ischemia is complete or incomplete and whether there is a tissue acidosis or not. Integrating the more recent investigations regarding apoptosis we must differentiate three types of ischemically induced morphological changes (Table 14.4):

1. *Pale nerve cell injury*, which will be observed in complete permanent ischemia without recirculation and which will be seen 30–60 min after strangulation (Arsenio-Nunes et al. 1973; Garcia et al. 1975 – including the postmortem situation): the cytoplasm appears watery, mitochondria show mild to moderate swelling, and the nuclear chromatin is slightly coarsened both in neurons and astrocytes. No definite edema is detectable. This type is aggravated (the clumping of the nuclear chromatin is more pronounced) if high levels of lactate are accumulated due to post-ischemic glucose loading (Kalimo et al. 1981; Rehncrona et al. 1981).
2. *Dark nerve cell injury*, which is seen in cases of incomplete ischemia or if severe complete ischemia is followed by reflow (Arsenio-Nunes et al. 1973; Jenkins et al. 1981). According to the description of Kalimo et al. (1982), this type of injury is characterized by marked condensation of neuronal cyto- and karyoplasm with extensive ballooning of mitochondria and swelling of perineuronal and perivascular astrocytic processes. The neurons become triangular with marked condensation of the karyo- and cytoplasm, whereby the cytoplasm contains microvacuoles. Perineuronal empty spaces and a markedly spongy neuropil are indicative of astrocytic edema. This type of cell injury will be expressed several days after ischemia and accompanies the eosinophilic ischemic nerve cell alteration indicative of necrosis.

Table 14.4. Ischemic neuronal injury and its dependence on reperfusion. Source: Kalimo et al. 1983

Cytologic alteration	Ischemic neuronal changes		
	Reperfusion: dark type	No reperfusion: pale type	Apoptosis
Neuronal structure	Triangular	Round and swollen	Round
Nucleus	Marked condensed, irregular clumped chromatin	Slightly coarse chromatin	Smoothly contoured, spherical-shaped, or lunar crescent-shaped masses of uniformly condensed chromatin, apoptotic bodies
Cytoplasm	Markedly condensed, acidophilic; peripheral chromatolysis	Microtubules and other filamentous structures are absent	Dark and pyknotic, some vacuolation, not eosinophilic
Edema	Perineuronal vacuoles, spongy neuropil	–	–

3. *Apoptotic nerve cell changes* are described elsewhere (Chap. 4, pp. 60 ff). Meanwhile there are some reports on apoptosis in the CA1 region of the hippocampus caused by ischemia, especially following short durations of global ischemia in rats (Heron et al. 1993) and gerbils (Kihara et al. 1994). Apoptotic cells are present in great numbers 24 h after permanent, or 1 h after temporary, focal ischemia in mouse; in the penumbra, they constitute approximately 5–10% of the total number of cells (Murakami et al. 1998). Not more than 10% of apoptotic cells were co-labeled with glial fibrillary acidic protein (Li et al. 1995). In contrast to the dark (and pale) type in the apoptotic cell change, the nucleus is characterized by uniformly condensed chromatin, apoptotic bodies, and a darkened, pyknotic cytoplasm, without astrocytic edema. According to Lipton (1999), we should say that presently there is good morphological evidence that apoptosis occurs after focal ischemia, but there is no convincing evidence that apoptosis occurs after global ischemia (Colbourne et al. 1999). Moreover, apoptosis is not a suitable criterion for differentiating between the morphology of the perfusion and no-perfusion types of ischemia.

14.2.4.1 Acute Death after Strangulation

Summarizing the above-mentioned negative morphological findings in macroscopic and microscopic brain examination, we conclude that to date there is no specific neuropathological evidence that strangulation causes acute damage to the CNS. All types of strangulation may be characterized by brain swelling, brain edema, brain congestion and – sometimes – by perivascular hemorrhages (Oehmichen 1990). These findings are in contrast to the massive structural alterations in survived cases of strangulation (see below).

14.2.4.2 Delayed Death after Strangulation

Delayed death after strangulation is a rare event. While Maxeiner (1987) could summarize the findings in seven cases, other authors published only single cases. There are no common findings as each case is characterized by an individual history regarding age, biomechanics of strangulation, duration of strangulation, survival time, etc. Two cases in Maxeiner (1987) are "brain death" after resuscitation; four of his cases are characterized by regionally elective parenchymal necrosis. The two cases described by Hori et al. (1991) and two cases described by Lumb et al. (2001) at autopsy revealed hemorrhages in the central cerebrum, i.e., the lentiform nuclei and caudate as well as in the internal capsule. In contrast Pollak et al. (1987) could demonstrate an infarct in the fronto-basal region, obviously as a result of an embolic occlusion of an arterial vessel resulting from a mechanical lesion of the large arterial vessels of the neck (Hausmann and Betz 1997). Further detailed microscopic features are summed up below in Sect. 14.3.

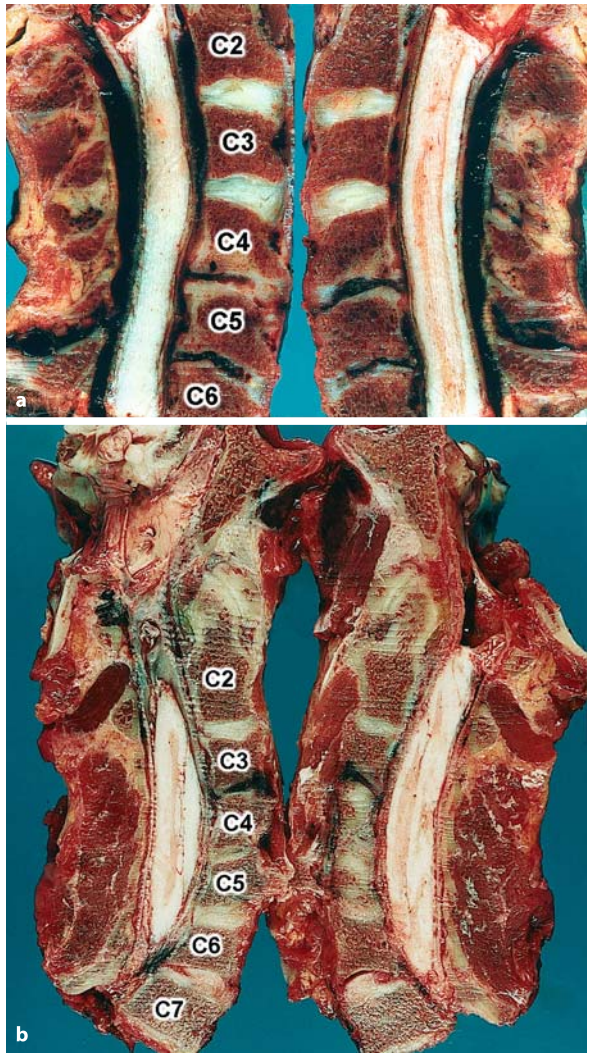

Fig. 14.1a, b. Cervical spine in hanging. **a** Epidural hemorrhages and hemorrhages in the intervertebral discs C4/C5 and C5/C6; **b** total disruption of the intervertebral disc C3/C4 and C6/C7

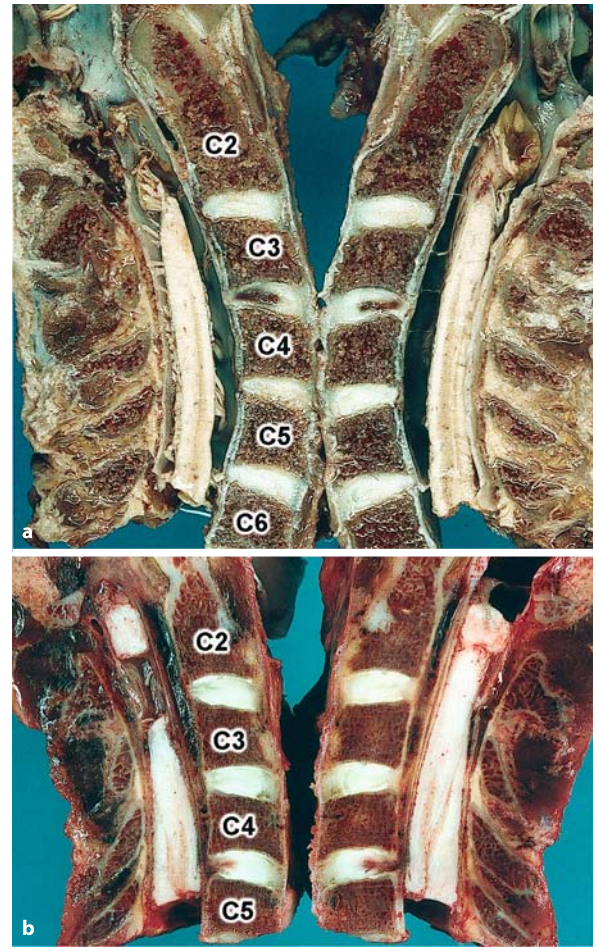

Fig. 14.2a, b. Cervical spine in cases of death by ligature and manual strangulation. **a**, **b** Combination of ligature and manual strangulation with hemorrhages in the intervertebral discs C3/C4 (**a**) and C4/C5 (**b**) associated with an epidural hemorrhage in both cases

14.2.5 Cervical Spine and Strangulation

Bony lesions of the spine are not seen in any types of strangulation with the exception of hanging. However, in suicidal hanging fractures of the cervical spine are also extremely rare while hemorrhages within the muscles of the neck are common (Saternus et al. 1978) as is hemorrhage between the ventral ligament and the lumbar spine, which is caused by traction forces (Simon 1968; Saternus et al. 1979). Injury of the cervical spine may also be seen after hanging in victims with advanced degenerative diseases of the cervical spine, such as osteoarthritis, in combination with complete suspension of the body after hanging with a sudden drop and, sometimes, with obesity (DiMaio and DiMaio 2001). Though the fracture in combination with a displacement in single cases may explain the death, in most cases the fracture is only an additional marker of mechanical forces on the neck.

As mentioned above, in judicial hanging there is a special biomechanical force which – in rare cases – may lead to a spine fracture which is called "hangman's fracture" marked by fracture lines through the pedicles of C2 with the posterior arch remaining fixed to C3 (Schneider et al. 1965; Spence et al. 1999 – for further discussion, see Saternus et al. 1978). In this case, consciousness is lost immediately though the heart may continue to beat for 8–20 min. But also in judicial hanging the mechanically caused lesion may differ markedly as recently described by Wallace et al. (1994).

In contrast to the very rare bony fractures of the cervical spine, lesions of the dura and intervertebral discs are more often seen. Saternus (1978) described

Table 14.5. The time course of cytopathological phenomena as evaluated by Schröder. Source: Schröder (1983)

Reactive phases	Histological reactivity	Time course
1	Leukocytes	30 min to 4 days
2	Macrophages, foam cells/gitter cells	7 h to 7 days
3	Aggregated macrophages	9 –44 days
4	Increased liquefaction of necrosis	21–70 days
5	Development of cysts, party filled with detritus	51 days to 15 months
6	Cysts containing a few macrophages	11 months to 4 years
7	Cysts containing no or single macrophages	>24 months

hemorrhages in the neck, epidural hemorrhages at the occipito-cervical junction (41%), and hemorrhages in the intervertebral discs in about 70% of 107 examined cases after hanging, mainly at the C5–C6 level. As demonstrated in Fig. 14.1, a laceration and hemorrhage of the anterior or dorsal part of the intervertebral disc is seen in suicidal hanging as well as in homicidal ligature or manual strangulation (Fig. 14.2). These lacerations within the intervertebral discs are an indication of a sudden hyperextension (anterior hemorrhage) or hyperflexion (posterior hemorrhage) of the head and cervical spine – in combination with death agony and/or strangulating forces by the perpetrator.

Moreover any type of strangulation may also be accompanied by lesions of the large neck vessels, especially the carotid arteries. A mechanically induced endothelial lesion may become the source of a delayed thrombotic occlusion of the carotid artery in surviving cases. Hartshorne and Reay (1995) reported two cases of bilateral vertebral artery lacerations associated with a basilar subarachnoid hemorrhage after judicial hanging. In one of the cases there was also a separation at C2 and C3 with complete dissection of the cord, bilateral carotid intimal tears, and subdural hemorrhage. The fall of the victim was about 165 cm with the knot slipping to the subaural area.

14.3 Time Course of Ischemia

The time dependency of brain tissue alterations in ischemia are comprehensively described by Müller (1930), Baggenstoss et al. (1943), Környey (1955), Peters (1955), and Schröder (1983). The following text sums up more recent investigations, especially Schröder's (1983) review which evaluates a great deal of case material involving prolonged ischemia (see Table 14.5).

14.3.1 Macroscopic Findings

Between 10 and 12 h after an ischemic event, the first gross alterations are seen, characterized by a diffuse loss of demarcation between white and gray matter, a gelatinous tissue appearance, and a tissue softening (encephalomalacia). A gray or dark staining (edema, congestion, and hemorrhages) will be seen in the cortical structures of the sulci, especially between the 1st and 2nd frontal gyri (Fig. 14.3a), within the thalamic nuclei, hippocampal area (Fig. 14.3b), and the pallidum (Fig. 14.3a), partly associated with hemorrhages. After a survival time of some days the pallidum will be softened and cystically transformed (Fig. 14.4). A survival time of more than 1 week leads to a cortical atrophy of the cerebrum and cerebellum and to cystic alterations of the basal ganglia (Fig. 14.5). The combination of ischemia and arterial hypotension may be associated with involvement of the brain stem and the medulla (Fig. 14.6).

14.3.2 Edema

The very early microscopic features are marked by a *spongious alteration* caused by edema involving gray and white matter, which is demonstrable at 2 h up to 8 h of survival time (Peters 1955). The *cortical edema* (cytotoxic edema) will be extremely expressed; for example, in the depth of the sulcus between the 1st

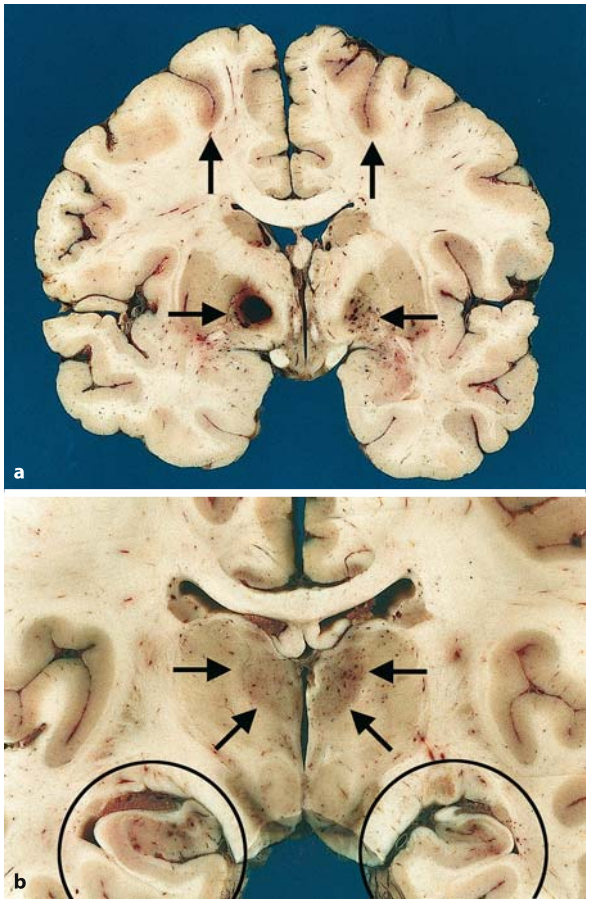

Fig. 14.3a, b. Global brain ischemia (pan-necrosis) with reperfusion (24 h after reperfusion). Ischemia causes dark discoloration of the cortex in the sulci between the 1st and 2nd frontal lobe gyri (**a** *vertical arrows*), the globus pallidus (**a** *horizontal arrows*), the median thalamic nuclei (**b** *arrows*) and hippocampus (**b** *circles*), which are microscopically characterized by edema, congestion, and perivascular hemorrhages

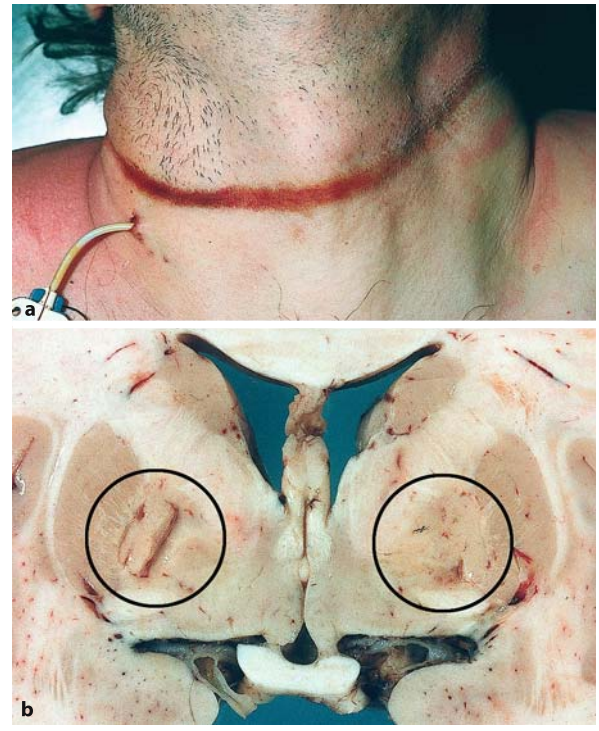

Fig. 14.4a, b. Global brain ischemia (pan-necrosis) caused by hanging survived for 4 days. **a** Ligature mark; **b** delayed symmetrical necrosis and cystic transformation of the pallidum (*circles*)

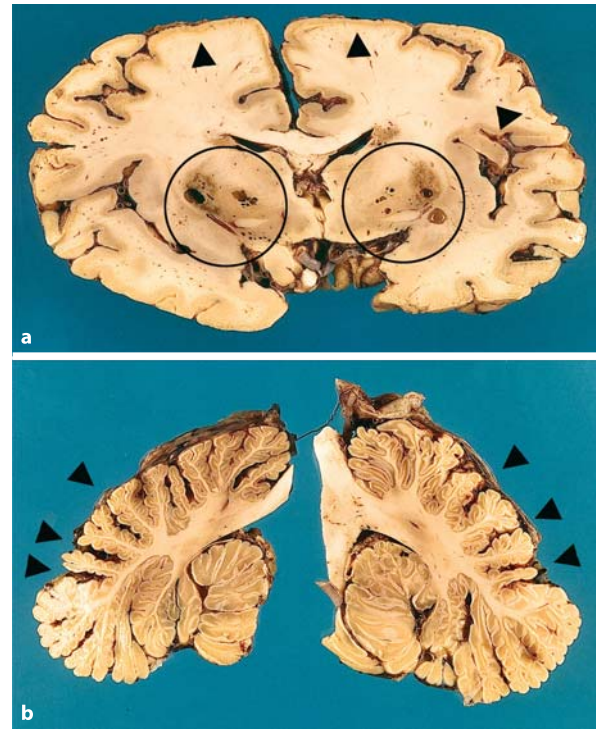

Fig. 14.5a, b. Global brain ischemia (pan-necrosis) survived for about 3 weeks. **a** Cortical atrophy of the cerebrum and **b** cerebellum (*arrowheads*) associated with cystic alteration of the basal ganglia (**a** *circles*)

and 2nd frontal and parietal gyri (Fig. 14.7a) as well as along the cortical subpial vessels (Fig. 14.7b). A *reduction of myelin staining* pattern (Luxol fast blue staining) is demonstrable within 2–14 h. An irregular map-like *demarcation of edema*, especially in the cortex, is first seen after 14 h (Fig. 4.6c, d). Shinnou et al. (1998) could experimentally demonstrate that, in gerbils after ischemia of 30 min duration and a reperfusion time of 90 min, the blood–brain barrier in some vessels along the hippocampal fissure in the medial parts of the hippocampus is more vulnerable to ischemic insults than those in other brain areas: it was clearly demonstrated that intravascular macromolecules display a transendothelial leakage (see also Fig. 14.9a). In contrast, monkeys subjected to 3 or 9 min of global cerebral ischemia were neurologically normal and had normal CA1 histology (Scheller et al. 1992). Monkeys subjected to 15 min of ischemia showed moderate to severe CA1 damage and signi-

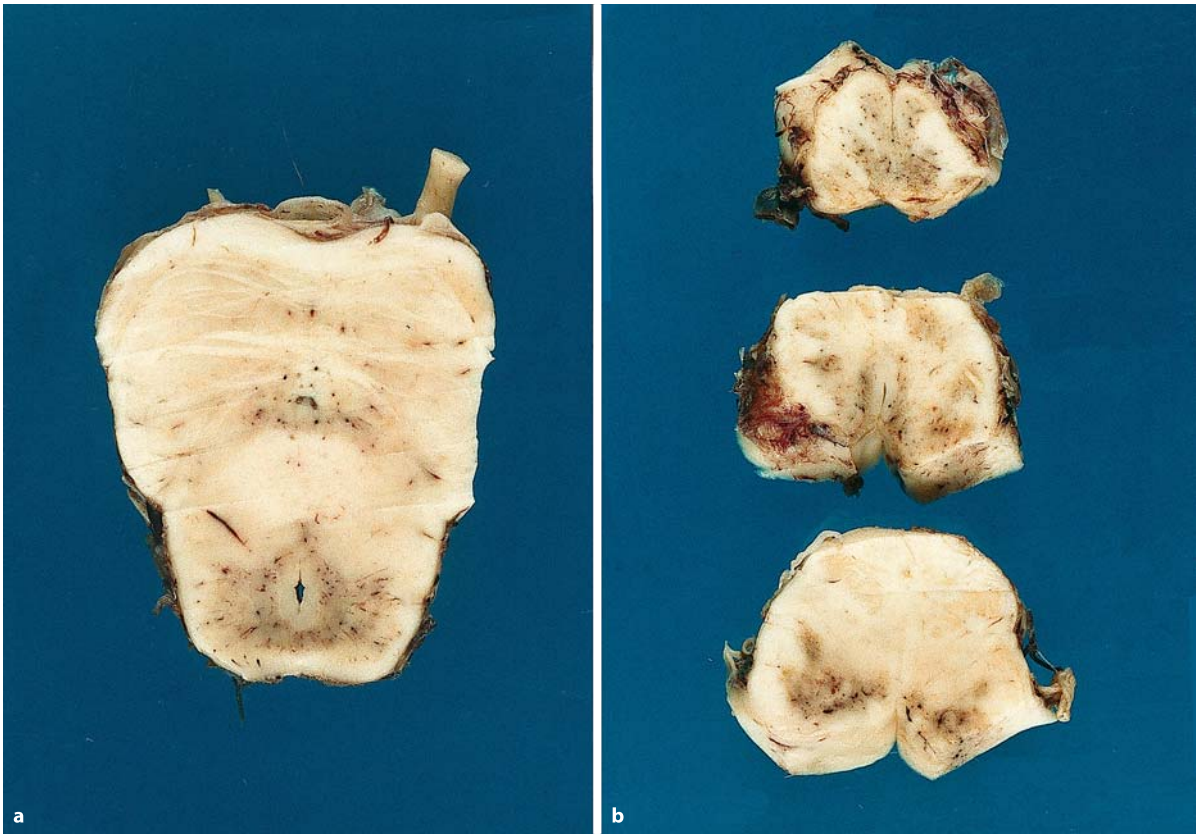

Fig. 14.6a, b. Global brain ischemia (pan-necrosis) with a gray staining pattern in brain stem and medulla. Periventricular alterations, i.e., edema, congestion, and perivascular hemorrhages, in the pons (**a**) and medulla (**b**)

ficant quantifiable neurobehavioral deficits compared with historical control animals (McSweeny et al. 1985).

14.3.3 Microthrombosis and Fibrin Deposition

In ischemia the microcirculation is impaired by hemorrheological failure: the *microthrombosis* (Petito 1979; Obrenovitsch and Hallenbeck 1985). The thrombi are composed of platelets, and a network of fibrin. In some vessels there is only a thick layer of fibrin coating the endothelium and surrounding the platelets. The number of microthrombi increases in humans as the necrotic process ages, and peaks in such stages in which acute ischemic changes coexist with the beginning of phagocytosis: between 7 and 15 days (Figols et al. 1987).

Extravascular *fibrin* deposition was significantly increased by 24 h of reperfusion in adolescent male baboons (Okada et al. 1994) after 2 h or 3 h of middle artery occlusion. These results suggest that microvascular fibrin deposition accumulates in a time-dependent manner during focal cerebral ischemia/reperfusion and that exposure of plasma to a perivascular tissue factor is partially responsible for occlusion formation. During ischemia the large plasma protein fibrinogen extravasates and interacts with parenchymal tissue factor, forming significant extravascular fibrin by 24 h of reperfusion.

14.3.4 Neurons

In the reperfusion type of ischemia *ischemic nerve cell alterations* in Nissl stain are characterized by tigrolysis (loss of Nissl bodies) and/or microvacuolation (Fig. 13.4c) within 1–3 h (Steegmann 1968). In H&E stain ischemic cortical nerve cell necrosis in layers III, V, and VI is seen within 4 h (Schröder 1983) or 5 h (Horn and Schlote 1992) marked by a homogenizing cell change consisting of eosinophilic or dark Luxol fast blue cytoplasm, a hyperchromatic, pyknotic nucleus, and a pericellular space as described in Chapter 4 (Figs. 4.5c, d, 13.4). After 5 min of ischemia and 1–2 days of recirculation, numerous calcium-containing neurons appeared in the CA4 sector, but only a few were present in the CA1 sector (Bonnekoh et al. 1992).

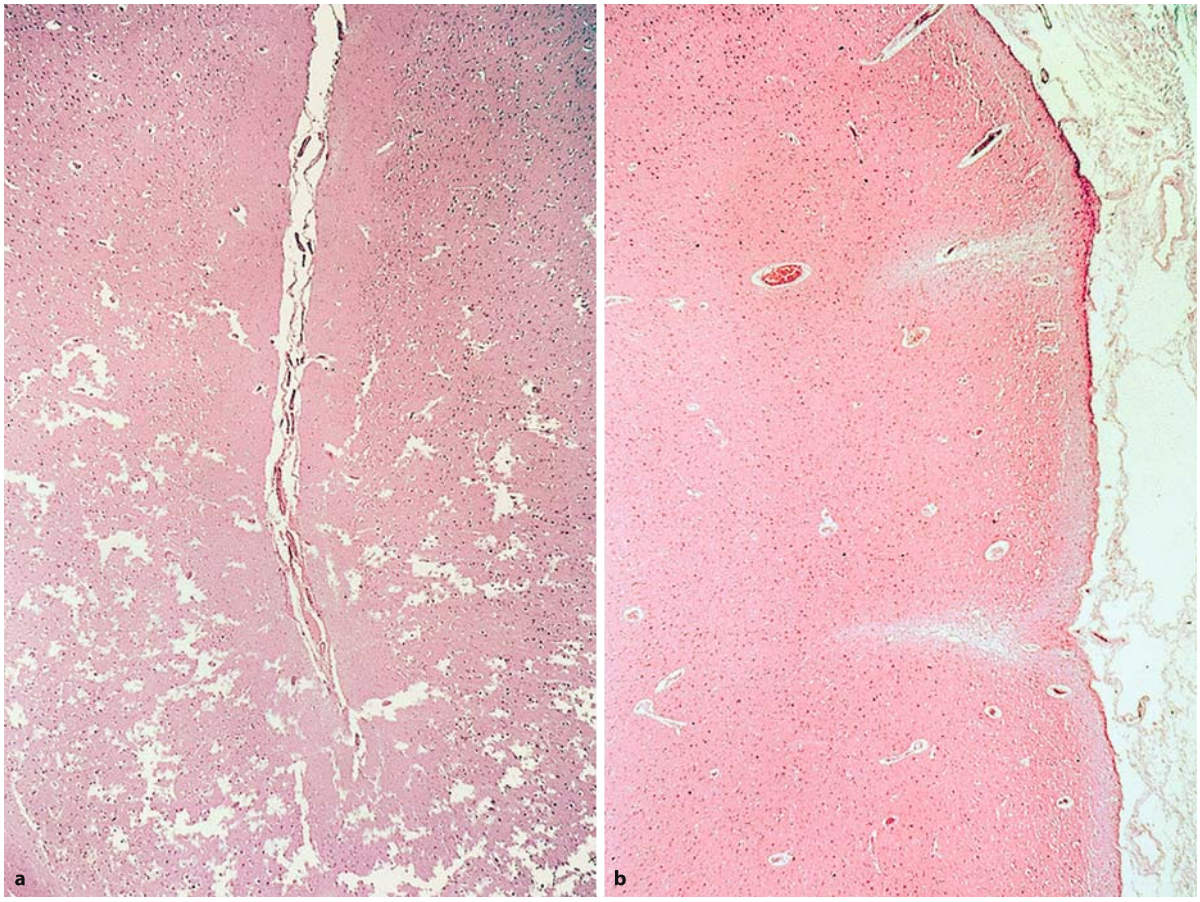

Fig. 14.7a, b. Ischemia induced edema in the cerebral cortex. **a** Edema in the sulcus between the 1st and 2nd frontal gyri (watershed edema) as well as **b** along the subpial cortical vessels (H&E; magnification **a, b** ×50)

Two relevant clinicopathologic investigations of ischemic neuronal death in human autopsy material (Petito et al. 1987; Horn and Schlote 1992) gave evidence of an early and delayed neuronal death, as had already been demonstrated by animal experiments (Ito et al. 1975). In 1982, Kirino demonstrated that the CA1 damage in the gerbil hippocampus takes place with a delay of about 48 h after brief forebrain ischemia, and is completed by the fourth day following an ischemic insult. Horn and Schlote (1992) evaluated 26 human brains and observed the earliest manifestations of ischemic neuronal necrosis by 5 h following cardiac arrest in cortical layers III, V, and VI, whereas hippocampal CA1 and Purkinje cell layers did not yet reveal any definite ischemic cell damage. CA1 pyramidal cell death does not occur until 4 days following global ischemia (cardiac arrest) but afterwards develops rapidly, exceeding the extent of neocortical neuronal injury by about 5 days post arrest. Finally, it seems to be completed no earlier than 7 days after the ischemic insult.

These findings allow the conclusion to be drawn that two types of neuronal damage, an early and a delayed one, exist in human brain too. Additionally it is known that the current data substantiate that the cell process determining the fate of CA1 neurons – delayed death or recovery – is related to the first 40 min of post-ischemic reperfusion, thus underlining the particular clinical importance of delayed neuronal death as a therapeutic window of post-ischemia treatment (Kuroiwa et al. 1990). Within the Purkinje cell layers neuronal death takes place significantly earlier and more gradually than in CA1 of the hippocampus.

A retrograde reaction of neuronal perikaryon, i.e., a neuronal swelling, a central chromatolysis, and an eccentric localization of the nucleus (Fig. 3.1b), is seen within 35 h and 15 months after ischemia (Schröder 1983; see also Schlote 1970; Torvik and Skjörten 1971); Jacob and Pyrkosch (1951) described "neuronal necrosis" in 3 of 20 cases of hanging. We agree with Schröder (1983) that these alterations may be supravital or postmortem phenomena. Though ischemic changes are mainly consistent with necrosis of neurons we have to accept that DNA fragmentation (apoptosis) occurs after the development of neuronal death in CA1 neurons subjected to 10 min of global ischemia (Petito et al. 1997; Love et al. 2000).

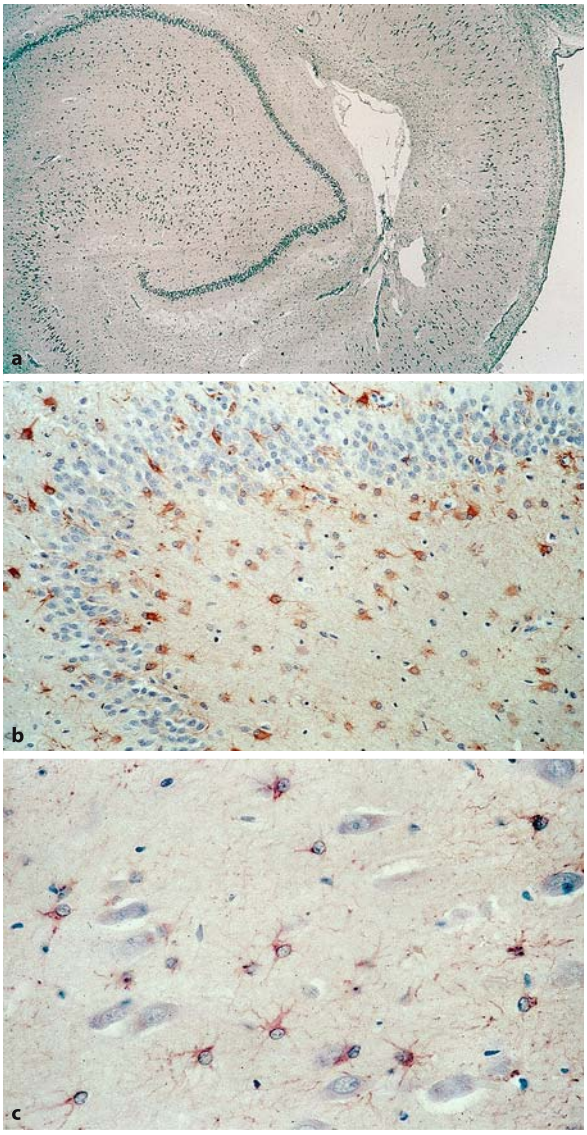

Fig. 14.8a–c. Astrocytic reaction in ischemic cornu Ammonis and cerebral cortex. **a** Intact, non-injured cornu Ammonis; **b** activation, i.e., astrocytic proliferation and upregulation of GFAP, in the CA4 sector; **c** upregulation of GFAP in the cerebral cortex (GFAP immunoreactivity; magnification **a** ×10; **b, c** ×500)

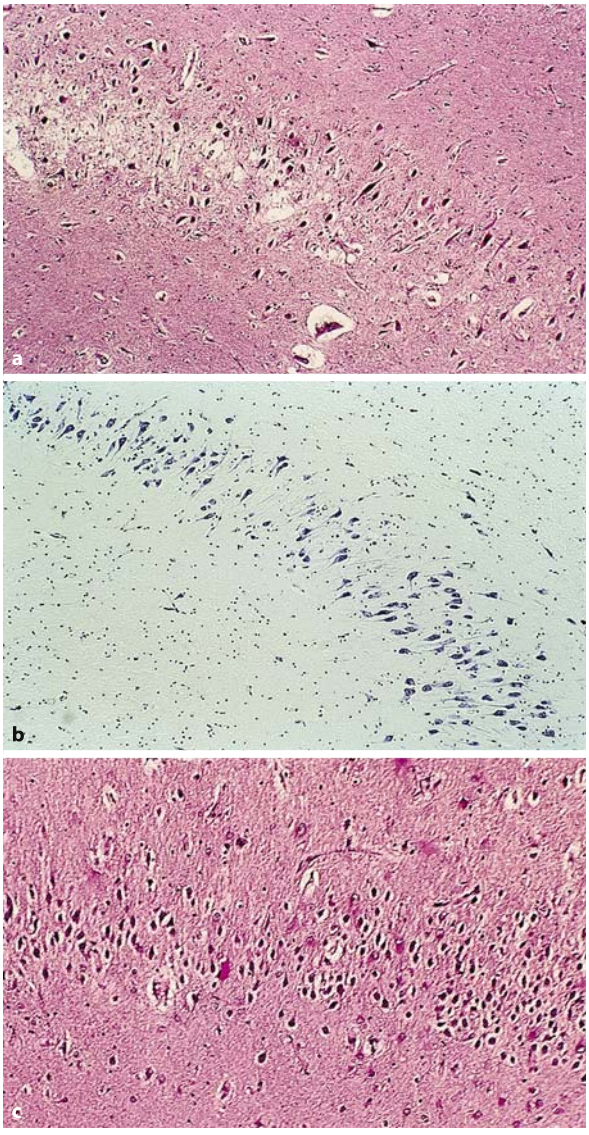

Fig. 14.9a–c. Selective neuronal injury in the cornu Ammonis (CA1 sector) and reactive astrocytes. **a** Edema with selective neuronal loss; **b** neuronal loss without visible edema; **c** astrocytic reaction (**a, c** H&E, **b** Nissl stain; magnification **a–c** ×300)

The temporal profile of neuronal, astrocytic, and microglial cells was studied in rats (Lin et al. 1998). In the striatum, normal neuron counts were first decreased significantly at 2 weeks after the ischemic event. In the CA1 hippocampus, a decreased number of normal neurons was seen at 1 week post ischemia, together with a significant increase in immunoreactive microglia at that time; the latter normalized after 2 weeks. Reactive astrocytes in the CA1 hippocampus and cerebral cortex were significantly increased at 1–2 weeks after ischemia (see also Figs. 14.8, 14.9c).

14.3.5 Neuronal Proteins

The *intracytoplasmic proteins of neurons* give information on neuronal function. Tomimoto and Yanagihara (2000; see also Tomimoto et al. 1996) could demonstrate that microtubule-associated proteins (MAPs) are more vulnerable than tubulin to ischemic insults. Using immunohistochemistry for MAPs, the earliest ischemic lesion in gerbils occurred in the CA1 and CA2 sector of the hippocampus after transient global ischemia for 3 min (see also Fig. 14.14).

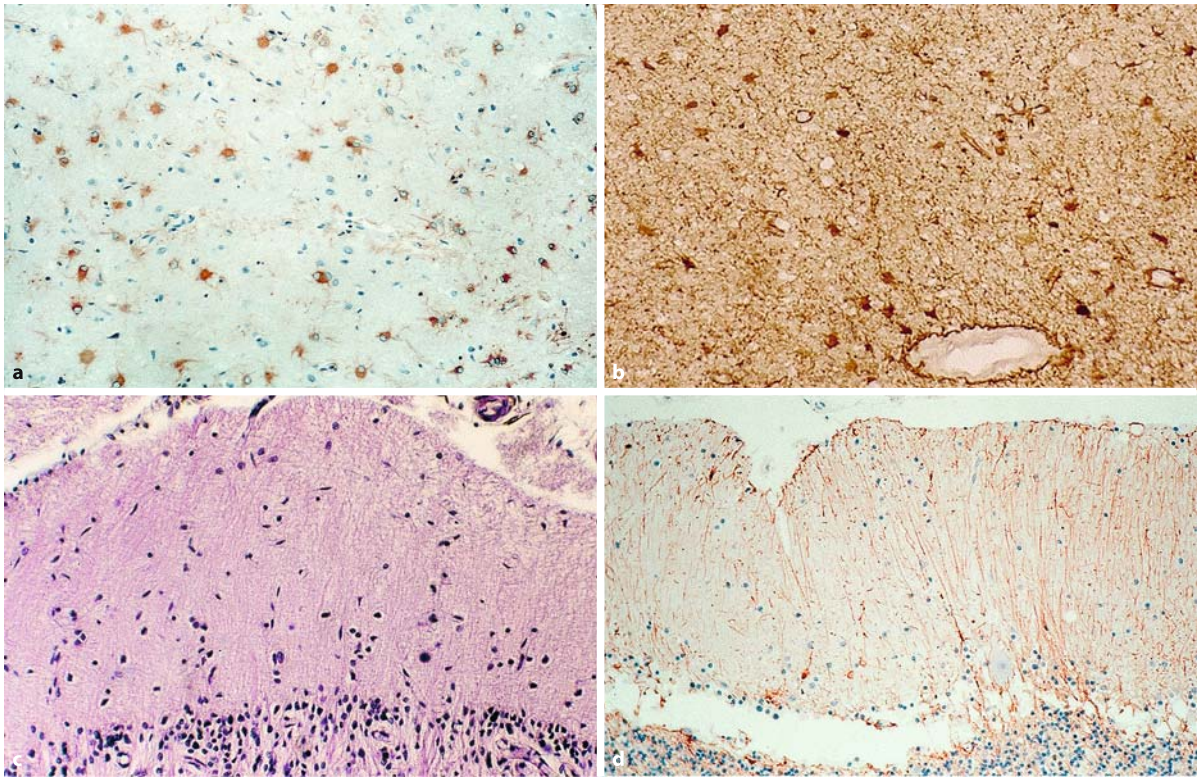

Fig. 14.10a–d. Astrocytic reactivity in brain ischemia. **a** Astrocytic hyperplasia in white matter; **b** increase of astrocytic fibers; **c** loss of Purkinje cells which are during the final stage of reactivity **d** partly replaced by astrocytic fibers (**a, b, d** GFAP immunoreactivity; **c** H&E; magnification **a, b** ×200, **c, d** ×300)

These lesions were reversible but became irreversible when the duration of ischemia was extended to 4 min.

The immunoreactivity of so-called *motor proteins*, such as cytoplasmic dynein (CD) and kinesin, begins to decrease at 1 h in CA1 neurons (Abe et al. 1995); the decrease becomes more evident at 3 h after ischemia, whereas the immunoreactivity of other neurons remains at a normal level. The motor proteins are linear motors that convert the energy of ATP hydrolysis into mechanical work and move cellular organelles such as mitochondria along microtubules. CD, also referred to as MAP-1C (Paschal et al. 1987), translocates organelles to the proximal end of microtubules. Kinesin is thought to mediate axonal transport to the peripheral end of microtubules. Moreover, we also know that one consequence of ischemia will be a non-disruptive axonal injury (AI), i.e., axonal swellings, and axonal bulbs as described by Maxwell et al. (1997 – see also: Oehmichen et al. 1998, 1999; Kaur et al. 1999) will be demonstrable 1.5–3.0 h after the incidence of the ischemic insult by application of an antibody to β-*amyloid precursor protein (β-APP)*.

Martí et al. (2001) described the temporal pattern of expression of proteins of the *chromogranin/secretogranin family* by immunohistochemistry. In gerbils, these authors could demonstrate a strong increase in reactivity of chromogranin A and secretoneurin in the CA3 sector, starting at 12 h with a peak at 24 h and a decrease at 48 h after transient ischemia.

14.3.6 Astrocytes

It is generally accepted that astrocytes are highly resistant to ischemic insults. But a specific loss of glial fibrillary acidic protein (GFAP) and immunolabeling in protoplasmic astrocytes occurred within minutes in the area with total depletion of regional blood flow, whereas "classic" gliosis was observed in areas with remaining cerebral blood flow (Lukaszevicz et al. 2002; Zhao et al. 2003). Severe disturbance of cell function, as suggested by decreased GFAP content and increased permeability of the blood–brain barrier to macromolecules, was rapidly followed by necrotic cell death.

Astrocytic alterations as demonstrated by cytoplasmic swelling (ameboid glia) are demonstrable within 2–5 h (Müller 1930; Rand and Courville 1932; Blakemore 1971). Hypertrophic astrocytes with eccentric nuclei are first seen 6 days after ischemia

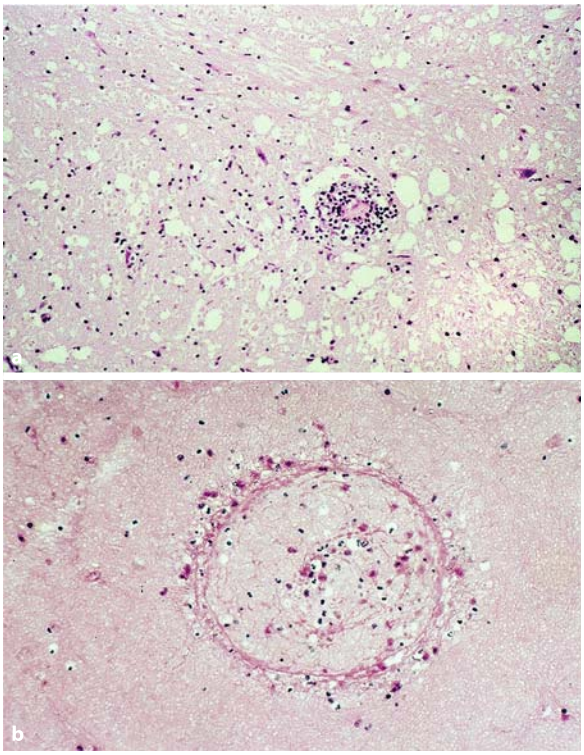

Fig. 14.11a, b. Leukocytic emigration in ischemic injured brain. **a** Perivascular aggregated leukocytes; **b** thrombotic occluded vessel associated with emigrating leukocytes (magnification **a** ×100, **b** ×300)

(Link and Schleussing 1955; Schröder 1983), in the cornu Ammonis (Figs. 14.8a, 9), cerebral cortex (Fig. 14.8c), the cerebral white matter (Fig. 14.10a, b), and cerebellar cortex (Fig. 14.10c, d). Moreover, in the cerebellar cortex an increase of glial fibers is demonstrable replacing lost Purkinje cells (Fig. 14.10b, c).

The *astrocytic activation* is extensively described by Archer and Walz (2000), who could demonstrate upregulation of GFAP as a first expression of reactivity associated with an increase of GFAP-reactive astrocytic mitosis. The astrocytic activation obviously is protective to neurons subjected to an ischemic insult (Louw et al. 1998). Moreover, a local gliotic response could be distinguished from a remote gliotic response. Schwab et al. (2000) could demonstrate that the number of astrocytes expressing connective tissue growth factors was significantly higher in border zones adjacent to the core, corresponding to the penumbra. These numbers were significantly increased in the first and third days and remained persistently elevated up to several months post infarction.

14.3.7 Polymorphonuclear Leukocytes

The early blood cell reaction is characterized by a *neutrophilic emigration* within the first 2 h of survival time (Fig. 14.11), especially in the cortex, where focal perivascular aggregation is seen. The peak occurs 12–48 h after ischemia (Baggenstoss et al. 1943; Chelnikov 1979). The infiltration is more distinct in hemorrhagic infarcts than in pale infarcts. The number of leukocytes commonly decreases after 5 days, to vanish by 7 days. This is useful in timing or dating infarcts.

14.3.8 Mononuclear Phagocytes/Microglia

Mononuclear phagocytes were first seen 7 h after ischemia by Schröder (1983; see also Wisniewski 1961) in a perivascular position (Fig. 14.12a, b), diffusely distributed (Fig. 14.12c), focally aggregated or perineuronal (Fig. 14.12d). Mononuclear phagocytes – in the first stage – are seen in a perineuronal location (Fig. 14.12d, 14.13), and later after a neuronal loss – in the second stage – these phagocytes replace the neurons (Figs. 14.14, 14.15). These cell types will be transformed into an *ameboid cell* type after 14 h, and into a *gitter cell* after 32–48 h (Escourolle and Poirier 1973; Schröder 1983). They are accumulated perineuronally in the central cortex and/or basal ganglia and are obviously of hematogenous origin (Schroeter et al. 2001). The earliest microglial response was observed in the rat hippocampal formation after 20 min of reperfusion following global cerebral ischemia in the four-vessel occlusion model (Morioka et al. 1991). In another study, a biphasic microglial reaction was detected in the hippocampus evoked by cerebral ischemia or kainic acid administration (Jørgensen et al. 1993). An early, widespread activation of microglial cells could be seen in all hippocampal regions on the first day after ischemia. This reaction subsided during the next few days in the areas devoid of neuronal degeneration, while it progressed into a protracted, lesion-specific reaction in the areas where neuronal degeneration occurred (Freund and Maglóczky 1993; Jørgensen et al. 1993).

Ábrahám and Lázár (2000) could demonstrate an activation of resting microglia within 20 min after ischemia, but no increase of the number of cells. Beschorner et al. (2002) could show an upregulation of CD14 antigen in mononuclear phagocytes in cases of focal cerebral infarction within 1–2.5 days that remained elevated until late stages. This early CD14 expression is suggested to be an essential part of CD14 in the acute inflammatory response following stroke. As mentioned above, Lin et al. (1998) induced

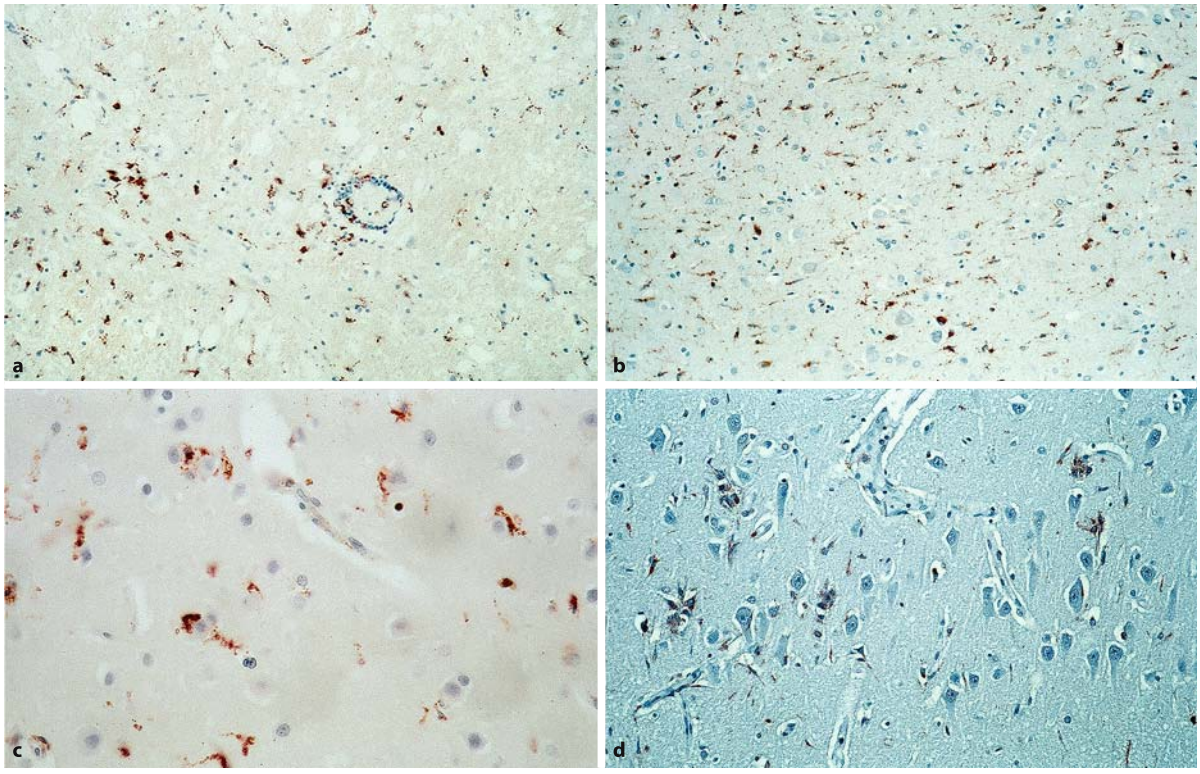

Fig. 14.12a–d. Increase of activated mononuclear phagocytes in an ischemic injured brain. CD68-positive macrophages are seen **a** in a perivascular position and **b** diffusely distributed in the white matter as well as **c, d** in the cornu Ammonis (**a–d** CD68 reactivity; magnification **a, b** ×200, **c, d** ×500)

global ischemia in rats and observed reactive microglia in the striatum which peaked at 1 week, as in the CA1 hippocampus.

Single hemosiderin-containing macrophages may be demonstrated after 3 days of survival time (Hammes 1944; Oehmichen and Raff 1980). Lipid-containing foam cells are demonstrable after 3–8 days (Baggenstoss et al. 1943; Strassmann 1945), while myelin-containing macrophages are described after a survival period of 44 h (Schröder 1983).

14.3.9 Mesenchymal Reaction

The reactivity of *endothelial cells* as well as the release of *collagenous fibers* by *fibroblasts* will characterize the *mesenchymal reaction*. The endothelial cells will increase by proliferation with the consequence of an intense vascularization which is evident at the 6th to 10th day after the ischemic event (Garcia and Kamijyo 1974). The increase of collagenous fibers will accompany the endothelial cell proliferation and will peak 1 week after ischemia has occurred (Baggenstoss et al. 1943). The time course of fibroblast proliferation and increase of collagenous fibers in brain wounds remain unknown.

14.3.10 Cytokines

According to recent investigations cytokines play an important role in ischemia, functioning partly as neurotoxic and partly as neuroprotective (for review see Garcia et al. 1997; Stoll et al. 2000). Feuerstein et al. (1994) could demonstrate *tumor necrosis factor*-α (TNF-α) mRNA within 1 h after ischemia and upregulation of *interleukin-(IL-)6 mRNA or protein* preceding the emigration of neutrophils. Microglia may be the source of TNF-α (Gregersen et al. 2000). Kita et al. (1997) measured the level of TNF-α protein in rat cerebrospinal fluid and found a gradual increase during the first hour to a maximal elevation at 3 h and 6 h. The cerebral ischemia caused by permanent occlusion of the middle cerebral artery produces a dramatic increase in IL-6 bioactivity in the ischemic hemisphere within 2 h with further increases at 8 h and 24 h (Loddick et al. 1998). An increased expression of the various isoforms and their receptors of the transforming growth factor-β (TGF-β) by means of immunohistochemistry has been observed as early as 6 h in neurons, endothelial cells, astrocytes, and inflammatory cells (Ata et al. 1997; Ata 2000).

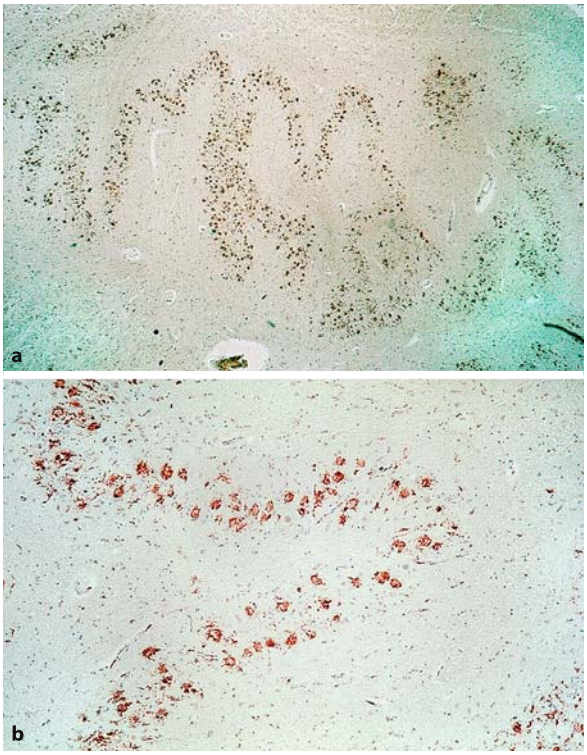

Fig. 14.13a, b. Selective neuronal necrosis of the inferior olivary nucleus of the medulla and reactive mononuclear phagocytes. Perineuronal aggregation of CD68-reactive mononuclear phagocytes indicating their scavenger function (**a, b** CD68 immunoreactivity; magnification **a** ×50; **b** ×300)

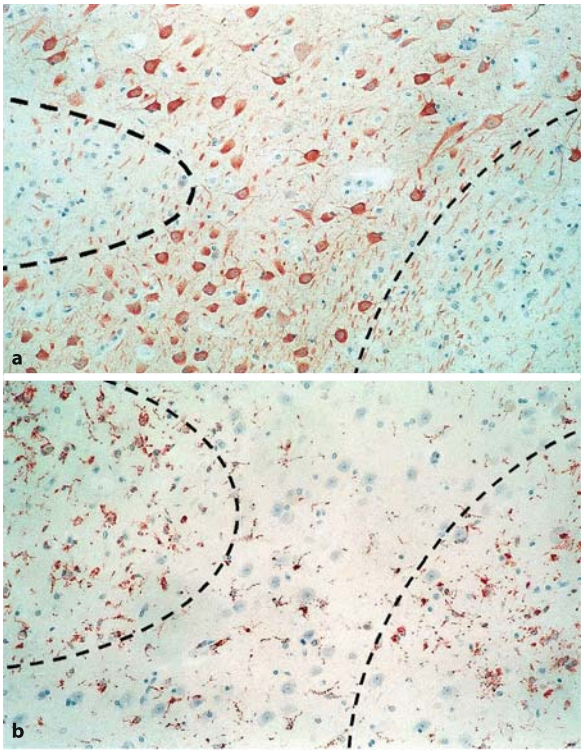

Fig. 14.14a, b. Selective neuronal necrosis in the cornu Ammonis and reactive mononuclear phagocytes (see also Fig. 4.19). **a** Intact neurons as demonstrated by MAP immunoreactivity; **b** the same area (CA1 sector) demonstrates CD68-reactive mononuclear cells which replace the lost neurons of the hippocampal cortex (magnification **a, b** ×500)

A dramatic upregulation of surface expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial-leukocyte adhesion molecule-1 (E-selectin) occurred in human endothelial cell culture of cerebral vessels by 4–24 h of exposure (Stanimirovic et al. 1997; Stanimirovic and Satoh 2000) and in rat brain up to 24 h after reperfusion (beginning between 1 and 3 h after reperfusion – see Matsuo et al. 1994a). Acarin et al. (2000) could observe expression of the signal transducer and activator of transcription 3 (STAT 3) in astrocytes as early as 2–4 h after ischemia. The platelet-derived growth factor-β chain (PDGF-β) is distinctly expressed in human neurons (CA1 sector) 6 h after ischemic insult (Kaneko et al. 1998). TGF-β was demonstrable in human autopsy material 1–3 days after insult in perifocal neurons, reactive astroglial cells, endothelial cells, and macrophages (Ata et al. 1999). Immunohistochemistry revealed enhanced reactivity of PDGF-β in neurons in the infarct and in the peri-infarct area from 16 h to 4–7 days, with a peak at 24 h (Iihara et al. 1994).

14.3.11 Enzymes

An ischemic insult leads to a significant expression of *nitric oxide synthase-2* (Loihl and Murphy 1998), which was demonstrated to occur in permanent vessel occlusion in rats on the second to third day post ischemia returning to baseline within 7 days. Recently Tomimoto et al. (2002) demonstrated by means of immunohistochemistry that cyclooxygenase 2 (COX2) was induced robustly in neuronal cell bodies and dendrites during the acute stages of focal ischemic damage and was also upregulated in microglial cells.

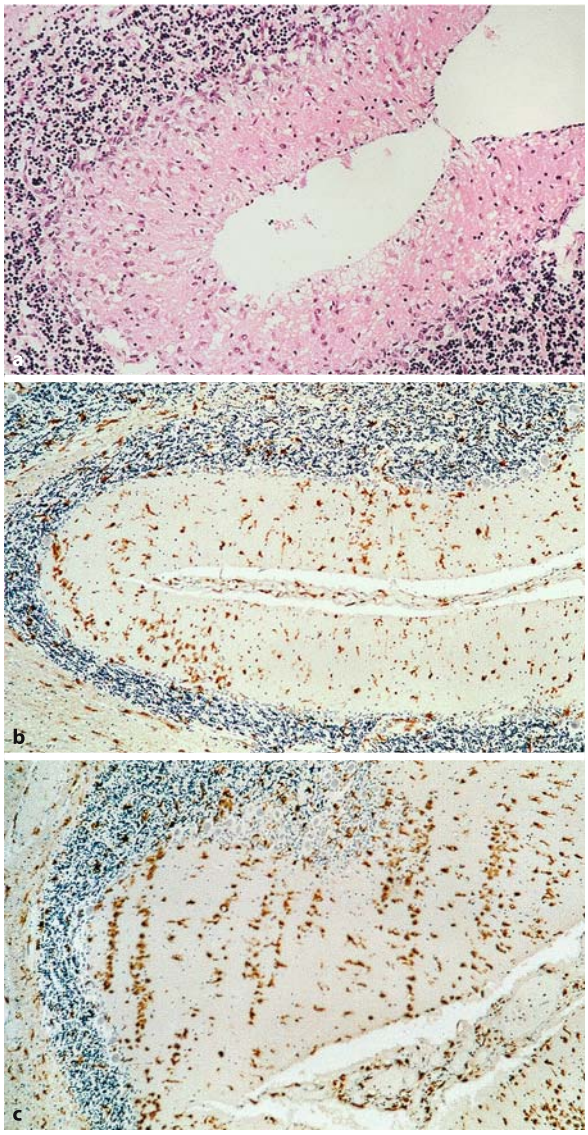

Fig. 14.15a–c. Selective neuronal injury to Purkinje cells and reactive mononuclear phagocytes. **a** The lost Purkinje cells were replaced, **b** by an increase in GFAP-reactive astrocytes and **c** increase of CD68-reactive mononuclear phagocytes (**a** H&E; **b** GFAP immunoreactivity; **c** CD68 immunoreactivity; magnification **a, b** ×200; **c** ×400)

14.4 Clinical Features of Acute Asphyxia

If the carotid circulation is totally occluded for an unremitting period of 4 min or more, then irreversible cerebral damage may occur. Permanent brain damage is very unlikely if the supply has been cut off continuously for less than 4–5 min. Total recovery has often been recorded after total ischemia of considerably longer than this, even in normothermic conditions, with 9–14 min being quoted. When the body has been exposed under hypothermic conditions, a longer time has been recorded, e.g., 2 h (p. 247).

Experimental data cited by DiMaio and DiMaio (2001) give evidence of additional features. Rossen et al. (1943) conducted experiments on 126 normal male volunteers by using an inflatable pressure cuff placed on the lower third of the neck that produced 80 kPa (600 mmHg) within one-eighth of a second of inflation. Acute occlusion of the arterial circulation resulted in blurring of vision, constriction of the visual fields, loss of consciousness, and convulsions. Half of the volunteers lost consciousness in 6–6.5 s; the overall range was approximately 5–11 s. The pressure cuff was released upon loss of consciousness with complete recovery within 1–2 min after the procedure and no subsequent neurologic sequelae. The electroencephalogram showed large, slow waves correlating with the loss of consciousness.

The same team studied the effects of prolonged occlusion of cerebral circulation in 11 volunteers. Cervical pressure was maintained for as long as 100 s in some tests. The subjects regained consciousness in 30–40 s and were able to leave the room in 2 min. Convulsions, cyanosis, involuntary urination and defecation in some subjects, bradycardia, and dilatation of the pupils followed loss of consciousness. Bradycardia developed, with the heart rate dropping as much as 50%. Respiration continued throughout the test, increasing in rate.

The hemodynamics as well as the respiratory regulation were also documented in children surviving a strangulation. Hanigan et al. (1996) could record a dissociative vasoparalysis with loss of autoregulation and preservation of CO_2 reactivity in two cases. Ashwal et al. (1991) observed four cases and noticed that although cerebral blood flow (CBF) was normal in these four children, the hyperventilation response was depressed, variable, and even paradoxical which may be important in the evolution of further brain injury and is a critical factor in deciding whether hyperventilation may be of clinical benefit. Three factors correlated with poor outcome and ultimately death in two patients: an initial blood glucose >300 mg/dl and a CBF/pCO_2 response of <1.2 ml/(100 g min) per torr pCO_2.

In all fatal cases of ligature and manual strangulation there are *petechiae* of the conjunctivae, which – of course – are not specific to strangulation (Rao and Weti 1988). In attempted strangulation petechiae were observed in 14 victims of 70 surviving individuals, only 8 of whom became unconsciousness and with only 4 experiencing *sphincter incontinence* (Harm and Rajs 1981). Harms and Rajs (1981) studied 37 dead victims and 22 (60%) had an empty urinary bladder as an indication of sphincter incontinence – compared with 14% of 54 control autopsies whose causes of death were other than violence. The

fractures of the thyroid and/or hyoid cartilage are rare in hanging but often in ligature. However, these fractures do not cause death, they are just markers of mechanical neck injuries.

14.5 Transient Ischemia

The term "transient ischemic attack," or TIA, refers to a clinically detectable event that is neurologically transient; implicit in the definition is the assumption that the underlying cerebro-vascular occlusion is also transient, i.e., that there is an arterial occlusion responsible for the symptoms, the obstruction is relieved and, through the restitution of flow, there is no residual injury but rather a complete recovery from neurologic symptoms (del Zoppo 2004).

There is clinical and experimental evidence that continuous discharge of material from carotid artery atheromatous lesions and more proximal sources (atheromatous emboli) have an impact downstream and that microvessel or small-vessel occlusion and reperfusion can occur.

The outcome of the ischemic impact is mainly determined by post-ischemia factors (Hossmann et al. 1973). Early brain tissue perfusion after either total or focal brain ischemia (and also after incidence of MBI, see Forbes et al. 1998) will be – without doubt – the basic principle of neurological recovery. But we also know that reperfusion is associated with additional deleterious events. Experimental data and therapeutic investigations give evidence of a reperfusion-induced acute inflammatory reaction associated with secondary brain damage, so-called *reperfusion injury*.

Molecular adhesive events and cytokine production occur early in ischemia and reperfusion and underlie the transition from ischemic to inflammatory injury. The subsequent recruitment of leukocytes to the ischemic zone may lead to reocclusion of microvessels, contributing to the "no-reflow" phenomenon in which recirculation remains poor after clot lysis (Ames et al. 1968). The same leukocytes also produce proteolytic enzymes, oxygen free radicals, and other molecular effectors which, in addition to direct neuronal damage, may injure the endothelium and lead to subsequent hemorrhages (Kontos 1989; Fisher et al. 1990; Matsuo et al. 1994, 1995; Iadecola et al. 1996). The most recent data suggest that inflammatory cells may even lead to increased apoptotic neuronal cell death (Witte and Stoll 1997).

Oxygen free radicals (Chan 1998) and arachidonic acid metabolites are both part of this inflammatory response, and their role in secondary brain damage after ischemic stroke and reperfusion has been reviewed elsewhere (Kontos 1989; Clark et al. 1994). Permanent ischemia also leads to inflammation in the injured area, but the response is distinct from that which occurs during reperfusion (Clark et al. 1994; Zhang et al. 1994; Barone et al. 1995). In a review, Jean et al. (1998) highlighted the experimental evidence of inflammatory injury during cerebral ischemia/reperfusion.

The recruitment of neutrophils to the area of ischemia, the first step of inflammation, involves the coordinated appearance of multiple proteins. Intracellular adhesion molecule-1 (ICAM-1) and integrins are adhesion molecules that are upregulated in endothelial cells and leukocytes (Baethmann 2000). Tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and platelet-activating factor (PAF) also participate in leukocyte accumulation and subsequent activation.

According to Jean et al. (1998) three lines of evidence support this contention:

1. There is a notable correlation between the time course of neutrophil accumulation/adhesion in the ischemic zone and the expansion of cerebral damage during reperfusion (Clark et al. 1994; Zhang et al. 1994).
2. There is a distinct beneficial effect of neutropenia. Experimental data give evidence that granulocytopenic dogs had a better recovery of cortical somatosensory-evoked responses and fewer areas of "low flow" after cerebral reperfusion (Dutka et al. 1989). Neutrophil depletion also leads to reduced edema and better cerebral blood flow during the reperfusion period (Schürer et al. 1990; Shiga et al. 1991; Connolly et al. 1996).
3. There is a protective effect of treatment that prevents neutrophil activity (Matsuo et al. 1994b).

Moreover, it is known that TIA is a risk factor for stroke and death (Sacco 2004). The annual risk for stroke after a TIA is between 1% and 15%, with a relative risk ranging between two- and fivefold (Benavente et al. 2001). Data of the Mayo Clinic involving 330 residents demonstrated an 11% risk of death at 1 year and about a 35% risk at 5 years, with corresponding rates for subsequent stroke of 14% and 28%, respectively.

Neuropathology. Temporary occlusion of a brain-supplying artery can result in permanent neuronal injury as demonstrated by Memezawa et al. (1992): a transient occlusion of the middle cerebral artery lasting 30 min in the rat produced the evidence of modest ischemic injury of neurons.

14.6 Selective Neuronal Necrosis

Selective neuronal (parenchymal) necrosis was first described by Scholz (1953) and is called "elektive Parenchymnekrose." This mild type of tissue injury in comparison with the pan-necrosis is marked by an isolated necrosis and a loss of neurons while glia cells and the neuropil remain intact. No granulocytic emigration is observed, but a discrete astrocytic and microglial reaction occurs.

The neurons shrink and become eosinophilic while the pericellular space increases (Fig. 13.4b). The neurons are lost within 11–13 days (cornu Ammonis – Fig. 13.6, Purkinje cells – Fig. 13.8), or within 14–34 days (cortical neurons) (Schröder 1983). GFAP and vimentin will be upregulated in astrocytes within 1 week as an indication of their activation (Figs. 14.8b, c, 14.10). But the most important type of reactivity is the monocyte-macrophage/microglial increase, which becomes evident about 2–3 days after ischemia and is distinctly seen in all cases between the 5th and 9th day (Schröder 1983) – partly perineuronal (satellitosis), partly diffuse infiltrating the neuropil. This type of reaction is demonstrated in Figs. 14.13–14.15.

14.7 Apallic Syndrome

The term "apallic syndrome" describes a loss of the "pallium," i.e., the cortical gray mantle that covers the telencephalon (Kretschmer 1940). Other terms are "persistent vegetative state" (Jennet and Plum 1972), "decerebrate state", "coma prolongé," "coma dépassé" (Mantz et al. 1965) or "cerebral death" (Korein et al. 1977, Korein 1978) – in contrast to "brain death" or "non-perfused brain" where the entire brain is affected.

The more recently termed persistent vegetative state is caused by a transient severe global cerebral ischemia with blood reflow in contrast to global permanent ischemia (respirator brain, non-perfused brain). As described by Ingvar et al. (1978), the victim is characterized by a uniform clinical feature with complete loss of higher functions (speech, voluntary motor activity, emotional reactions, signs of memory), but with good retention of brain stem functions, including spontaneous respiration. These patients can be aroused by afferent stimulation, responding by primitive motor reactions, chewing, swallowing, respiratory changes, etc. The EEG is in all cases highly depressed, and in some cases isoelectric. The supratentorial cerebral blood flow is very low in the most chronic cases, and less so in a case with shorter duration.

Diffuse axonal injury (DAI) and diffuse ischemic brain damage seem to be the most common causes of persistent vegetative state after cardiac arrest or blunt head impact in patients who survive their injuries for more than 4 weeks (Strich 1969). This is one of the conclusions of a comprehensive study (McLellan et al. 1986) analyzing 25 patients who remained vegetatively or severely disabled for more than 4 weeks after a traumatic event: DAI was found in 22 cases; moderate to severe ischemic brain damage in 10 cases; secondary midline lesions in the brain stem as a consequence of raised intracranial pressure and tentorial herniation in 2 cases. These results contradict various studies on cases of prolonged consciousness after a traumatic event which demonstrate either secondary damage to the brain stem (Jellinger 1977) or transtentorial herniation (Peters and Rothemund 1977).

Neuropathologic studies additionally showed a uniform picture with severe anoxic changes, an almost total destruction and a disappearance of the telencephalic neurons. The neuronal loss was especially marked in patients who survived for several years, in whom the cortex had been replaced by a thin gliotic and fibrous tissue (Fig. 14.5).

A more recent morphological analysis (Adams et al. 2000) could demonstrate that in every case studied (n=49 patients; 35 patients sustained blunt head injury, 14 patients sustained acute brain damage not caused by external violence) there was profound damage to the subcortical white matter or to the major relay nuclei of the thalamus, or both. These authors found a structurally normal cerebral cortex, cerebellum, and brain stem in some of these cases.

From the forensic point of view it must be stressed that patients in a vegetative state can suddenly and unexpectedly die. In such cases, death may be due to CNS failure (seizures), cardiac arrhythmias or sudden and unexplained cardiac arrest caused by vegetative or metabolic decompensation, when other causes such as pneumonia, pulmonary thromboembolus or other gross pathological findings can be excluded at autopsy.

14.8 Ethical Implications

The ethical (and forensic) issues in diagnosis and management of patients suffer from the sequelae of global ischemic brain damage or patients in the persistent vegetative state are still in discussion – since the discussion of the case of Karen Ann Quinlan (Kinney et al. 1994). The ethical implications are summed up by Nacimiento (1997) and Wade

(2001), while the difficulties of the clinicians in the management and care of patients are summarized by Grubb et al. (1996) in connection with a questionnaire which was answered by 1027 doctors in Great Britain. More than 90% of responding doctors considered that it could be appropriate not to treat acute infections and other life-threatening conditions; 73% of doctors considered that withdrawal of artificial nutrition and hydration could be appropriate. About two-thirds of doctors who thought that treatment-limiting decisions might be appropriate thought that such decisions ought to be considered for patients in a persistent vegetative state within the first 12 months. This problem was recently worldwide discussed on ocassion of the dying process of Terri Schiavo (USA – March 2005).

The decision not to resuscitate after cardiac arrest is a common problem with great ethical, economic, social, and legal consequences, which is dependent on the prognostication of the extent of ischemic brain damage. For neurological outcome prediction after cardiac arrest many methods have been applied, such as clinical neurological testing, electrophysiological examination, neuroimaging tests, and laboratory parameters in serum and cerebrospinal fluid; nevertheless, there remains a considerable degree of uncertainty. Berek et al. (1997) recommend the useful application of early prognostication after cardiac arrest ranging from counseling of families, triage decisions, and do-not-resuscitate decisions to future clinical investigations of brain resuscitative measures.

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Permanent Global Ischemia 15

15.1 Classification

In 1968, an Ad Hoc Committee at the Harvard Medical School, Boston, Mass. proposed "a new criterion for death": total and irreversible loss of functioning of the whole brain. The motivation was clearly stated as follows: (1) to relieve the "burden" imposed by severely brain-damaged patients; and (2) to quell the "controversy in obtaining organs for transplantation" (see Youngner 1992).

It was not until 13 years had passed (1981) that James Bernat and his colleagues offered the first comprehensive effort to provide a conceptual framework for the ad hoc committee's criterion (Bernat et al. 1981). "We define death," they wrote, "as the permanent cessation of functioning of the organism as a whole," which they further explained as "the spontaneous and innate activities carried out by the integration of all or most subsystems."

As each individual human brain constitutes a human individual, a patient without a vital brain must be considered a "non-individual," i.e., a dead person, irrespective of the condition of the rest of the body including organs other than the brain. This classification caused in different countries long and heated debates (Backlund 1999) but is still accepted by the Western community (Capron 2001) though single problems remain unresolved (Swash and Beresford 2002). The currently accepted standards in clinical criteria and confirmatory tests for diagnosing death with the use of brain-based criteria were recently summarized by Wijdicks (2001). The determination of brain death requires documentation of unresponsive coma, absence of brain stem reflexes, and apnea. Though the process of organ transplantation is now accepted worldwide along with the classification of brain death, there is no global consensus in diagnostic criteria. Wijdicks (2002) pointed to differences in accepting the apnea test and could describe other major differences in the procedure of diagnosing brain death in adults.

15.2 Pathophysiology

The sequelae of non-perfusion of the brain as a "permanent global ischemia" are dependent on the time interval of cerebral blood flow interruption. As we learned by experiments of Hossmann and Kleihues (1973; Kleihues and Hossmann 1973; Bodsch et al. 1986), under certain circumstances of experimental post-ischemia treatment, reperfusion will succeed – and recovery of neuronal function could be established – even after a period of 20–60 min of total ischemia of the brain.

However, under the common circumstances of human resuscitation, these results could not be reproduced. Reperfusion is accompanied by an initial brief period of hyperemia followed by a prolonged phase of cerebral hypoperfusion. The complex problem of no-reflow may be based on vascular swelling and micro-aggregation within vessels during the period of ischemia which result in irregular patchy

Table 15.1. The primary causes of a non-perfused brain (*N*=503) Source: Walker 1985, modified

Cause	n	%
Cardiac disorders	105	20.9
Cerebral trauma	94	18.7
Cerebral hemorrhage	74	14.7
Exogenous intoxication	36	7.2
Metabolic disorders	36	7.2
Subarachnoid hemorrhage	34	6.8
Other	124	24.6

perfusion in certain circumstances (Symon 1993). The question of vascular occlusion by physical factors such as endothelial swelling remains controversial, but both increased vascular smooth muscle tone as a result of vasoactive substances released during ischemia, and permeability changes resulting in pericapillary edema could produce the increased cerebrovascular resistance.

As mentioned in Chapter 14, the sequelae of persistent brain ischemia by suffocation or strangulation as well as by cardiac arrest for a time of 5–10 min will, under normothermic circumstances, finally lead to an irreversible interruption of cerebral blood flow in the cerebrum and cerebellum with the consequence of a respiratory arrest, while the circulation of the body may be stable. The same phenomenon will be observed as a result of an increase of intracranial pressure, especially that caused by extreme edema, hemorrhages, inflammation or tumors. Under conditions of artificial respiration, general circulatory and cardiac function will still persist with the exception of the brain circulation, i.e., non-perfused brain or respirator brain or brain death. On the other hand, accidental hypothermia may allow successful resuscitation within a period of nearly 4 h of cardiac arrest (Walpoth 2004). Depending on the time between interrupted cerebral blood flow and the final cardiac arrest the morphology of the brain will vary.

Permanent global ischemia constitutes brain death, and is a direct result of a decrease in the cerebral perfusion pressure (CPP=MABP–ICP, where MABP is mean arterial blood pressure and ICP is intracranial pressure). This, in turn, usually arises from either an increase in ICP or a decrease in MABP to bring CPP (the difference between the two) to less than 6 kPa (45 mmHg) for a protracted period. After some time has elapsed, the brain can never be reperfused due to capillary closure, and "brain death" ensues (Fischer 1973). The term "brain death" is used (Black 1978; Korein 1978) as well as respirator brain (Towbin 1973) or dissociated (brain) death (Kramer 1966). Non-perfused brain is the extreme, irreversible form of permanent global ischemia, in which blood flow to the intracranial contents is never restored. The primary causes of non-perfused brain are summed up by Walker (1985; Table 15.1).

Complete interruption of the cerebral circulation for a period of 5 min irreparably damages the brain. A fall in cerebral blood flow of even 50% depletes the store of high-energy phosphates, and the brain begins to cannibalize itself (Walker 1985).

Various attempts have been made to extend the reversible period of normothermic cardiac arrest beyond the 5-min limit (Hirsch and Müller 1962; Hirsch 1982; Safar et al. 1987). Ames and Nesbett (1983) reported that retinal neurons can tolerate up to 20 min of anoxia. Hossmann and Kleihues (1973) and Hossmann (1988) showed that most cerebral neurons can recover electrical and chemical activity after up to 60 min of normothermic complete global ischemia (see Bodsch et al. 1986). Studies by Siesjö (1981, 1988) indicated that treatable pathogenic factors are involved.

The secondary derangements associated with normothermic cardiac arrest have at least four interacting components (Safar et al. 1982; Safar 1986) (compare with Table 15.2). Safar et al. (1993) have additionally shown that the outcome is determined by the duration of the no-flow insult and the temperature. However, flow arrest caused by asphyxiation is more injurious (Vaagenes et al. 1984) to the brain than the same period of normovolemic ventricular fibrillation arrest, while that caused by isolated exsanguination (Negovsky et al. 1983) may be less injurious (Safar 1988).

In addition to the 5-min limit, a relationship exists between the duration of cerebral anoxia and disturbances of brain function. On the biochemical and cellular level, changes resulting from systemic or local anoxia proceed in the following sequence: intra- and extracellular acidosis develops increasingly (Lindenberg 1972; Jabre et al. 2000), leading to activation of hydrolytic enzymes with swelling of lysosomes, especially in astrocytes (Plesnila et al. 1999: cytotoxic brain edema – see p. 47), whose breakdown causes a disturbance in the osmotic balance. The consequently marked uptake of water produces a brain edema. The endothelial cells swell, reducing the lumen of vessels, which become plugged with deformed erythrocytes. The permanent arrest of cerebral circulation begins. Once ischemic total cerebral ischemia occurs, the autolytic process begins; since the relatively high temperature of 37°C is maintained, autolysis proceeds faster than under postmortem conditions.

Table 15.2. Interacting secondary derangements associated with normothermic cardiac arrest that have at least four interacting components Source: Safar 1986

Perfusion failure
Reoxygenation injury
Self intoxication from post-anoxic viscera
Blood dyscrasias after stasis

15.3 Clinical Features

The Uniform Determination of Death Act has classified brain death according to the following criteria (cf. Ad Hoc Committee in Brain Death 1987):

> Brain death has occurred when cerebral and brain stem functions are irreversibly absent. *Absent cerebral function* is recognized clinically as the lack of receptivity and responsivity, that is, no autonomic or somatic response to any sort of external stimulation, mediated through the brain stem. *Absent brain stem function* is recognized clinically when pupillary light, corneal, oculocephalic, oculovestibular, oropharyngeal, and respiratory reflexes are irreversibly absent.

Thus, apnea (tested for longer than 7 min), dilated pupils, cerebral unresponsivity, absence of brain stem reflexes including the oculovestibular (doll's eyes) reflexes, and the vestibulo-caloric reflex are indicative for brain death. An isoelectric (flat) electroencephalogram (EEG) for 30 min, at least 6 h after ictus, is needed for final diagnosis (Guidelines for the Determination of Death 1981; Hamburger 1988). There is cessation of blood flow through the carotid arteries at the foramen lacerum. Angiography and strict electroencephalographic criteria are rarely applied to diagnose this condition any longer; rather clinical criteria are relied upon. This underscores once again the importance (see above) of distinguishing brain death or even neocortical death from the various types of hypoxic damage outlined above.

> *Irreversibility* is recognized when the cause of coma is established and is sufficient to account for the loss of brain function, and when the possibility of recovery is excluded by observation for an appropriate period of time.

The period of observation will vary, depending on the circumstances and possible causes. In most cases in which the cause is established and seems appropriate, such as in severe inoperable head trauma, a period of 6 h seems reasonable and is commonly recommended, whereas with hypoxic–ischemic encephalopathy, observation for 24 h may be more appropriate. These short time intervals commonly used nowadays render the development of the neuropathologic changes of brain death less well developed and observable than when longer intervals of brain death precede autopsy. Confirmatory laboratory findings may be appropriate in determining primarily the irreversibility of brain death, and possibly accelerating the determination of irreversibility. However, if cause and irreversibility are established and the clinical examination yields unequivocal findings, confirmatory tests are unnecessary. When they are appropriate, confirmatory laboratory examinations that may prove helpful include electroencephalography, radionuclide brain scan, and brain-stem-evoked potentials.

15.4 Neuropathology

The exact morphological sequelae depend in part on the age of the patient, time on the respirator, and the cause of the non-perfusion. The pathological changes of the non-perfused brain take about 12 h to develop (Black 1978), although they become more obvious in 24 h (Walker 1985), an important interval if the neuropathologist is called upon to confirm brain death. As a rule, the typical changes are observed in cases of clinically diagnosed non-perfused brain (Table 15.3, – p. 327). The following parameters merit particular mention (Walker 1985; Oehmichen 1994).

15.4.1 Gross Examination

The brain mass commonly is increased (1.6–1.8 kg), but the increase is definitely a function of time on the respirator (Schneider 1970; Walker 1985).

Depending on the primary cause of ischemia and time on the respirator, the following macroscopic changes are observed: a distinct swelling of the total brain (Fig. 15.1a); the cerebrum may be well-preserved and gray-colored (Fig. 15.1b) or a nondescript friable or mushy mass; the swollen and congested cerebral hemispheres have a dusky hue; the

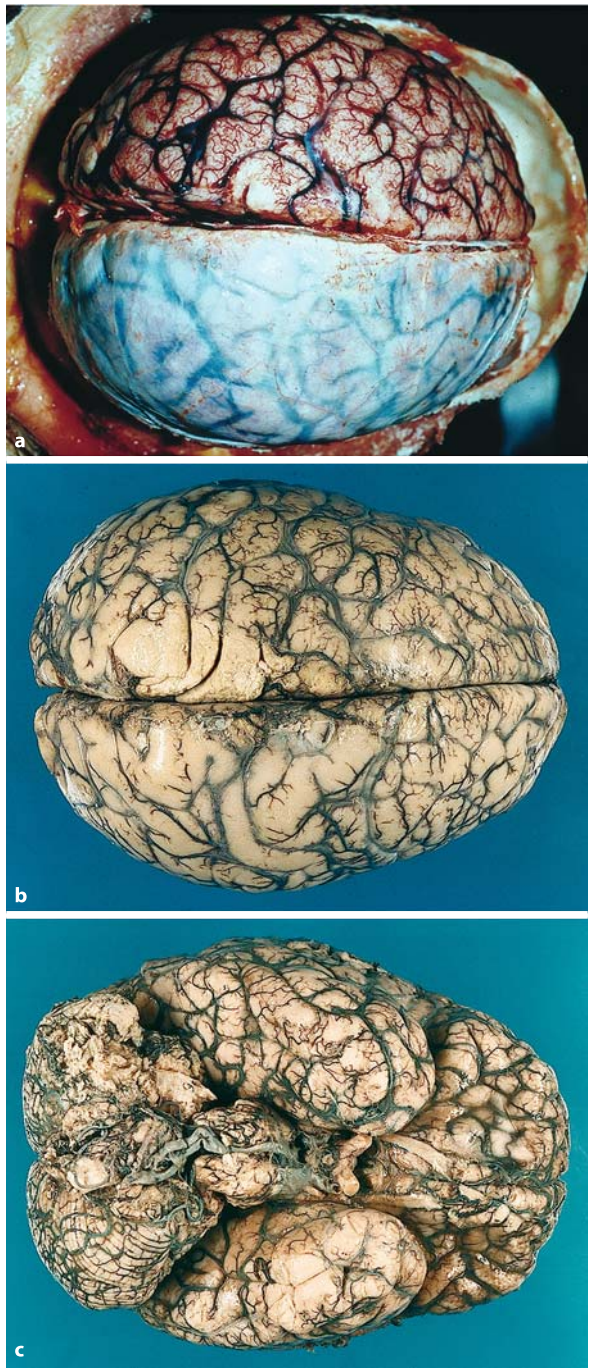

Fig. 15.1a–c. Gross external findings in respirator brain. **a** Extreme brain swelling (autopsy specimen); **b** the external surface may be well preserved, and is gray colored with indications of different regional no-reflow phenomena (formalin-fixed specimen); **c** distinct indications of herniation with uncal and tonsillar necrosis are seen

leptomeninges often show a quantitatively different extent of congestion and fibrin precipitation as an indication of different regional no-reflow phenomena (Fig. 15.1b); transtentorial herniations are common (Fig. 15.1c). Gross sections of the brain show a lead-colored, grayish cortex, a partly extreme compressed ventricular system, and sometime focal hemorrhages in white and/or gray matter, which is demonstrated in Fig. 15.2a, b in comparison with a normal-colored edematous brain section after formalin fixation. The brain stem is often torn and is characterized by congestion and hemorrhages; the softened herniated cerebellar tonsils are commonly necrotic (Fig. 15.3b), with necrotic tissue of tonsillar cerebellum lodged along the spinal cord anywhere from the cervical segment to the cauda equina (Fig. 15.3c–e). This phenomenon is considered characteristic of brain death lasting more than 36 h (Schneider and Matakas 1973) and may be one neuropathologic-diagnostic sign of brain death (Sayer et al. 1981). In addition, hemorrhagic softening of the upper few segments of the cervical spinal cord occurs, but is often overlooked if that part of the cord is not dissected. In about 10% of cases, the cut sections appear grossly normal, but in more than half of brains the white matter is edematous and soft (Fig. 15.3f).

15.4.2 Microscopic Examination

As a general rule, ischemic neuronal alterations are only observed after reperfusion lasting at least 2 h (Pendl 1986). The brain stem is almost always changed by edema, secondary hemorrhage, infarction, necrosis, and/or neuronal loss. The mesencephalon is distorted by local edema or external compression by herniating tissue of the medial temporal structures or the anterior cerebellar lobes. The striking feature of the cerebellum is swelling and congestion; autolysis of the granule cell layer of the cerebellar cortex (Fig. 15.2c) is often observed (Ogata et al. 1986). The diencephalon is characterized by edema and often by patchy lytic changes in the neurons. The cortex is most frequently and severely damaged. Primary ischemic infarcts or hemorrhagic infarcts result in primary or secondary occlusion of cerebral arteries. The cortex is diffusely congested and edematous, and the cortical neurons exhibit various degrees of acute ischemic changes, characterized by dark staining nuclei and, in hematoxylin and eosin preparations, a pink-staining cytoplasm. Neither a glial nor a hematogenous inflammatory reaction is seen.

"Brain death" or "respirator brain" is characterized by the autolysis of the brain. The diagnosis early during the period of non-perfusion may be difficult but in the late phases the diagnosis will be evident. The brain death syndrome during the early phase will microscopically be characterized by the following two phenomena:

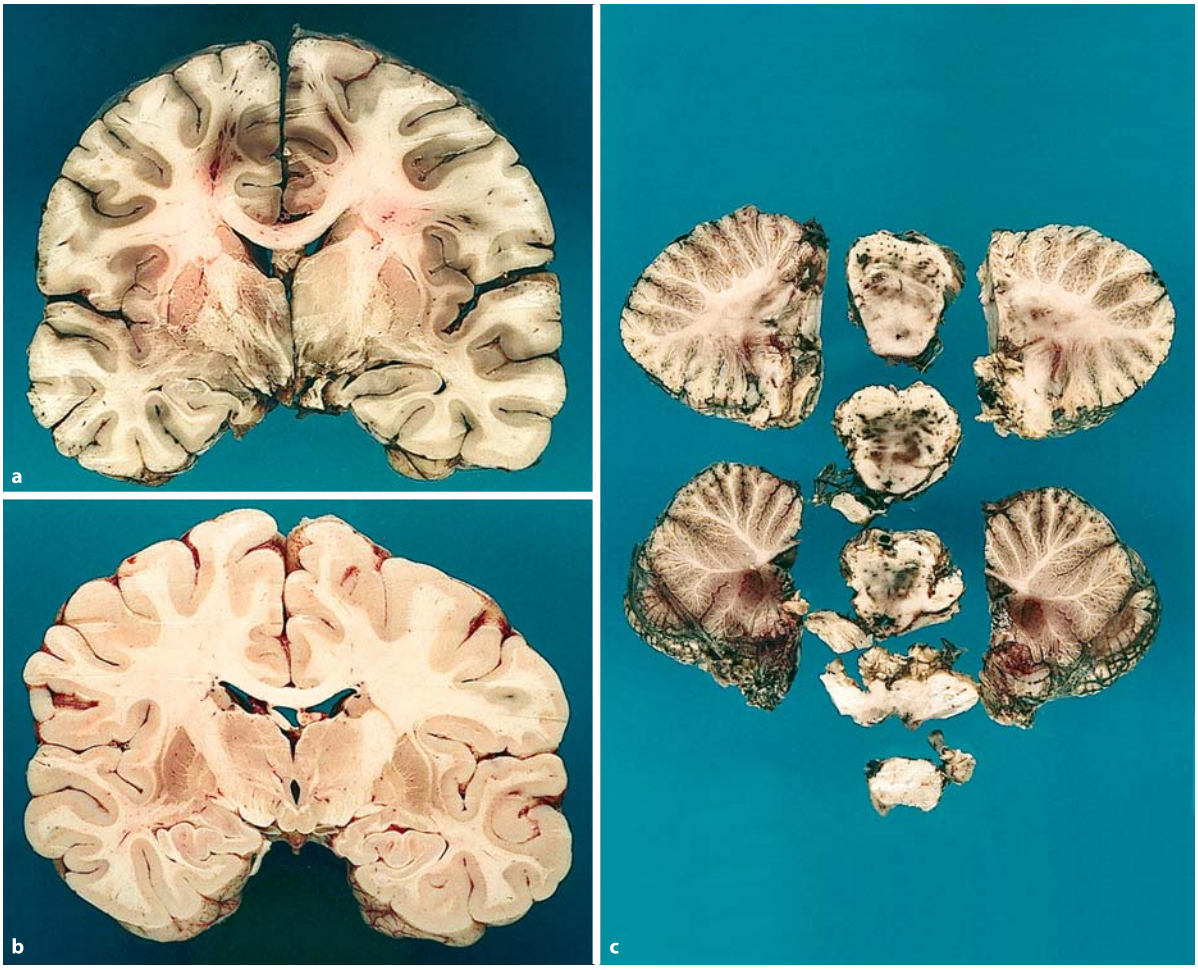

Fig. 15.2a–c. Gross findings on brain sections in formalin-fixed respirator brain. Demonstration of a brain section in respirator brain (**a**) in comparison with an edematous, but non-respirator brain (**b**); **c** hemorrhagic necrosis and color alterations in brain stem, pons, and cerebellum

1. Border zone reactions (demarcation zone): leukocytic infiltrations accompanied by hemorrhages in the upper segments of the cervical spinal cord (Fig. 15.4), in the optic nerve (Fig. 15.5a), and in the hypophysis (Fig. 15.5b, c).
2. Reactivity and alterations of the leptomeninges of the spinal cord: very early after cessation of brain perfusion a leukocytic infiltration within the subarachnoid space of the spinal cord is seen (see Figs. 15.6b, 15.5a). Some time later, necrotic tissue components, especially cerebellar tissue, will appear within the subarachnoid space (Fig. 15.6b–d), partly mixed with leukocytes.

15.5 Forensic Implications

15.5.1 Respirator Brain and/or Postmortem Autolysis

Schneider et al. (1969) maintained that most of the alterations described in respirator brain are not pathognomic of brain death. They suggested that only after 36 h of brain death do the more specific changes appear, namely herniation and fragmentation of necrotic cerebellar tissue into the spinal subarachnoid space, hemorrhagic softening of the upper cervical segments, and necrosis of the anterior lobe of the pituitary gland.

The question arises as to whether changes occur within the first 36 h that can be distinguished from

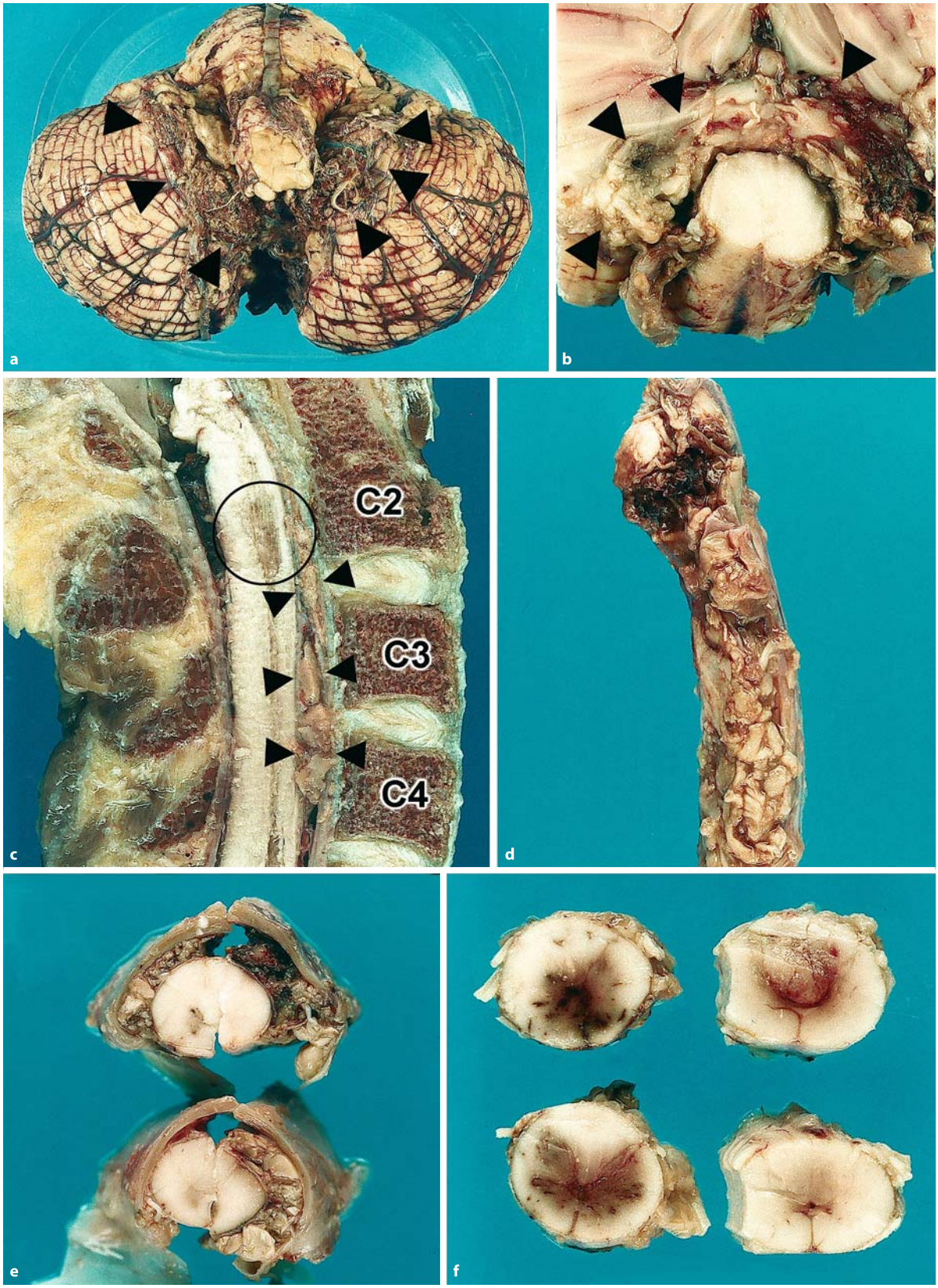

Fig. 15.3a–f. Cerebellar tonsillar herniation and hemorrhagic tonsillar necrosis. The necrotic tonsillar tissue (**a, b,** *arrowheads*) is lodged along the subarachnoid and subdural space (**c** *arrowheads*) along the surface of the spinal cord (**c, d, e**). Hemorrhagic necrosis of the upper segments of the cervical spinal cord (**c,** *circle*, **e, f**) as an indication of a demarcation zone: necrotic brain tissue versus well preserved spinal cord which is supplied by a brain-independent vasculature

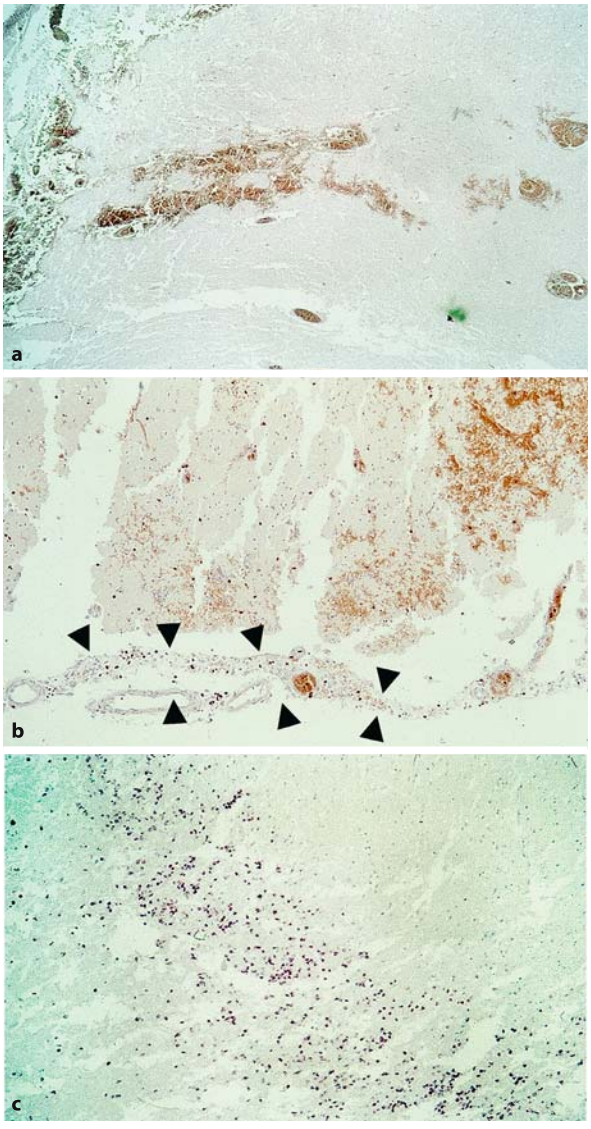

Fig. 15.4a–c. Microscopy of the demarcation zone in the cervical spinal cord. As macroscopically demonstrated (Fig. 15.3c) an intraspinal bleeding occurs (**a**) which is accompanied by a leukocytic infiltration of the leptomeninges of the spinal cord (**b**) and – during the last stage of demarcation – by a leukocytic wall within the neuropil of the spinal cord (**c**) (**a** H&E, **b, c** N-AS-DCIAE; magnification **a** ×100; **b** ×200; **c** ×300)

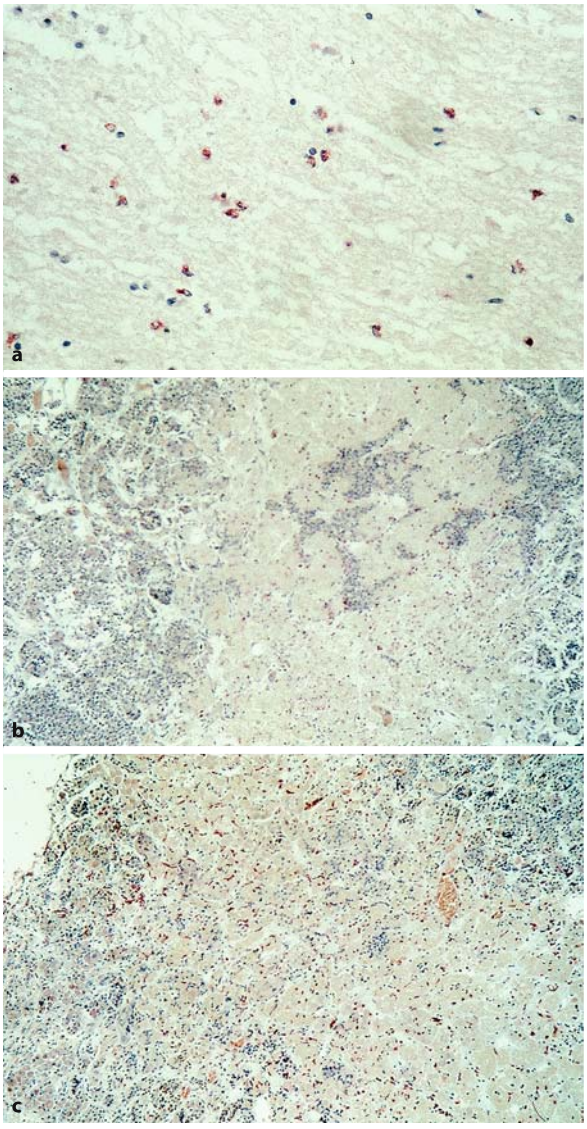

Fig. 15.5a–c. Demarcation zones in: **a** the optic nerve and **b**, **c** the hypophysis, with **a** disseminated leukocytes (*red colored*); **b** necrotic, non-stained hypophysial tissue (in the *center*) near the stained tissue and **c** diffuse leukocyte infiltration of parts of necrotic hypophysial tissue (**a–c** N-AS-DCIAE; magnification **a** ×500; **b** ×200; **c** ×300)

postmortem changes in the sense of a delayed fixation. The following features are indicative of respirator brain: extreme swelling, and dislocation of the brain. In most cases, however, the neuropathologist will have difficulties in differentiating between brain death and postmortem alterations, if both anoxic and autolytic factors are operating to varying degrees in different regions of the brain.

15.5.2 Declaration of Death

Artificial respiration enables the physician to discontinue respiration at any time or to continue it ad infinitum. Termination of support, however, can be regarded as unlawful killing (Gerber 1984) or euthanasia (Oehmichen 1996), an issue that was exhaustively discussed, for example, also in the controversy

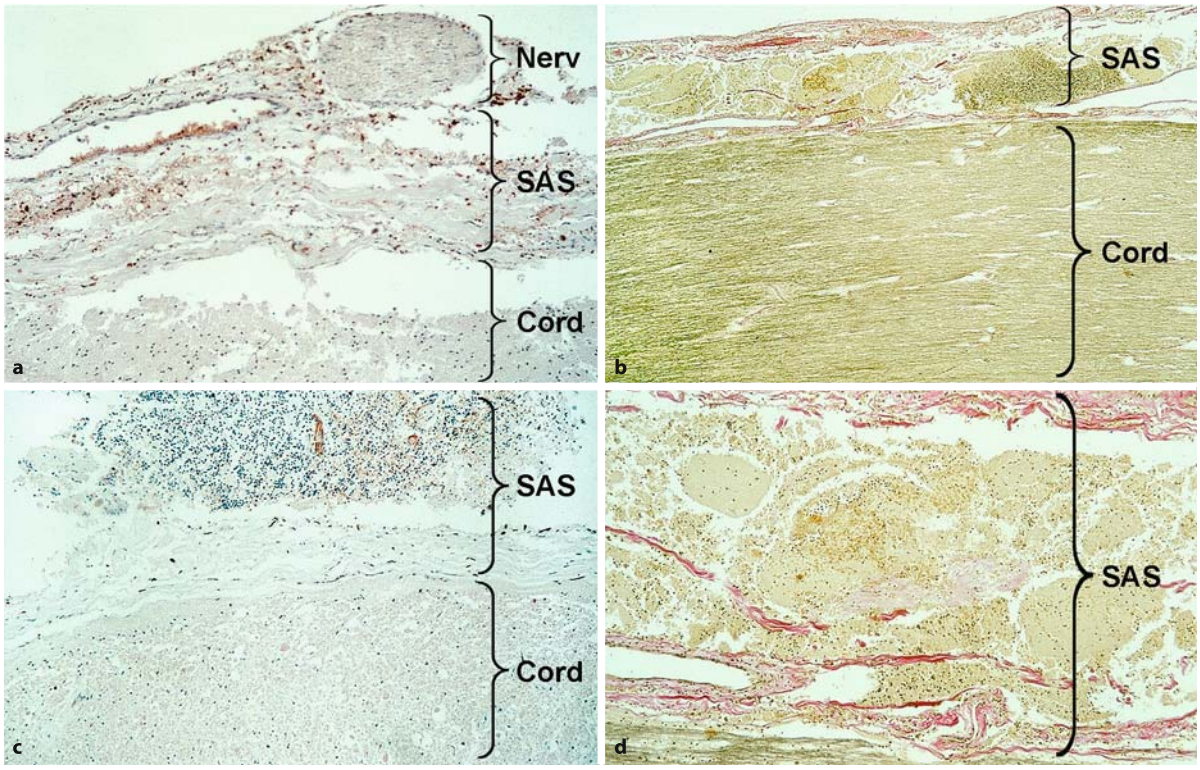

Fig. 15.6a-d. Leptomeningeal reaction of the spinal cord. **a** Early leukocytic infiltration of the hemorrhagic subarachnoid space (SAS) and **b–d** late demonstration of hemorrhagic necrotic tissue within the SAS commonly originating from the cerebellar tonsils. (**a, c** N-AS-DCIAE; **b, d** van Gieson stain; magnification **a–c** ×300)

surrounding the Quinlan decision (Beresford 1977). Prolongation of artificial respiration can conflict, on the other hand, with the individual's "right to die with dignity." This in turn may be opposed by the necessity for removal of vital organs for transplantation and by the prohibitive cost of extended time on a respirator.

In cases with an unfavorable prognosis, therefore, irreversible loss of brain function is a cogent criterion on which to base declaration of death. Of fundamental importance are the clinical and technical criteria on which the diagnosis is based. In Germany, the criteria for brain death are set by the Scientific Advisory Committee of the Bundesärztekammer, as last issued in 1998 (*Deutsches Ärzteblatt* 95:B1509–B1516). Similar criteria exist in other countries (Walker 1985). These criteria resulted in a new definition of "death" that was readily accepted by physicians and judges (Grassberger 1973; Roxin 1973).

The definition of death is based on the irreversible loss of total brain functions, and – when the stipulated criteria have been met – on the termination of artificial respiration. It also enables the discontinuation of resuscitative measures if it can be assumed that brain death has already occurred. In theory then, death can be declared after circulatory arrest lasting for a period of at least 10 min; however, to allow a margin of safety, attempts at resuscitation are generally continued for 15–20 min.

15.5.3 Time of Brain Death

The time of death, i.e. the end of brain perfusion or the beginning of brain death, is defined as the time of the first manifestation of intracranial circulatory arrest. However, declaration of death is only made after the patient has been observed long enough to establish the irreversibility of this state. Hence, the time at which brain death begins is not known (Deutsch 1997).

Even today, retrospective estimation of the time of intracranial circulatory arrest is scarcely possible by means of macroscopic or microscopic criteria (Kramer 1973). Schröder (1983a) lists the criteria of a brain death diagnosis for estimating the time of brain death (Table 15.3) and provides evidence of the time-dependent alterations (Schröder and Richard 1980; Schröder 1983a, b). The *gray color of the brain surface* as well as the beginning of brain *softening* will occur 2 days after interruption of the CBF (Schneider 1970). The *myelin staining intensity* is reduced after

Table 15.3. Neuropathological findings in brain death which support the postmortem diagnosis of non-perfusion brain

Gross examination
Increased brain mass (>12%)
Extensive brain swelling
Herniation (hippocampal, tonsillar)
Brown discoloration
Pink centrum semiovale due to poor fixation
Poorly defined demarcation of gray and white matter
Microscopic examination
Structural effacement/washed out tissue picture due to poor staining
Eosinophilia without tissue reaction
Regressive neuronal changes
Congestion
Borderzone alterations (hemorrhages, cell reactions)
Anterior pituitary lobe
C1/C3 cervical segments of the cord
Displacement of cerebellar tissue of the subarachnoid space of the spinal column
Infarction of the optic tract

16–21 h. Single *eosinophilic neurons* are seen >48 h after cessation of intracranial blood flow in nearly all cases within the cerebral cortex and, especially, within the medulla oblongata. This late eosinophilic expression allows the supposition that the stagnant blood flow prevents the eosinophilic transformation of neurons. *Inflammatory reactions* within the subarachnoid space do not correlate with the survival time.

Reduction of Luxol fast blue stain in the optic nerve and cervical cord are still observed after 8 h of survival time. Spongious demarcation develops after 12–16 h. Demarcating hemorrhages are observed after 30 h of survival time, especially in the cervical cord, and only in one-third of cases (Schneider et al. 1969). Demarcating emigration of leukocytes is seen as early as 24 h; especially in the leptomeninges. A demarcating macrophage reaction is observed 38 h after cessation of intracranial blood flow in the spinal cord (but not in the optic nerve), while an astrocytic reaction is absent.

A number of forensic practitioners have dealt with the forensic implications of determining the time of brain death (Schwerd 1969; Spann 1973; Holczabek 1973) with an overview by Pendl (1986). The time of death is of particular importance in questions of civil law, such as inheritance rights, insurance law, etc.

Example 1. An example of implications in *insurance law*: a car leaves the highway without any explanation and hits a tree at high speed, killing the driver. The diagnosis at autopsy: myocardial infarction; while the postmortem reveals crushing of the skull and brain. The lawyer contends that myocardial infarction – also cardiac arrest – does not meet the criteria for determining death under the brain death classification, and that the death, in fact, resulted from the crushing of the brain in the accident. A claim on the accident insurance was therefore made.

Berg and Helwig (1990) have shown that the time of brain death can also have a bearing on certain aspects of criminal law.

Example 2. A doctor refuses to come to the aid of a child severely injured in an accident, who continues to exhibit gasping for breath. The question here is whether brain death had already occurred within 30 min after the accident, that is at a time when the doctor could have come to the aid of the child.

15.5.4 Time of Causal Event Leading to Brain Death

If brain death occurs as a result of ischemic (→ edema) or mechanical (→ hemorrhage) violence, the time of the causal event must be determined, especially in cases involving more than one causal event.

Example. A 30-year-old man suffers occult craniocerebral trauma in a fight; the injury, however, does not require immediate medical treatment. Twenty-four days later the man collapses under unknown circumstances and is found unconscious. A subdural hematoma is diagnosed and drained. A secondary hemorrhage develops, leading to intracranial circulatory arrest. The question of concern for criminal law is whether death was a result of the fight or of injury sustained from the collapse. In this case, demonstration of reactive cells, i.e., of siderophages, proved that death was a result of the fight.

Particular importance attaches to the difference in the case of crimes of violence creating conditions that predispose to brain death when the significance of a further violent act, e.g., stabbing with resultant hemorrhage, has to be assessed. The simple vital reaction of bleeding does not in itself constitute proof in such a situation, unless it is possible to say with a good degree of certainty that brain death did not occur at the moment when the victim was stabbed. It may, however, be possible to state that brain death

that could have been caused by violence has not yet occurred if complex vital reactions, such as inflammation of a wound, are seen (Adebahr 1986).

Adebahr (1986) discussed another point of view in forensic pathology: the diagnosis of poisoning as the cause of brain death can be checked by toxicological examination of brain tissue and of blood in the sinus of the dura mater, since the metabolism in the brain and sinus blood is markedly reduced while drugs and toxic substances continue to be broken down in other organs.

15.5.5 Morphological Statement of Intracranial Circulatory Arrest

Brain death is characterized by morphological changes without accompanying glial or hematogenous cell reactions, with one exception: the demarcation reaction (see above). In contrast, if reperfusion occurs, reactive cells will be present, as pointed out by Pearson et al. (1977, 1978). Thus, the near-complete lack of reactive changes must be regarded as a definitive indicator of total intracranial circulatory arrest.

Schröder (1978, 1983a), by contrast, observed inflammatory alterations beginning in the posterior cranial fossa as a consequence of a partial recirculation 2 days after intracranial circulatory arrest. Hemorrhagic inflammatory phenomena can even be the consequence of reperfusion due to a diminution of the high intracranial pressure, first in the posterior cranial fossa and then also in the supratentorial region. These findings were confirmed, although to a much lesser extent, by Ito and Kimura (1992).

Usually there are no difficulties in declaring morphological proof of brain death on the basis of necrosis of the whole brain. In case reactive cells appear, this should not be proof of a (at least partly) successful reperfusion. Otherwise, the reactive changes at the border zones of the optic nerve, hypophysis, and the cervical cord may provide some evidence of the survival time of the intracranial circulatory arrest.

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Intoxication IV

Introductory Remarks 16

16.1 Biological Principles

Poisoning refers to the damaging physiologic effects of ingestion of, inhalation of, or other exposure to, a range of pharmaceuticals, illicit drugs, and chemicals, including pesticides, heavy metals, and gases/vapors. Poisoning can be caused by common household substances, such as bleach and ammonia, as well as by animals and plants.

In the United States the death rate from poisoning increased from 5.0 per 100,000 population in 1990 to 7.8 in 2001, i.e., 56%. In 2001, of 22,242 poisoning deaths, 14,078 (63%) were unintentional (*Morbidity and Mortality Weekly Report* 2004, 53:233–238).

Intoxication involving the central and peripheral nervous systems (CNS and PNS) can be classified in several ways. The present Part presents, in alphabetical order, neurotoxic poisonings based on groups of substances ingested, injected or otherwise absorbed. Intoxication due to alcohol or the use of illicit drugs will be treated separately as the effects of these substances are encountered with incomparable frequency in forensic pathology and neuropathology.

Poisoning occurs intentionally (suicide, addiction, homicide) or unintentionally (occupational, environmental or iatrogenic poisoning). Poisoning with homicidal intent rarely occurs today and its consequences are seldom seen in institutes of forensic pathology. When deliberate poisoning does occur, it usually affects elderly, helpless patients and is often done to shorten the dying process (active euthanasia). Sometimes, from the criminological point of view, it occurs for financial reasons (Oehmichen 1996; Oehmichen and Meissner 2000) or in the spectrum of deranged physician behavior, as in the recent Shipman murders, in the United Kingdom. Meanwhile the risk of biological and chemical terrorism is in discussion, especially by cyanide poisons, organophosphate poisons, botulinum toxin, and anthrax, which affect the nervous system (Martin and Adams 2003). However, the majority of poisonings today are accidental and affect children (Ashton 1981; Proudfoot 1989; Kruse and Oehmichen 1994; Bays and Feldman 2001). Many are also due to pollution of the environment or workplace, and accidental or iatrogenic medication overdose. Nevertheless, the current public discussion is predominantly focused on the problems associated with chronic alcoholism and drug abuse.

The severity of any given case of poisoning depends on the *solubility*, *dosage*, *route of administration* (oral or parenteral), as well as the degree of *absorption*, *the distribution and elimination*, which finally determine the effective *concentration* of the toxic substance within the CNS or PNS or the body. As a rule, *poisoning can only be verified* by chemical-toxicological analysis. This is true not only for acute poisoning, which can be demonstrated by determination of the levels of foreign substances and/or their metabolites in the blood, but also for poisoning that is chronic, intermittent or occurred in the distant past, which can be confirmed qualitatively (and within certain limits also quantitatively) by the demonstration of the presence of the toxic substance in urine, hair (Frisch et al. 1997; Sachs 1997) or – even in long-dead cadavers – in the bone (Rochholz et al. 1999). A suspicion of poisoning should be raised in cases for which no other plausible explanation for an illness or death is forthcoming, whenever the clinical symptoms and/or morphological changes detected by the pathologist/neuropathologist are generally consistent with a state of poisoning, or when specific characteristic symptoms or morphological alterations are present. Morphological changes are especially helpful in establishing the occurrence of poisoning in cases with long subsequent periods of survival.

The *nervous system is the primary target organ* for many toxic substances or it may suffer *secondary damage* mainly affecting the neurons and their processes. It is well known that not all areas of the brain and not all neuronal systems react to toxins in an identical manner. The term "pathoclisis" introduced by Cecile and Oskar Vogt (1937) indicates a specific affinity of certain toxins for certain systems of organs, but this term of the Vogts was applied broadly, to include ischemia as well. It includes the selective vulnerability of specific neurons to respective toxins in specific topographic areas of the brain. As is known from cases of status epilepticus, cardiac arrest and hypoglycemia, a loss of neurons may be observed in various combinations involving or sparing anatomical structures in neocortex, hippocampus, thalamus, and brain stem (Auer and Siesjö 1988). The same general phenomenon of selective vulnerability is observed in poisonings (Whetsell 2002). Abnormalities in energy homeostasis as the triggering or causative mechanism have been suggested as an explanation for this phenomenon, but this explanation does not hold up, since epilepsy, for example, does not even involve energy failure. It has been discovered that when endogenous glutamate reaches high concentrations in the synaptic cleft, it binds at specific sites, initiating a series of receptor, ionic, and metabolic events that can lead to neuronal destruction (Collins 1987). The phenomenon of pathoclisis, or selective vulnerability, also enables the experimental simulation of pathological processes associated with topographically circumscribed foci of neuronal or axonal degeneration (Ceccarelli and Clementi 1979; Baumgarten and Zimmermann 1992). It is known that insecticides, methanol, heavy metals, and organic solvents are sources of striatal injury (Whetsell 2002).

As reviewed by Whetsell (1996, 2002) the *selective vulnerability of neurons* is partly caused by the differing receptor binding capacity of the neurons. Heptachlor, for example, has demonstrated its toxicity to γ-aminobutyric acid (GABA-ergic) neurons. More recently it was found that heptachlor alters dopamine transporter functions such that dopamine uptake at dopamine terminals in the striatum is decreased at higher levels of exposure (Kirby et al. 2001). In contrast, chloropyrifox is shown to cause persistent impairment of cholinergic synaptic function (Slotkin et al. 2001). Moreover, the selective vulnerability is explained by the different expression of glutamate receptors. Those receptors are the basis of disastrous excitotoxicity when excessively stimulated by glutamate or its structural analogs. Endogenous glutamate analogs of particular importance are aspartate and quinolinic acid, since these are not the natural ligands, yet have high affinity for the receptor, with the ability to activate it. The phenomenon of excitotoxicity is described as "axon-sparing, postsynaptic degeneration" based on its electron microscopic appearance, occurring specifically at glutamatergic synapses which are, of course, the prototypic excitatory synapses (Whetsell 1996).

Astrocytes may also suffer structural and/or functional injury, e.g., after water or lead poisoning. Proper CNS function involves interactive signaling between astrocytes and neurons (Aschner et al. 2002). For example, an alcohol-induced decrease in glial cell proliferation and increased cell death in response to cytokines has been suggested as an important mechanism involved in the neurological and neurobehavioral dysfunction associated with prenatal alcohol exposure (De Vito et al. 2000).

Abnormalities in glutamate metabolism and glutamatergic neurotransmission appear to play an important role in the pathogenesis of hyperammonemia and hepatic encephalopathy (Norenberg 1995). Both conditions result in excessive ammonia accumulation within the CNS due to liver failure. The exclusive site for the detoxification of glutamate to glutamine is within astrocytes. This process requires ATP-dependent amination of glutamate to glutamine, a process mediated by the astrocyte-specific enzyme glutamine synthetase. In vivo chronic exposure to ammonia leads to decreased glutamine metabolism within the astrocytes and impairment of astrocytic energy metabolism (Norenberg 1995).

Oligodendrocytes in the CNS may suffer selective damage, e.g., from diphtheria toxin or ethidium bromide.

The possibility of poisoning and its severity also depends – among other factors – on the *biological age of the victim* (Auer 1991). The fetus for example passes through phases of particular vulnerability to toxic effects, the sequelae of which include malformations (dysmelia) and long-term functional impairment (Ashton 1981). In children, even small doses can have a toxic effect not seen in adults, and there is an unknown consistent correlation between dosage and body mass (Bays and Feldman 2001). The elderly, too, are especially vulnerable because of age-related changes in vascular walls, fluctuations in blood pressure, changes in the immune system, and functional impairment of single organ systems such as liver or kidney. Regardless of age, however, the chronic application of small doses of many substances during gestation may have teratogenic effects.

For *interpretation of chemical analytical findings* the following experiences are to be considered: it is known that – for example – cardioactive drugs such as digoxin accumulate in the heart during an individual's life time and are released into the cardiac blood after death. Therefore, it is basically advisable to use peripheral blood or vitreous humor when screening for cardiac drugs to avoid obtaining spuriously high levels in blood from the heart.

The clinical and morphological effects of poisoning by different neurotoxic agents can be roughly differentiated according to their principal target site, i.e., toxic encephalopathy or toxic neuropathy.

16.2 Toxic Encephalopathy

The *suspicion* of poisoning must always be raised in cases exhibiting clinically conspicuous psychophysical changes not attributable to illness or known disturbances in CNS function. This is also true in diagnosis in the field of anatomical pathology: if a morphological finding is not characteristic of any known disease of the CNS, then poisoning must be considered.

Circumstances (environment, heavy drinking, drugs) or external markings (changes in the mouth, needle marks on the arms, constricted or dilated pupils, known or unknown smell, etc.) can also suggest a possible poisoning. Among the *general clinical symptoms* of poisoning are changes in global cognitive function, level of consciousness and vigilance. Dementia, seizures, headache, hydrocephalus, cerebellar syndromes, tremor, and disturbances of the visual, auditory, vestibular, or olfactory systems may also be observed.

Morphologically, the following changes are almost universally present:

- *Cerebral edema* (Klatzo 1977), which is dependent upon the relative lipophilia of the toxic agent, its molecular weight, carrier-mediated transport mechanisms (e.g., cationization or glycolysation) and transport capacity. *Cytotoxic edema* resulting from membrane damage (heavy metals, triethyltin) and/or injury of the membrane enzyme system (heavy metals, cyanide) must be differentiated from *vascular edema* caused by, for example, alcohol, although the two types of edema may occur simultaneously or sequentially (for review see Oehmichen et al. 2001, see also p. 47).
- *Neuronal and axonal injury*, which is due to impaired *axoplasmic transport* (Müller and Jeschke 1970) resulting in isolated neuropathy or polyneuropathy (cf. toxic neuropathy), characteristic of, for example, aluminum, acrylamide, colchicine, organophosphate or alcohol poisoning.
- *Neuronal injury*, which is due to faulty *energy metabolism* (Krieglstein and Kuglisch 1992), the chief cause being carbon monoxide, but including also ethanol and organophosphates. Without ischemia due to heart failure, neither cyanide- (MacMillan 1989) nor sulfide-induced (Baldelli et al. 1993) inhibition of energy metabolism causes necrosis.
- *Injury of the white matter*, i.e., leukoencephalopathy, which is a structural alteration of cerebral white matter in which myelin suffers the most damage (Shields et al. 1998; Filley 1999; Filley and Kleinschmidt-DeMasters 2001). Toxic leukoencephalopathy may be caused by exposure to a wide variety of agents, including therapeutic agents, the misuse of drugs, environmental toxins, and cranial irradiation (see Table 16.1).
- *Focal necrosis*, which is caused by, for example, hyperbaric oxygen or carbon monoxide, methanol, heavy metals, and methotrexate.
- Injury of and functional impairment of *cholinergic transmission* (Dolly 1992; Hörtnagel and Hanin 1992), which is caused by, for example, phosphate esters, clostridium, botulinum and tetanus toxins, colchicine, alcohol, and aluminum.
- Damage to and functional impairment of the *noradrenergic system*, which is caused by, for example, alcohol, amphetamines, cocaine, and cannabinoids.
- Effects on a neurotransmitter system (Dolly 1992), in particular the *receptors*, with the excitatory receptors being most affected (GABA and acetylcholine receptors) in the absence of an obvious morphological equivalent.
- Effects on the *visual system* (Merigan and Weiss 1980), for example due to methanol, carbon disulfide, methyl mercury, and organophosphate poisoning.
- *Teratogenic effects* on the fetal nervous system caused by, for example, ethanol, methyl mercury, or *carcinogenic effects*, e.g., caused by cadmium.

At the cellular level, the following additional functional distinction can be made (Haschek and Rousseaux 1998):

- *Neuronal oxidative metabolism*: this may be impaired by ischemia or hypoxia secondary to poisoning.

Toxic agents can also disturb the homeostasis of the electrolyte balance by:

- Inhibition of protein synthesis (e.g., adriamycin).
- Damage to the cytoskeletal structure (e.g., platinum).
- Triggering of a glial reaction (astrocytic changes in liver disease, oligodendroglial changes caused by triethyltin poisoning).
- Injury of capillaries, caused for example by heavy metals such as arsenic or inhalation of methyl bromide.

Table 16.1. Causes of toxic leukoencephalopathy. Source: Filley and Kleinschmidt-DeMasters 2001

Anti-neoplastic agents	
Cranial irradiation	Fluorouracil
Methotrexate	Levamisole
Carmustine	Fludarabine
Cisplatin	Thiotepa
Cytarabine	Interleukin-2
	Interferon-α
Antimicrobial agents	
Amphotericin B	Hexachlorophene
Drugs of abuse	
Toluene	Intravenous heroin
Ethanol	Inhaled "heroin" pyrolysate
Cocaine	Psilocybin
3,4-Methylenedioxymethamphetamine	
Environmental toxins	
Carbon monoxide	Carbon tetrachloride
Arsenic	

16.3 Toxic Neuropathy/Polyneuropathy

Excellent reviews are published by Dyck et al. (1975) and by Schröder (1999). The *clinical features* of toxic neuropathy are dependent upon the specific target site of the toxin in the PNS. A predominantly motor neuropathy can usually be distinguished from a predominantly sensory neuropathy. A distinction may also be made between primary involvement of the autonomic nervous system (vegetative neuropathy), cranial neuropathy, and changes in neuromuscular transmission and toxic myopathy. A causal distinction must be made between nutritionally produced neuropathy (e.g., vitamin B deficiency, alcohol) and endotoxic neuropathy secondary to a systemic metabolic disorder (e.g., diabetes mellitus, uremia, etc.).

Neuropathy caused by poisoning must be suspected in the presence of the following clinical features (Schaumburg 2000):

1. Gradual insidious onset
2. Initial findings in the lower extremities
3. Stocking glove sensory and motor loss
4. Early and symmetrical loss of ankle jerk reflexes
5. Normal to mildly retarded motor nerve conduction
6. Normal protein level in the cerebrospinal fluid (CSF)
7. Slow recovery
8. Coasting
9. Signs of CNS disease
10. Pain (Schröder 1999)

Pathogenetically, different systems can suffer damage, including the neuronal and axonal systems, the myelin sheath and oligodendrocytes, and/or the macrophage system. Various types of neuropathy must be differentiated (Thomas 1980) depending upon the primary localization of the respective functional impairment or morphological changes.

The *distal axonopathy* denotes a selective distal degeneration of axons, progressing in a centripetal fashion: Cavanagh (1964) attributed this to a *"dying-back" process*, which he was able to produce experimentally in cats by administration of organophosphates. The process begins with degeneration of the large diameter sensory fibers, known also to be caused for example by acrylamide, organic hydrocarbons, or by carbon disulfide-induced poisoning.

The axons display focal enlargements due to aggregations of neurofilaments.

In contrast to distal axonopathy, *proximal* and *focal axonopathies* are mainly of theoretical and experimental interest.

Demyelination and Schwann cell alteration occur secondary to axonopathy. Some substances inflict primary injury of myelin, e.g., lead, diphtheria toxin or triethyltin and hexachlorophene (intramyelinic edema). Selective injury of Schwann cells is caused by 6-aminonicotinamide, for example.

The *pathological features* are attributable mainly to primary or secondary degenerative changes and may also vary according to the target site. Axons, myelin, and/or Schwann cells may exhibit extensive disintegration. In the majority of cases, neuropathy produces macroscopically apparent neurogenic muscular atrophy (see Chaps. 2–5). Microscopy of a cross section of muscle reveals a neurogenic, i.e., panel-like, atrophy of the muscle fibers (see Chaps. 6–12).

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Specific Types of Neurotoxins 17

17.1 Metals and Metallic Compounds

17.1.1 Aluminum (Al)

Source. Aluminum (Al) is ubiquitous in its oxidized form, present in air, food, and water. Its main industrial use is in the metal working industries. Aluminum hydroxide is frequently used as an antacid without producing clinical symptoms. However,

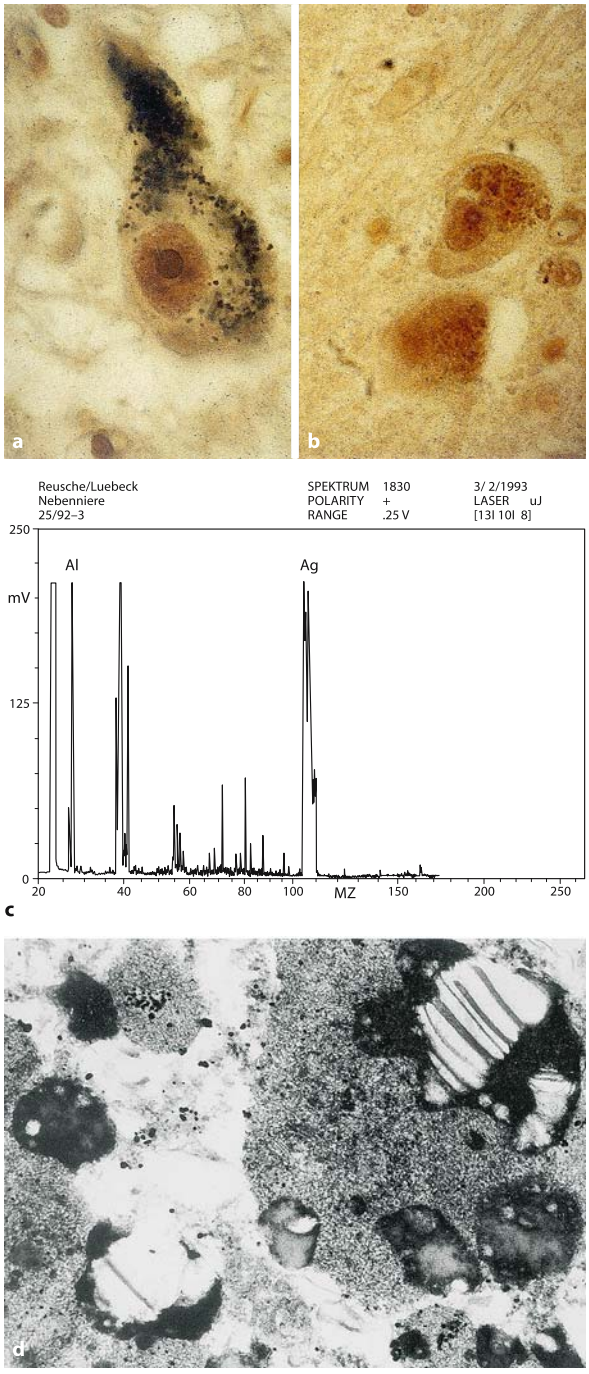

Fig. 17.1a–d. Dialysis-associated encephalopathy. **a** Hypoglossal neuron with pathognomonic deeply black, fine-granular cytoplasmic inclusions in dialysis-associated encephalopathy in comparison with the brownish neuronal lipofuscin in neurons of the inferior olivary nucleus (**b** – silver staining; ×2000). **c** Laser microprobe mass analysis with aluminum peak at *m/z* 27, confirming the high aluminum content of silver-stained inclusions (peaks at *m/z* 104 and 106 result from silver staining). **d** Electron microscopy with partly electron-dense, partly bizarre electron-lucent material of (aluminum-containing) inclusions (×40,000). The figure was kindly provided by Professor Dr. E. Reusche, Lübeck

clinical features attributed to aluminum intoxication have been described after *chronic dialysis* (see also p. 613 f) with dialysis fluid containing aluminum as well as following oral administration of phosphate-binding agents containing aluminum (McLaughlin et al. 1962; Alfrey et al. 1976; Elliott et al. 1978; Martyn et al. 1989). A relationship has been hypothesized between exposure to aluminum in food and water and Alzheimer's disease (Wisniewski et al. 1979). The normal concentration of aluminum in the brain is ≤10 µg/l, which increases with age.

Pathogenesis. If the blood contains elevated levels of aluminum in association with a compromised blood–brain barrier (McDermott et al. 1978), the brain will also have elevated levels of aluminum (Crapper McLachlan et al. 1983). Plasma levels above 100 µg/l are potentially toxic; levels exceeding 500 µg/l are indicative of acute aluminum poisoning. At the cellular level, aluminum is known to disrupt the slow transport of neurofilament proteins (NFP), which leads to an accumulation of NFP at the proximal end of the axon (Bizzi et al. 1984; Bin and Garfinkel 1994) and a proliferation of microfilaments in the perikaryon (Klatzo et al. 1965; Weinstein 1974).

The similarity of clinical symptoms in association with elevated levels of aluminum demonstrated in the brains of victims of *dementia of Alzheimer type* (Crapper McLachlan et al. 1983) has given rise to a theory that Alzheimer's disease may be caused by an accumulation of aluminum in the brain (Martyn et al. 1989). This hypothesis has fallen out of favor.

Clinical Features. Aluminum poisoning is characterized by *progressive dementia* with speech impairment, myoclonus, focal and/or generalized epileptic seizures, focal neurological symptoms, and loss of consciousness. An aluminum-induced *degeneration of motor neurons* must be distinguished from a *dialysis encephalopathy*. The disease can end in death. The differential diagnosis must include *Alzheimer's disease*. Desferrioxamine is the specific chelating antidote.

Morphology. The morphological changes caused by aluminum intoxication are non-characteristic in H&E preparations (McLaughlin et al. 1962). *Ganglion cells* are *shrunken*, but usually there is *no clear decline* in their numbers. Some differences can be demonstrated immunohistochemically: in aluminum poisoning, neurons do not react to microtubule-associated protein 2 (MAP-2), β-tubulin or ubiquitin, while in Alzheimer's disease they do (Strong et al. 1991). Aluminum poisoning is also associated with proliferation of microglia and astrocytes as well as a spongiform disintegration of the neuropil in the second and third cortical layer.

Using new variants of silver staining, Reusche described in 1991 a new effective method for the demonstration of Alzheimer changes by light- and electron microscopy (Reusche et al. 1992). The same methods allowed for the first time the demonstration in ten long-term hemodialyzed patients of characteristic and pathognomonic aluminum-containing inclusions in the cytoplasm of choroid plexus epithelia, glia, and neurons of the CNS (Reusche and Seydel 1993). Argyrophilic proteinaceous deposits of this "dialysis-associated encephalopathy" (DAE) were shown by light- and electron microscopy. They obviously result from long-standing and futile cytoplasmic lysosomal degradation of aluminum. Similar deposits could be demonstrated in peripheral organs as well (Reusche et al. 1996). Laser microprobe mass analysis confirmed high cellular levels of aluminum (Fig. 17.1). The morphology is completely different from neuronal changes in Alzheimer's disease (Reusche and Seydel 1993; Reusche 1997). The evaluation of 50 long-term hemodialyzed patients – with ingestion of aluminum-containing drugs, up to 2.5 kg "pure" aluminum – presented no increase in the incidence of Alzheimer's disease (Reusche et al. 2001).

17.1.2 Arsenic (As)

17.1.2.1 Inorganic Arsenicals

Source. Inorganic arsenicals are used in the manufacture of glass (smelting industry), in the preservation of wool, and as a pesticide. Intentional acute or chronic arsenic (As) poisoning often occurs in criminal cases (Geldmacher von Mallinckrodt 1975).

Clinical Features. *Acute arsenic poisoning* is characterized by gastrointestinal symptoms including nausea, vomiting, and diarrhea, accompanied by confusion, delirium, coma, circulatory collapse, and death. Arsenite is a strong inhibitor of the pyruvate dehydrogenase system (glycolysis) forming a stable complex with the thiol groups of the enzyme complex (Devlin 1997). Victims who survive develop symptoms of peripheral neuropathy with sensory defects (Le Quesne and McLeod 1977; Heaven et al. 1994). Victims of *chronic arsenic poisoning* exhibit symptoms of peripheral neuropathy with loss of motor function, but gastrointestinal disturbances are sometimes lacking. At the same time, hyperkeratosis of the hands and feet is observed in most cases (plus so-called Mees' lines on the fingernails). Progression of an arsenic-induced polyneuropathy can be halted by administration of water-soluble 2,3-dimercaptopropanesulfonate (DMPS).

The toxicity of arsenic is based on its capacity to uncouple mitochondrial oxidative phosphorylation. Arsenic binds in the place of inorganic phosphate, forming arsenic analogs of high-energy phosphates, which are unstable and break down to regenerate inorganic arsenic (Vahter 1999). The pentavalent form, arsenate, is much less toxic than the trivalent form, known as arsenite.

Morphologically, the effects of arsenic poisoning are characterized by axonal degeneration of the peripheral, large fibers (Hörtnagel and Hanin 1992), sometimes combined with segmental demyelination (Crapper McLachlan and De Boni 1980), occasionally presenting as a Guillain–Barré-like syndrome (Donofrio et al. 1987). No changes are apparent in the CNS.

17.1.2.2 Organic Arsenicals

Source. Organic arsenicals are used mainly in the treatment of syphilis and trypanosomiasis. *Clinically*, poisoning by organic arsenicals produces symptoms of encephalopathy and exfoliative dermatitis as well as peripheral neuropathy. Treatment with British anti lewisite (BAL, =2,3-dimercaptopropanol; dimercaprol) has proven effective. It is assumed that the clinical symptoms are *caused* less by the direct toxic effect than by an allergic reaction (Adams et al. 1986).

Morphologically, arsenic encephalopathy is characterized by pericapillary bleeding, mainly in the midbrain (hemorrhagic encephalopathy) (Hurst 1959). Sometimes the disease manifests as an acute hemorrhagic leukoencephalitis (Adams et al. 1986), which suggests an allergic pathogenesis. Finally, a Guillain–Barré-like syndrome has been attributed to treatment with melarsoprol (Gherardi et al. 1990).

17.1.3 Bismuth (Bi)

Source. Bismuth (Bi) is used to treat constipation, gastric ulcers, and indigestion following removal of the large bowel. It is also used in dental procedures and as a radiographic contrast medium.

Clinical Features. The predominant clinical features of bismuth intoxication are functional disturbances, osseous changes as well as gastrointestinal disturbances with diarrhea and bleeding. Insoluble inorganic compounds are particularly neurotoxic. Brain involvement is usually characterized by mental and/or neurological symptoms, such as anxiety, depression, ataxia, tremor, dementia, memory loss, confusion, delirium, psychosis, and irritability. The disease process may lead to coma and end in death.

Pathogenesis. The pathogenesis of bismuth poisoning is not yet clear and sensitivity to its effects varies from individual to individual.

Morphology. Morphological changes in the nervous system typical of bismuth poisoning include a predominant loss of Purkinje cells in the cerebellum and of neurons in the neocortex (laminar necrosis) and hippocampus (Liessens et al. 1978). There is also a loss of neurons and proliferation of microglia in the basal ganglia, especially the putamen (Jungreis and Schaumburg 1993). Elevated bismuth levels have been observed in the frontal cortex, basal ganglia, and cerebellar cortex (Drenckhahn and Lüllmann-Rauch 1979).

17.1.4. Cadmium (Cd)

Source. Exposure to cadmium (Cd) is always in combination with zinc and – occasionally – with lead. Today it is almost impossible to avoid exposure to cadmium since this metal is ubiquitous in the environment. Cadmium is highly toxic and has an extremely long biological half-life (15–20 years), so that it accumulates within tissue. It can cause sterility and is teratogenic, carcinogenic, and may also play a role in aging (Bin and Garfinkel 1994). Cadmium does not penetrate the blood–brain barrier and thus it may be assumed that its neurotoxic effects derive secondarily from its interference with zinc metabolism (Jin et al. 1998).

Pathogenesis. Cadmium is thought to bind competitively at Ca^{2+}-rich binding sites on the cell surface as well as to intracellular receptors (Gabbiani et al. 1967). This hypothesis is supported by the observation that cadmium inhibits endothelin-binding activity (Wada et al. 1991). In nerve cells, cadmium blocks NMDA-gated channels (Reynolds and Miller 1988) as well as N-, L- and T-type Ca^{2+} channels on neurons (Gadbut et al. 1991) and glia (MacVicar 1984, 1987).

Morphology. (For review see Schröder 2000.) Cadmium affects mainly the lung (acute intoxication: pneumonia; chronic intoxication: emphysema). In Japan, a series of cadmium poisonings occurring between 1939 and 1945 produced a clinical syndrome called "itai-itai disease," which caused bone pain among other symptoms, apparently due to involvement of the spinal ganglia (Murata 1971). Cadmium-related encephalopathy has been described in a male adolescent in East India (Provias et al. 1994) with brain swelling, herniation, and perivascular edema indicating a disturbance of the blood–brain barrier.

17.1.5 Gold (Au)

Gold (Au) solutions, aurothioglucose and sodium aurothiomalate, are used to treat rheumatoid arthritis today (chrysotherapy). The side-effects are dermatitis, renal damage with hematuria and impaired hematopoiesis. *Neurological deficits* are uncommon and include encephalopathy, cranial neuropathy, myokymia and peripheral neuropathy, possibly Guillain–Barré syndrome. Psychiatric symptoms have been described in a few instances (Fam et al. 1984; Pery and Jacobsen 1984). It is unclear as to whether the neurotoxic mechanism involves a hypersensitivity reaction, a direct toxic effect, or both. *Morphological changes* in the NS have not been described.

17.1.6 Lead (Pb)

17.1.6.1 Inorganic Lead Compounds

Source. Lead accumulates in the body and reaches especially high levels in the blood, bone marrow, and soft tissues as well as in skin, muscle, and bone. Sources of exposure are manufacturing processes releasing lead or lead compounds in the form of dust, smoke or steam. At one time, lead paint, lead pottery glazes, and lead pipes in water systems were major sources of lead poisoning. Today, automobile emissions and exposure to tetraethyl lead are the principal sources of lead poisoning.

Pathogenesis. In the United States, there are 12,000–16,000 new cases and 200 deaths from lead poisoning annually. Children are particularly at risk. Pathological lead values have been found in 10–25% of children in slum areas (Ludwig 1977a). Lead is taken into the body through the lungs and gastrointestinal tract. In the form of dust or vapor, metallic lead oxidizes to lead oxide. Lead concentrations in the brain are a function of blood lead levels.

The effects of lead at the cellular level are largely unknown. Absorbed lead is not metabolized and is excreted via the kidneys. An adult member of the general population will excrete lead at the rate of <634 ng/24 h. Lead affects the blood–brain barrier and appears to have a direct toxic effect on neuronal membranes, causing impairment of the potassium pump. It also affects neurotransmitters, especially the GABA-ergic system, the latter being implicated in lead encephalopathy (Schwedenberg 1959). It is assumed (Niklowitz 1977) that lead elevates tissue Cu levels, which inhibits cell membrane adenosine

triphosphatase, thus disturbing the potassium pump and simultaneously – possibly by way of non-specific membrane injury – allowing lead to reach the cell interior. This explains the ability of lead to breach the blood–brain barrier and the high risk of lead encephalopathy, especially in children. Recent experimental studies in rats have suggested that chronic prenatal and post-natal exposure to lead induces regional neurotoxicity in striatum, thalamus, and hippocampus because of increased intraneuronal (intracytoplasmic) lipid peroxidation and oxidative stress (Villeda-Hernandez et al. 2001). Moreira et al. (2001) caution, however, that oxidative stress may not be the main neurotoxic mechanism associated with experimental low-level lead exposure in the brain.

Clinical Features (Encephalopathia Saturnina). In adults, acute lead poisoning is characterized by colic, vomiting, and diarrhea; coma and convulsions are rare. Chronic lead poisoning in adults causes toxic anemia (microcytic anemia) with constipation, gastrocolic symptoms, and blisters and/or renal tubular destruction or chronic interstitial nephropathy with headache, nausea, and impaired renal function. Terminal chronic lead poisoning is associated with a severe organic psychosyndrome. In addition to the CNS, the PNS also suffers damage apparent in the neuromuscular syndrome, also known as lead palsy, especially prominent in the muscles of the upper limbs. In children, the clinical picture is dominated by severe brain edema with symptoms of intracranial pressure indicative of encephalopathy: seizures, hemiplegia, and other neurological sequelae.

The toxic mechanism has not yet been completely elucidated. In victims of lead poisoning who die of acute encephalopathy, a lethal mechanism other than cerebral swelling or herniation must be implicated as the cause of death.

Morphology. The morphological changes caused by lead poisoning of the brain are multifarious, not universal and non-specific (Krieglstein and Kuglisch 1992). *Macroscopically*, acute lead poisoning is recognizable by signs of brain edema and hyperemia; occasionally there is petechial bleeding in the gray and white matter; atrophy of the cerebrum and cerebellum has also been described (Valpey et al. 1978).

Microscopically, cases of *acute lead poisoning* exhibit signs of a disrupted blood–brain barrier with perivascular, albumin-rich exudates; in rare instances, edema of the white matter can cause diffuse demyelination and – in association with thinly dispersed lymphocytic infiltrates – a multiple sclerosis-like (Schilder's disease) picture.

Chronic lead poisoning is characterized by the proliferation of capillaries in the cerebral and cerebellar cortices as well as a proliferation of astrocytes and microglia in the molecular layer of the cerebellar cortex adjacent to microglial nodules (Pentschew 1965). The number of Purkinje cells is reduced and the granular cell layer is often atrophic. Hyalinosis of the arterioles has been described as well as Alzheimer's neurofibrillary tangles (Niklowitz and Mandybur 1975).

The lead content of the bone marrow correlates with the presence of relatively densely packed calcareous deposits in the granule cell layer of the cerebellar cortex and pallidum (Tonge et al. 1977; Silbergeld 1983). An expression of the degree of damage to the peripheral nerves (Wallerian degeneration) is apparent in the central chromatolysis of the anterior horn cells (Eto and Takeuchi 1978).

17.1.6.2 Organic Lead Compounds

Source. In the 1920s, tetraethyl lead was first used as an additive to gasoline. Since the removal of lead from gasoline, the median blood lead concentrations have fallen from 0.724 µmol/l in 1978 to 0.097 µmol/l in 1999. Exposure to lead from deteriorating lead paint in older homes continues. The Centers for Disease Control and Prevention (CDC) estimated that, in 2000, there were still 454,000 children in the United States with blood lead concentrations greater than 0.483 µmol/l (Rogan and Ware 2003). Today, lead poisoning is most frequently caused by sniffing gasoline (pp. 383 ff). Blood lead concentrations, even those below 0.483 µmol/l, are inversely and significantly associated with children's intelligence quotient (IQ) scores at 3 and 5 years of age (Canfield et al. 2003).

Morphology. The morphological picture is dominated by cortical and cerebral atrophy with selective loss of nerve cells in the hippocampus and cerebellum as well as chromatolysis of the reticular nuclei of the brain stem (Kaelan et al. 1986; Valpey et al. 1978).

17.1.7 Lithium (Li)

Lithium (Li) is used *therapeutically* in the therapy of cyclothymic psychoses. Lithium overdose produces symptoms such as diarrhea, vomiting, and dizziness as well as neurological effects such as tremor, cerebellar disturbances, truncal ataxia, broad-based ataxic gait, dyskinesia, dysarthria, and nystagmus. Lithium impairs both intermediary and DNA metabolism (Dempsey and Meltzer 1977). *Morphologically*, spongiform changes can be noted in the thalamus, midbrain, cerebellum, and spinal cord. There is also damage to cerebellar granular and Purkinje cells, gliosis in the dentate nucleus, the inferior olives, and

the red nucleus, and cytoplasmic inclusions in the neurons of cranial nerve nuclei (Peiffer 1981; Naramoto et al. 1993).

17.1.8 Manganese (Mn)

Source. Manganese (Mn) is mined in Chile, Morocco, and Cuba. Mn is used in the production of steel and of electric batteries. Mn poisoning (*manganism*) has been particularly described in miners in Morocco (Rodier 1955). Mn is taken in orally (ingestion of foodstuffs or water) or by inhalation. Since Mn^{3+} binds to transferrin and Mn^{2+} binds to plasma α_2-macroglobulin, it is also capable of penetrating the blood–brain barrier. In the brain, it accumulates in the globus pallidus and the substantia nigra, pars reticularis (Peiffer 1956; Mena 1979; Newland et al. 1989).

Clinical Features. The early phase of Mn poisoning is characterized by psychiatric symptoms such as states of agitation, disturbance of the sleep–wake cycle, affective instability, etc. Later symptoms include extra-pyramidal disturbances resembling Parkinson's syndrome: akinesia, dystonia, etc. (Mena 1979). The symptoms may be irreversible even after termination of exposure, and clinical symptoms do not respond to levodopa therapy (Pal et al. 1999).

Pathogenetically there is a reduction of dopamine and homovanillic acid levels in the corpus striatum (Bonilla and Diez-Ewald 1974) as well as a decline in adrenaline (Barbeau et al. 1976). Zheng et al. (1998) suggest that the mechanism of manganese neurotoxicity is alteration of brain mitochondrial aconitase activity leading to disruption of mitochondrial energy production; it is not understood why it appears to be selectively toxic in the globus pallidus (Whetsell 2002).

Morphologically, degeneration of the basal ganglia is noted, mainly of the medial segment of the globus pallidus, with relative sparing of the substantia nigra (Barbeau et al. 1976; Bernheimer et al. 1973; Yamada et al. 1986; Pal et al. 1999).

17.1.9 Mercury (Hg)

17.1.9.1 Elementary Mercury and Inorganic Mercury Compounds

Source. Mercury (Hg) is used in thermometers, thermostats, Hg-based paints, etc. In medicine, Hg was applied in the past principally in the treatment of syphilis. Inorganic Hg compounds are widely used in the *impregnation* and *preservation* of wood, as anti-corrosives in photography, and as a *disinfectant* (mercuric cyanide). Hg is often the vehicle of suicide or homicide, usually in the form of *mercuric chloride* (*sublimate)* (Geldmacher von Mallinckrodt 1975).

Since Hg vapor is colorless and odorless, it can be inhaled accidentally. The incidence of Hg poisoning, however, has decreased due to improvements in precautionary measures. The use of amalgam in dentistry has drawn criticism for being potentially toxic (Hahn et al. 1989; Boyd et al. 1991) and may cause or exacerbate degenerative diseases such as amyotrophic lateral sclerosis or Alzheimer's disease, but no firm proof of its toxicity has been presented (for review see Clarkson et al. 2003).

Clinical Features. Hg poisoning is characterized by affective instability, depression, erethism, ataxia, and – rarely – tremor (Ludwig 1977a, b; Kark 1994). Early clinical symptoms are memory loss, increased excitability, insomnia, and personality changes.

Morphology. Structural changes have been described in one case with classical signs of Hg intoxication (Escourolle et al. 1977). Macroscopically, neuronal loss and glial reactions are rarely seen in the nervous system, but, microscopically, Hg is found in the lysosomal "dense bodies" of numerous nerve cells (Fig. 17.2a, b) as well as in peripheral nerves (Fig. 17.2c), where the metal is concentrated - even years after acute vapor exposure, on occasion of an accidental explosion (Hargreaves et al. 1988). The mechanism underlying the related neurological and psychopathological symptoms is unknown, although inorganic Hg has been shown to alter ADP-ribosylation of brain neuronal proteins (Palkiewicz et al. 1994) and inhibit tubulin polymerization into microtubules (Leong et al. 2002).

Pathogenesis. Due to their lipophilic properties, Hg and its non-polar compounds easily penetrate the blood–brain barrier (Chang 1980). They inhibit mitochondrial respiration and synaptosomes (Verity et al. 1975), which can lead to a reduction in the level of cellular oxidation of brain cells (Grundt and Bakken 1986). This metabolic failure and the injury of the cell membrane leads to an increase in the calcium content of the nerve endings (Bano and Hasan 1989), which can ultimately lead to neuronal death.

17.1.9.2 Organic Mercury Compounds

Source. Improper *waste disposal* or waste processing can result in the formation of large amounts of organic Hg compounds. Since microorganisms in water can transform inorganic compounds into organic compounds (methylmercury), the ingestion of marine animals can pose a certain risk. Japanese

fishermen developed *Minamata disease* after eating mercury-contaminated fish caught in a bay polluted by industrial wastes (Eto and Takeuchi 1978). As an effective *fungicide*, methylmercury is used to treat wheat. Iraq experienced a widespread wave of poisoning attributable to wheat treated with methylmercury, resulting in over 500 deaths (Bakir et al. 1973). In Germany, there have been alarming reports of high Hg concentrations in tuna fish.

Pathogenesis. The neurotoxicity of Hg is based on its ability to penetrate the blood–brain barrier and accumulate in neurons, with a long half-life, exceeding 70 days (Magos 1975). Methylmercury impairs protein synthesis by inhibiting the incorporation of amino acids into the proteins of sensory ganglia and peripheral nerves (Cavanagh and Chen 1971). Recent experiments suggest that the primary effect results from incomplete phosphorylation of uridine leading to the inhibition of RNA synthesis (Sarafian and Verity 1986).

Clinical Features. The presence of a*cute intoxication* is highlighted by gastrointestinal symptoms, whereas *chronic intoxication* produces both a nephritic syndrome and symptoms of nervous system involvement: paresthesias, fatigue, dizziness, and ataxia. Scotomas have also been described (Ludwig 1977b). Methylmercury can pass the *placental barrier* and severely impair fetal brain development (Marsh et al. 1980).

Morphology. The morphological picture is characterized by neuronal loss in the cerebral cortex – which is especially pronounced in the calcarine cortex – and in the cerebellar cortex. Cortical atrophy is sometimes even macroscopically apparent. *Microscopically* there is a spongiform disintegration of the *cerebral cortex* mainly affecting the second to fourth cortical layers, with massive proliferation of glial cells (Takeuchi et al. 1979). The *cerebellum* shows a loss of granular cells, which is especially marked in the depths of the folia. The Purkinje cells appear to be unaffected. Axon torpedoes are common. The cerebellar cortex is marked by distinct changes in the dendrites of the Purkinje cells, with antler-like and morning star-like figures (Eto and Takeuchi 1978). The *basal ganglia* are generally well preserved, whereas the *spinal cord* exhibits demyelination of the posterior white column, and, less often, of the lateral pyramidal tract.

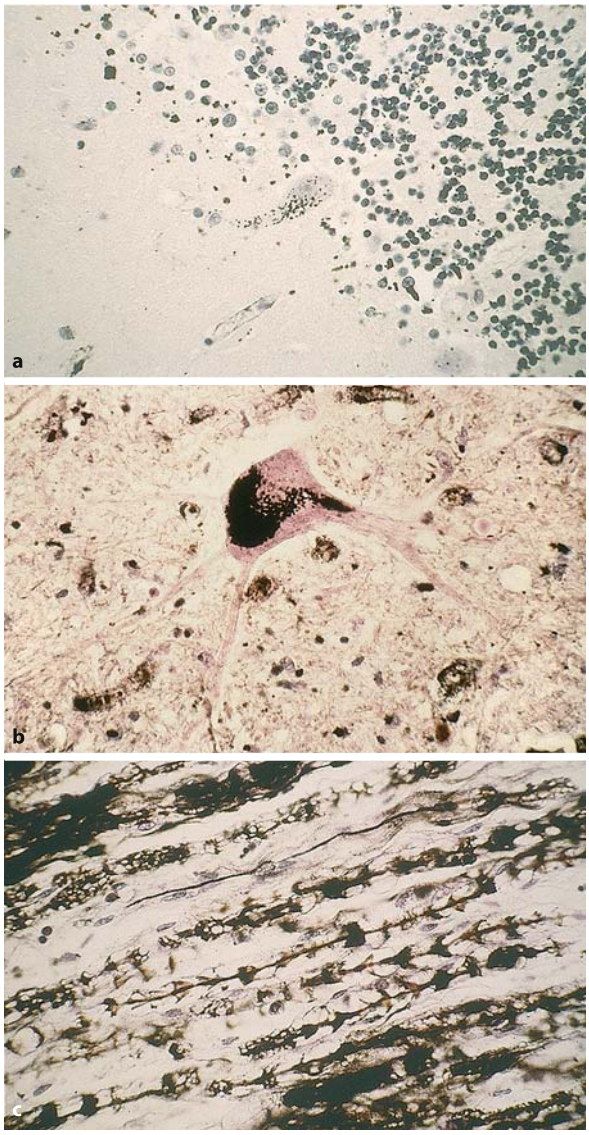

Fig. 17.2a–c. Mercury intoxication by inhaled inorganic Hg vapor. Demonstration of heavy metal granules in: **a** Purkinje cell, **b** pyramidal cell in the cerebral cortex, and **c** peripheral nerve from a patient with severe ataxia and tremor, who survived a boiler explosion in an amalgam distillery for 41 years . (Eosin stain, magnification **a** ×500; **b, c** ×1,000). The figures were kindly provided by Professor Dr. H. Wiethölter, Stuttgart

17.1.10 Platinum (Pt)

Source. In the 1970s platinum (Pt) was first used in conjunction with cyclophosphamide in chemotherapy in the form of cisplatin. Intravenous application was found to induce peripheral neuropathies and hearing defects. Intravascular application in the carotid arteries produced symptoms of CNS defects (Feun et al. 1984).

Morphology. There is axonal loss in large myelinated and unmyelinated fibers together with gliosis in the anterior horns of the spinal cord (Verity et al. 1975). Local intra-arterial injection is followed by severe

nerve damage, apparently caused by the direct neurotoxic effect of Pt (Freedman et al. 1987).

17.1.11 Thallium (Tl)

Source. Thallium (Tl) is an ubiquitous trace element in the soil and in plants (including vegetables). Metallic Tl is used in industry as a special alloy. Water soluble thallous salts are toxicologically important and have been used in recent decades in many types of *rat and mouse poisons*. Tl compounds are usually colorless, odorless, and tasteless, which accounts for their frequent use in homicides and suicides (Geldmacher von Mallinckrodt 1975; Moeschlin 1980; Moore et al. 1993). Tl compounds are both hepatotoxic and neurotoxic.

Pathogenesis. Tl is thought to interfere with oxidative phosphorylation by inhibition of ATPase in the mitochondria (Melnick et al. 1976). At the same time, axonal transport is disturbed, resulting in a "dying-back" neuropathy (Cavanagh 1979). High concentrations of Tl may affect both energy metabolism and the antioxidant protection of cell membranes in the NS (Cavanagh 1985, 1988, 1991).

Clinical Features. In cases of acute Tl poisoning, gastrointestinal symptoms such as diarrhea, vomiting, and convulsive stomach pains predominate. The first symptoms in chronic intoxication are paresthesias, followed by convulsions, states of delirium, and coma. There are also peripheral deficits, extrapyramidal and psychological disturbances (Bank 1980). The main visible symptom of chronic intoxication is hair loss and changes in the fingernail beds (so-called Mees' lines; cf. Arsenic Poisoning above) (Geldmacher von Mallinckrodt 1975).

Morphology. Macroscopically, cerebral edema is often associated with disseminated hemorrhages in the white matter and cerebellum (Cavanagh et al. 1974). Microscopically, edema and necrosis can be demonstrated mainly in the subthalamic region, the substantia nigra and at the level of the corticospinal tracts (Ceccarelli and Clementi 1979). In addition, there are primary degenerative changes in the nerve cells of the cerebral and cerebellar cortices, the hypothalamic nuclei, olivary nuclei, and the corpus striatum, with a conspicuously absent glial cell reaction. Peripherally there is axonal degeneration with changes typical of the "dying-back" process with chromatolytic changes in neurons in the motor cortex, substantia nigra and brain stem motor nuclei (Cavanagh et al. 1974; Kennedy and Cavanagh 1976; Cavanagh 1985, 1991).

17.1.12 Tin (Sn) and Tin Compounds

17.1.12.1 Triethyltin

Source. Metallic tin is practically non-toxic, whereas organic tin compounds are lipid soluble, rapidly absorbed, and can affect the nervous system. Organic tin compounds are used in the plastics industry and as disinfectants because of their fungicidal and insecticidal effects. Triethyltin (TET) made headlines in 1953/54 when the drug Stalinon, which contains the active agent diethyltin diiodide with 10% TET, caused 110 deaths in France (Alajouanine et al. 1958). The toxic dose for adults is estimated to be 70 mg of TET over a period of 8 days (Barnes and Stoner 1959).

Pathogenesis. TET-sulfate has a high affinity for myelin (Lock and Aldridge 1975). It has a toxic effect on mitochondria, uncoupling oxidative phosphorylation through inhibition of mitochondrial adenosine triphosphatase (ATPase) (Doctor and Fox 1983).

Clinical Features. Stalinon poisoning produced the following clinical features: dizziness, vomiting, headache, photophobia, and visual impairment as well as cerebral seizures, sensory disturbances, and loss of sphincter control. Death occurred after 4–10 days.

Morphology. The morphological hallmark of Stalinon poisoning was a pronounced cerebral edema with signs of increased intracranial pressure and herniation. Histologically, the sole finding was an edema of the white matter with spongiform degeneration which spared most axons (Cossa et al. 1958; Gruner 1958).

17.1.12.2 Trimethyltin

Source. Only a few cases of trimethyltin intoxication have been described (Besser et al. 1987). The main symptom was a deep depression, emotional disturbance, forgetfulness, and loss of libido (Ross et al. 1981).

Morphology. The morphological picture was characterized by swollen nerve cells with eccentric, sometimes pyknotic, nuclei and loss of the Nissl substance with cytoplasmic inclusions in the amygdaloid nucleus, in the temporal cortex, basal ganglia and the pontine nuclei (Besser et al. 1987).

17.2 Non-Metallic Inorganic Neurotoxins

17.2.1 Phosphorus (P) and Phosphorous Compounds

Source. Today so-called *white (yellow) phosphorus* is only used industrially as an intermediate product in the manufacture of incendiary bombs, etc. Poisoning occurs almost exclusively in suicides and homicides. Because white phosphorus is easily oxidized and fat soluble, it easily penetrates into the cell interior, where it impairs oxidative metabolism. The liver is the main target organ. *Phosphine* is a hydrogen compound of phosphorus (PH_3) used as a pesticide.

The *clinical picture* of phosphorus poisoning is dominated by gastrointestinal irritation with vomiting of luminescent stomach contents. After an interval of 2–3 days, a syndrome may ensue affecting the liver and kidneys (jaundice, uremia), as well as the CNS (stupor, delirium). *Morphological changes* in the CNS correspond to status spongiosus (spongiform encephalopathy).

17.2.2 Sulfur (S)

17.2.2.1 Carbon Disulfide

Source. Carbon disulfide poisoning usually occurs in the handling of rubber and cellulose fibers. It primarily affects the nervous and cardiovascular systems. The main *clinical features* include sensory neuropathy, followed by motor weakness of distal extremities. In rare instances, acute psychosis may develop as well as neurological deficits in the sense of extrapyramidal disturbances of the Parkinsonian type (Peters et al. 1988).

Morphology. The few cases described were characterized by disseminated neuronal degeneration in the cerebral cortex, basal ganglia, and cerebellum. Gliosis and demyelination of the spinal cord were also observed (Alpers and Lewy 1940).

17.2.3 Tellurium (Te)

Source. Tellurium is related to selenium and sulfur and is used in industry, where exposure occurs by inhalation of vapor containing Te. At one time, Te was used to treat leprosy, syphilis, etc.

Clinically, gastrointestinal changes, headache, fatigue, and nausea predominate. A black discoloration of the exposed areas of the skin is a conspicuous sign.

The *brain* tends to contain lower amounts of Te than other organs. Animal experiments have demonstrated severe neurotoxic properties. In humans, peripheral neuropathies (Lampert et al. 1970) and neuronal lipofuscinosis (Duckett and White 1974) have been described.

17.3 Gases

17.3.1 Carbon Monoxide (CO)

Source. Carbon monoxide (CO) is a colorless, odorless stable gas with a density similar to that of air. CO diffuses rapidly across the alveolar capillary membrane and binds tightly to iron centers in hemoglobin and other heme proteins such as myoglobin. CO is an insidious byproduct of incomplete combustion of carbonaceous substances such as coal and gas and is generated in toxic amounts by internal combustion engines, fossil-fuel furnaces, and fires. Most instances of CO poisoning are accidental, but some result from attempted suicide (introduction of engine exhaust into the interior of the car). About 800 deaths of CO intoxication are reported in the United States per year (Ernst and Zibrak 1998; Weaver 1999). Today, most municipal gas supplied contains no CO and cannot cause death by carbon monoxide poisoning, but in isolated cases as a result of hypoxia/ischemia.

Pathogenesis. (For review see Bour et al. 1967; Pankow 1981; Plantadosi 2002.) CO has indirect and direct effects on brain:

1. *Indirect effects* include hypotension due to pump failure of the heart: the circulation (also the brain circulation) is vasodilated by a vasodilatory effect of CO.
2. Moreover an effective anemia occurs because CO causes a competitive inhibition of oxygen transport: the affinity of CO for hemoglobin is 200–250 times that of oxygen. Thus, it readily combines with hemoglobin to form carboxyhemoglobin (CO-Hb). The normal CO-Hb level is 1–3%. Cigarette smokers increase their CO-Hb level by an average of 5% per pack smoked per day, and otherwise healthy smokers tolerate CO-Hb levels of 10% without having symptoms. Blood saturation with CO-Hb of 60–70% is invariably lethal. This causes an oxygen deficiency

in the heart and brain (Coburn and Forman 1987) with formation of cytotoxic brain edema. The globus pallidus is especially vulnerable (Song et al. 1983), but this can also be seen in cardiac arrest without CO (Garcia 1988).

This functional anemia induced by CO displacement of O_2 from the hemoglobin molecule would normally cause a hyperdynamic circulation, as seen in the cardiac compensatory mechanism to anemia. However, CO directly depresses myocardial function, obviating the possibility for a fully hyperdynamic systemic circulation, with high blood pressure. The brain circulation is vasodilated (Komuro et al. 2001) by even 2000 ppm CO (Mendelman et al. 2002) or smaller amounts, as in smoking (Boyajian and Otis 2000). The vasodilatory effect of CO is expected in view of its role, analogous to NO, in regulating cerebral blood flow (CBF). Indeed, in epilepsy, CO (produced by heme oxygenase) regulates CBF (Montécot et al. 1998).

Hypotension is the rule during CO poisoning, in spite of the expected cardiostimulatory effect of the functional anemia. The fall in blood pressure is due to depression of myocardial function by CO. This may lead to global cerebral ischemia with its anatomical distribution of necrosis within the brain (see above). To the extent that CO has the capability of inducing true histotoxic hypoxia (see below), one can attempt to distinguish the features within the brain due to global ischemia from those due to direct histotoxicity subsequent to CO poisoning. The distinction is problematical, however, because of the capacity for global ischemia to cause, on occasion, symmetrical globus pallidus necrosis (Garcia 1988) as is also seen, more characteristically, in CO poisoning.

3. In addition to indirect injury caused by the oxygen deficiency and global ischemia, CO has a *direct toxic effect* (Ernst and Zibrak 1998), which explains the clinical and morphological changes, above all in cases of intermittent exposure and/or a chronic course (for review see Oehmichen 2000). The true histotoxic effect obviously is due to the high affinity of CO to iron-containing structures, i.e., hemoglobin, as well as to the globus pallidus and pars reticulata of the substantia nigra. Reperfusion injury is caused by CO dissolved in the plasma (Yamada et al. 1986). CO causes a degradation of unsaturated fatty acids, which accounts for the demyelination of the white matter of the brain (Thom 1990); CO also causes oxidative stress to the cells with increased production of oxygen radicals (Thom 1992; Zhang and Piantadosi 1992).

Moreover, cyanide, sulfide, azide, and other agents do not have this histotoxicity in spite of being potent inhibitors of mitochondrial energy production. It is likely that transient binding to cytochromes is insufficient to cause CNS necrosis. But the inhibition of function naturally leads to apnea and immediate death. However, necrosis likely arises from a more prolonged binding with high affinity, as seen in CO poisoning.

CO is attracted to two nuclei within the brain which have a high heme iron content: the globus pallidus and the pars reticulata of the substantia nigra. These two nuclei, in spite of being anatomically distinct and somewhat removed from one another, should be considered as one for several reasons.

- They arise from a single embryologic nucleus which migrates upward to form the globus pallidus and downward to lie on the peduncular site of the substantia nigra pars compacta (the dopamine-rich portion of the substantia nigra involved in Parkinsonism). A few scattered neurons, termed the fields of Sano, contain large amounts of iron and are disseminated between the pars reticulata and the globus pallidus.
- The cytology of these two nuclei is quite similar, consisting of pauci-neuronal tissue with abundant neuropil. This is reflected in the name pars reticulata, denoting the reticular nervous tissue portion of the substantia nigra. In the globus pallidus, neuronal density is further reduced and diluted by interlacing and intersecting bundles of white matter which cross the globus pallidus. However, the gray matter component of the substantia nigra pars reticulata and of the globus pallidus is identical, consisting of iron-rich neurons. In fact, the highest concentration of iron within the brain is in the globus pallidus and the pars reticulata of the substantia nigra.
- The globus pallidus and the pars reticulata of the substantia nigra are both susceptible to the same series of human and experimental diseases. For example, in Hallervorden–Spatz disease (neuraxonal dystrophy) there is accumulation of iron in both structures. In experimental epilepsy, the rodent brain demonstrates hypermetabolic necrosis in both structures (Folbergrová et al. 1985; Ingvar et al. 1987). The globus pallidus suffers less hypermetabolic necrosis in this condition than the substantia nigra due to the dilution of its neuropil metabolism by the traversing white matter bundles, mitigating the metabolic rate increase and concomitant acidosis that occurs during hypermetabolism in that structure.

Although hypoxia alone cannot cause brain necrosis in an organism with an intact, beating heart, hypoxia does exacerbate ischemic brain damage (Miyamoto and Auer 2000; see pp. 275 ff). Anemia alone likewise does not cause brain damage. However, it is quite possible that the functional anemia accompa-

Table 17.1. The relationship between atmospheric concentration of carbon monoxide and clinical effect. Source: Davies 1991

Atmospheric carbon monoxide (%)	Clinical features
0.04	Nausea after 1–2 h
	Collapse after 2 h
	Death after 3–4 h
0.1	Difficulty in movement
	Death after 2 h
0.2	Death after 45 min
0.3	Death after 30 min
0.5	Rapid collapse
	Unconsciousness and death within a few minutes

nying CO poisoning exacerbates the global ischemic brain damage due to cardiac failure. Superimposed upon these two interacting factors is the true, direct histotoxicity of CO on nervous tissue, due to the high and prolonged binding of CO to heme iron. It is thus the tight CO binding to heme iron, whether it be on heme iron in hemoglobin or heme iron in the mitochondrial cytochrome systems, that causes the complex pathophysiological picture of CO poisoning.

17.3.1.1 Acute Intoxication

Clinical Features. The clinical picture of CO poisoning depends on the percentage of CO-Hb. Symptoms may range from headache (CO-Hb: 20%) and dizziness to nausea and stupor (CO-Hb: 30%) or unconsciousness (see Table 17.1). Cognitive sequelae lasting 1 month (Thom et al. 1995) or more (Weaver 1999) appear to occur in 25–50% of patients with loss of consciousness or with CO-Hb levels >25%. Incapacitation – which obviously increases the danger of continued exposure leading to death – usually occurs acutely at CO-Hb levels of 30–40%. Death is due to central respiratory and circulatory arrest (Geldmacher von Mallinckrodt 1975). The recommended treatment for acute CO poisoning is 100% normobaric oxygen, but meanwhile Weaver et al. (2002) have demonstrated that hyperbaric-oxygen therapy at 304 kPa (3 atm) absolute is superior to normobaric-oxygen therapy in reducing the incidence of delayed cognitive dysfunction at 6 weeks and 12 months after acute CO poisoning (see Hampson et al. 2001). The diagnosis is confirmed by measurement of blood CO-Hb.

A delayed neurologic deterioration is usually termed "talk and die" in the consideration of death after incidence of cerebral trauma (p. 472). However, a similar phenomenon of delayed death can occur after cardiac arrest, and especially after CO poisoning (Plum et al. 1962; Maxeiner 1987; Opeskin and Drummer 1994). The cause, as has long been known, is delayed white matter deterioration (Grinker 1925; Lapresle and Fardeau 1967; Salama et al. 1986). Obviously CO poisoning in these cases also causes adduct formation between myelin basic protein (MBP) and malonylaldehyde, a reactive product of lipid peroxidation, resulting in an immunological cascade (Thom et al. 2004). MBP loses its normal cationic characteristics, and antibody recognition of MBP is altered. Immunohistochemical evidence of degraded MBP occurs in brain over days, along with influx of macrophages and CD4 lymphocytes. Lymphocytes from CO-poisoned rats subsequently exhibit an autoreactive proliferative response to MBP, and there is a significant increase in the number of activated microglia in the brain. These results demonstrate that delayed CO-mediated neuropathology is linked to an adaptive immunological response to chemically modified MBP.

Morphology. If death is sudden, the sole macroscopically conspicuous feature is a bright redness of the blood and of brain sections at autopsy (Fig. 17.3a) – even after fixation in formalin (Fig. 17.3b, c). In rare cases with massive congestion, extravasation can also occur. If the acute poisoning is survived, changes occur which resemble those seen in global ischemia: laminar cortical necroses, nerve cell loss in the hippocampal formation, Purkinje cell loss, and white matter necrosis. A bilateral necrosis of the globus pallidus (Fig. 17.3d) and the pars reticulata of the substantia nigra are known as non-specific alterations. [For further details of the pallidal necrosis see Pankratz et al. (1988).] White matter deterioration in

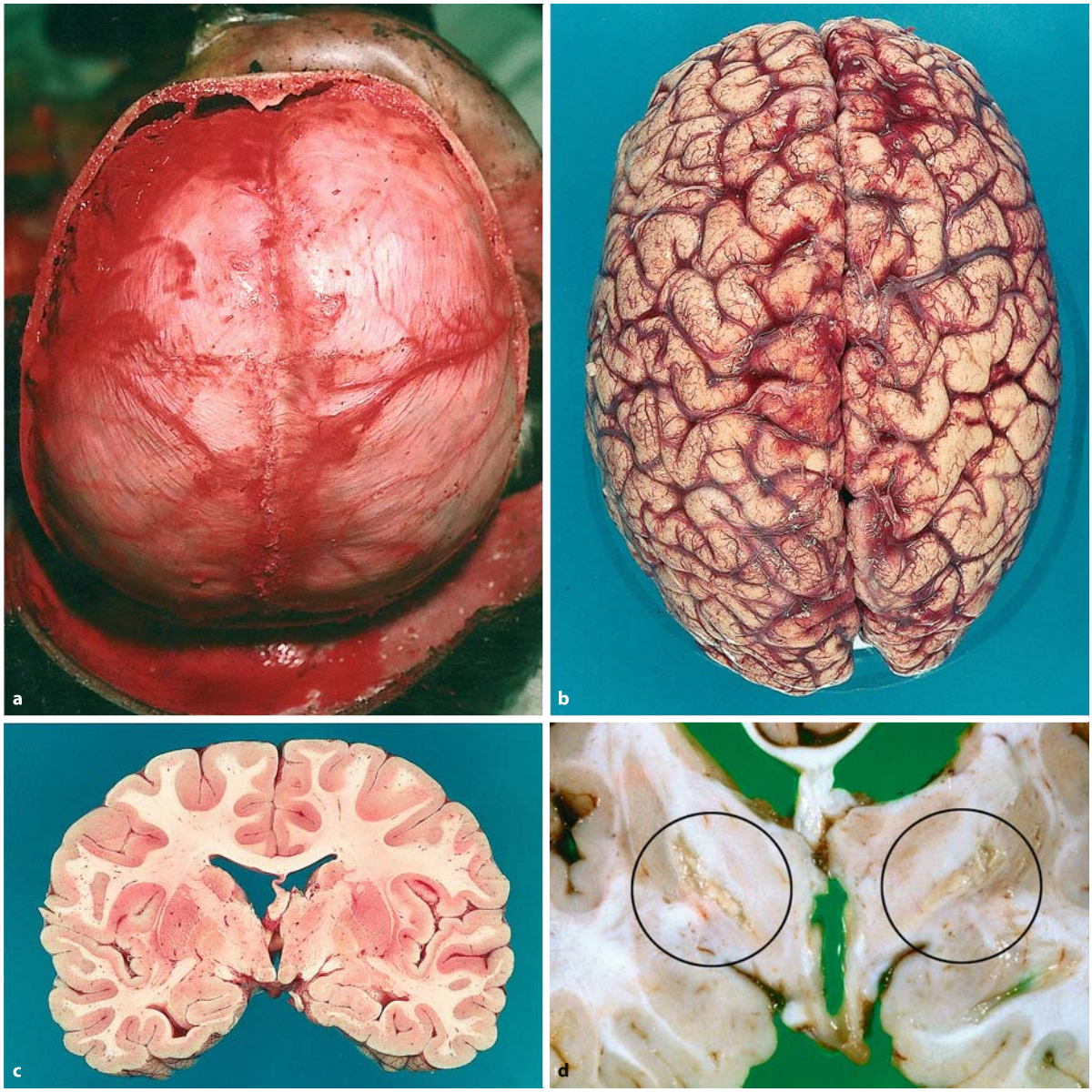

Fig. 17.3a–d. Carbon monoxide poisoning. Acute intoxication: bright redness of the dura (**a**) at autopsy and of the brain surface after formalin fixation (**b**) associated with brain swelling and (**c**) redness of the frontal section. Chronic intoxication: bilateral pallidal necrosis as demonstrated by *circles* (**d**)

the sensed multifocal leukoencephalopathy (see also Sect. 17.3.1.2) are the morphological sequelae of a delayed feature of CO poisoning.

17.3.1.2 Intermittent Exposure

Clinical Features. A coma lasting days or weeks in the first phase of illness may be followed by increasing clarity of consciousness. The second phase begins after 10–30 days with signs of progressive encephalopathy including dementia, akinesia and rigidity, and finally coma.

Morphology. The morphologic picture is characterized by confluent foci of demyelination with swelling of oligodendrocytes and proliferation of astrocytes. The demyelination with its patchy distribution and indistinct borders resembles the pattern of *multifocal leukoencephalopathy*; there is a continuous spectrum up to complete demyelination ("Grinkers' disease" or "Grinker's myelinopathy"). White matter edema is accompanied by a drop in blood pressure and increased acidosis (Brucher 1966).

Table 17.2. The relationship between atmospheric concentration of hydrogen cyanide and clinical effect. Source: Davies 1991

Hydrogen cyanide (%)	Clinical feature
0.004–0.005	Tolerated for 0.5–1 h
0.011–0.013	Death after 0.5–1 h
0.018	Death after 10 min
0.028	Immediate death

17.3.1.3 Chronic Intoxication

Clinical Features. Low levels of CO exposure can cause headache and nausea. The marked affinity of CO for Hb plus the resultant reduced expiration of CO results in an accumulation of CO-Hb in the blood, which over a period of days or weeks can produce all of the symptoms of acute intoxication and, if unchecked, lead to death.

Morphology. The aforementioned hypotensive hypoxic and ischemic necrosis and white matter injuries predominate.

17.3.2 Cyanides and Cyanide Compounds

Source. Deaths due to acute cyanide poisoning are relatively rare, largely owing to the restricted availability of cyanide. Nevertheless, cyanide is one of the most rapidly acting poisons known and is encountered today in cases of suicide or intentional killing (e.g., euthanasia/assisted suicide – Fernando and Busuttil 1991; Cina et al. 1994; for review see Musshoff et al. 2002). Chronic poisoning from ingestion of fruit seeds or plants containing cyanide, e.g., almonds, is rare. Of major importance is the occurrence of prussic acid in gas produced by the combustion of nitrogen-containing plastics (polyurethane, polyacrylnitrite, synthetic fibers, e.g., artificial wool or silk), which can cause mixed poisonings with CO. A few victims of acute poisoning have survived due to intensive medical measures.

The lethal cyanide dose is relatively small and, because death is usually immediate, attempts at medical intervention are nearly always futile. The minimal lethal dose of hydrogen cyanide is 100 mg; for sodium cyanide 150 mg and potassium cyanide 200 mg (Baselt and Cravey 1995); bitter almonds: 70 nuts for adults, 6–7 nuts for children. Hydrogen cyanide (HCN) and its salts are characterized by the smell of *bitter almonds*.

Pathogenesis. Cyanide is readily soluble in lipids and diffuses rapidly. It binds to the Fe^{3+} in the heme group of *cytochrome oxidase* and thereby *inhibits cellular utilization of oxygen*. This results in histotoxic anoxia at the cellular level; i.e.,"internal" suffocation and energy failure associated with lactate production and severe metabolic acidosis (Hall and Rumack 1986; Borron and Baud 1996; Musshoff et al. 2002). Central suppression of respiration is thought to result from changes in neuronal excitability (Greer and Carter 1995). However, hypotension due to heart pump failure is a critical and necessary determinant of brain necrosis, since structural brain damage is absent without ischemia, and direct necrotizing CNS histotoxicity seems not to occur (MacMillan 1989).

Clinical Features. Cyanide intoxication is characterized by dose-dependent impairment of neurologic function, beginning with non-specific symptoms such as headache or dizziness at one end of the spectrum and convulsions and coma at the other. Coma and convulsions may develop within seconds. The reconstructive analysis of 27 cases of lethal poisoning with cyanide by Vock et al. (1999) revealed that some victims had the capacity to act, especially for 5–10 min, though most victims lost consciousness within a few seconds to 1–2 min. Cardiac arrest follows, depending on the concentration, almost immediately with all the discrete signs of suffocation (Table 17.2). The diagnosis commonly is made by toxicological examination. Cyanide levels in serum >2.5 mg/l are associated with coma and are fatal without treatment. However, cyanide is unstable in blood and therefore cyanide levels may drop as a result of degradation into less toxic components if the postmortem interval before autopsy (and the storage time of blood until examination) is too long (Ballantyne et al. 1974; Musshoff et al. 2002).

Morphology. The morphology of acute lethal cyanide poisoning (see also p. 279) is similar to CO poisoning, but generally without the marked pallidal vulnerability due to CO binding of Fe. It cannot be distinguished from global ischemia, and is characterized by massive congestion, sometimes with perivascular and subarachnoid bleeding. Instances of long survival times, which are very rare, exhibit Purkinje cell loss, gliosis of the cerebral cortex, disseminated petechial bleeding, circumscribed white matter necrosis, and as can be seen in cardiac hypotension associated with critical illness (Burger and Vogel 1977) bilateral necrosis of the globus pallidus (Ule and Pribilla 1962; Kim et al. 1982).

Prolonged *cyanide poisoning* is accompanied by striatal degeneration with Parkinsonism and dystonia, which might also result from a glutamate-mediated neurotoxic effect comparable to that associated with CO (Spencer 1999).

17.3.3 Hydrogen Sulfide (H_2S)

Source. Hydrogen sulfide (see p. 279) is a colorless, combustible, heavier than air gas, which smells like rotten eggs. It is potentially explosive if mixed with oxygen. It can be encountered in volcanic areas, in "sour gas" wells, and artificially in the manufacture of hydrochloric and sulfuric acids. It is also emitted by furnaces. Being a by-product of decomposition of human, animal or plant organic matter, it is found in sewers (Adelson and Sunshine 1966). Hydrogen sulfide gas is usually inhaled, although experimentally Na_2S intravenous injection gives rise to a similar picture, without the pulmonary histotoxicity (Baldelli et al. 1993).

Pathogenesis. The mechanism underlying the toxicity of H_2S is similar to cyanide, with even tighter binding of the sulfide anion to cytochromes. This explains how it inhibits intracellular respiration (Geldmacher von Mallinckrodt 1975).

Clinical Features. The first clinical symptoms are reactions of the mucous membranes, followed by headache, dizziness, ataxia, respiratory distress, a drop in blood pressure, convulsions, loss of consciousness, and respiratory and cardiac arrest (Smith 1997). If the dose is very high, paralysis of olfactory nerves impedes smell and the ability to detect the telltale rotten egg smell. The associated sudden respiratory arrest that occurs within seconds or minutes, so called knockdown, thus results in continued, lethal exposure. Often, those attempting rescue and removal of the poisoned individual become overcome themselves, starting a chain reaction of victims.

Morphology. Morphologically, acute cases (Osetowska 1971) of hydrogen sulfide poisoning exhibit congestion and edema; in cases with longer periods of survival, the morphological picture includes signs of generalized hypoxic ischemia (Tvedt et al. 1991) and changes associated with intravital brain death (Bersch et al. 1974; Snyder et al. 1995). Physiologically controlled experiments in animals show that, as in cyanide poisoning, inhibition of heart pumping action and severe hypotension are critical, necessary prerequisites of brain necrosis (Baldelli et al. 1993).

17.3.4 Nitrous Gases and Nitrites

Source and Clinical Features. Nitrous gases are produced by heating nitric acid or by the combination of nitric acid with metals or organic substances, during welding, for example. NO_2 and N_2O_4 chiefly affect the respiratory passages and can cause pulmonary edema leading to death. *Inhalation*, for example of nitrous oxide (N_2O) as an anesthetic, can cause methemoglobin, respiratory distress, cyanosis, vomiting, dizziness, and falling blood pressure resembling the symptoms induced by nitrite poisoning. *Nitrite*, especially *sodium nitrite*, is used in the dye industry. Sodium nitrite gives color to stored meat. Spinach contains nitrate, which can transform into nitrite. Children are especially at risk.

Pathogenesis. Oxidation of the Fe^{2+} in hemoglobin to Fe^{3+} (methemoglobin) results in an inadequate oxygen transport capacity of the blood that causes central cyanosis.

Morphology. Morphologically, both nitrifying gas and nitrite intoxication produce the sequelae of oxygen deficiency. In a few instances, *purpura cerebri* has been described.

17.3.5 Oxygen (O_2)

Source. Pulmonary changes caused by high oxygen pressure have long been known, and nervous system effects were first described in the late 1800s by Paul Bert. Changes are seen in neonates, deep-sea divers, with decompression sickness and in the treatment of *Clostridium* infection. They have also been described within the context of the US space program (Balentine 1982).

Clinically, the syndrome of oxygen toxicity is dominated by convulsions, which can sometimes be fatal. *Morphologically*, the picture is non-specific. Necrosis has not been found in humans, although in animal studies it has been shown to result from

a toxic effect on enzymes of cellular respiration in various organelles as well as cell membranes (Balentine 1982).

17.4 Industrial and Environmental Toxins

17.4.1 Acrylamide

Source. Acrylamide is used industrially in the manufacture of paper, fibers, and dyes. It is a cumulative neurotoxin; i.e., symptoms only occur when threshold values have been exceeded. The *clinical symptoms* correspond to peripheral neuropathy (acrylamide neuropathy), which begins with reversible paresthesia, followed by motor weakness and, possibly, ataxia (Spencer and Schaumburg 1974; Kesson et al. 1977).

Morphology. Axons in the peripheral nervous system are the most affected, but axons in the CNS may be involved as well: there is axonal degeneration in the gracile nucleus (Schaumburg et al. 1989) as well as progressive degeneration of Purkinje cell dendrites in cerebellar cortex (Lehning et al. 2002). Distal swelling and eventual degeneration of axons in the CNS and PNS are the characteristic morphological features. Based on accumulating evidence, LoPachin and his team (2003b) have demonstrated that nerve terminals, and not axons, are the primary site of acrylamide action and that compromise of corresponding function is responsible for the autonomic, sensory, and motor defects that accompany acrylamide intoxication. Substantial evidence, therefore, indicates that axon degeneration is a secondary effect (LoPachin et al. 2003a, b).

17.4.2 Aliphatic Hydrocarbons

Source. Aliphatic hydrocarbons are used as solvents in the glue and mineral oil industries. *N-Hexane* and *methyl-n-butyl ketone (MBK)* are especially neurotoxic. Poisonings occur by oral ingestion (children) and glue sniffing. In the latter, the liquid glue or solvent is typically poured into a plastic bag and inhaled to achieve a psychotropic effect. Acute exposure is associated with dizziness, signs of sedation and irritation, narcosis, and euphoria. During inhalation, death can occur from suffocation and acute cardiac arrhythmia.

Pathogenesis. The solvent can cause *axonal injury*, which via a "dying back" mechanism gives rise to symptoms primarily of the peripheral nervous system (McLean et al. 1980). *Morphologically* ascending axonopathies have been described.

17.4.3 Halogenated Hydrocarbons

Source. Halogenated hydrocarbons are used as solvents and cooling agents, chiefly in the plastics industry. They are incorporated via the respiratory tract and because they are lipid soluble, they also can cross the blood–brain barrier.

17.4.3.1 Methyl Chloride

Source. Methyl chloride (chloromethane) is a colorless gas used mainly as a coolant for domestic and commercial refrigeration units. *Clinically*, acute poisoning begins with headache, nausea, vomiting, dizziness, tremors, and weakness followed by convulsions, coma, and death (Thomas 1960). Chronic intoxication leads to somnolence and signs of extrapyramidal system defects and to polyneuropathies.

Morphology. Necrosis is seen in the inner granule cell layer of the cerebellum, as well as axon torpedoes in the same layer and in the Purkinje cell layer. The nerve cells of the dorsal horns of the spinal cord are characterized by marked chromatolysis and vacuolation. The nerve cells of both the posterior and anterior horns of the spinal cord contain argentophilic deposits. Signs of neuroaxonal dystrophy are invariably present (Thomas 1960; Kolkmann and Volk 1976).

17.4.3.2 Trichloroethylene

Trichloroethylene is *used* as an industrial solvent and degreasing agent as well as a narcotic by sniffers, which is also true of toluene. *Clinically*, a cranial neuropathy develops with impaired coordination in the form of ataxia and dysarthria (Baker 1958; Malm and Lying-Tunell 1980) as well as dysphagia and trigeminal anesthesia (Lawrence and Partyka 1981). Vasomotor and gastrointestinal disturbances develop in some cases. *Morphological* findings have been shown only with neuroimaging techniques described as cerebral atrophy (Juntunen et al. 1980).

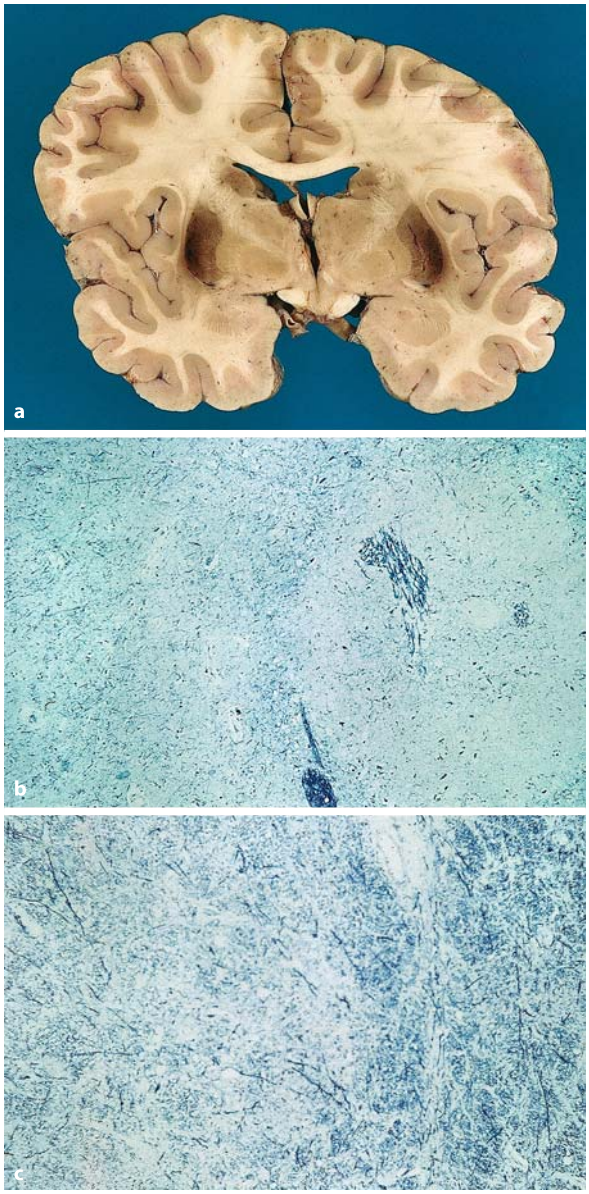

Fig. 17.4a–c. Methanol intoxication. **a** Symmetrical putamen necrosis and intense demyelination with cystic changes (**b**) are characteristic due to direct neuronal toxicity and secondary demyelination (**c**). (**b, c** Luxol fast blue; magnification **b** ×100, **c** ×300)

17.4.4 Chlorinated Cyclic Hydrocarbons

17.4.4.1 Hexachlorophene (HCP)

Hexachlorophene is used because of its *bactericidal effect* (antimicrobial agent) as a *preservative in cosmetics and soaps*. Hexachlorophene has a toxic effect on the myelin sheaths and leads to a *vacuolar encephalopathy* (Powell et al. 1973; Marinez et al. 1974; Shuman et al. 1974) with extensive vacuolar degeneration in the white matter of the cerebrum and cerebellum (Mullick 1973). Severe granule cell necrosis also occurs in the cerebellum with proliferation of Bergmann glia and degeneration of dendritic spines (Diemer 1976). The changes caused by *thiophene intoxication* are similar (Herndon 1968). There is a splitting of the myelin sheaths and spongy changes in the cerebral white matter, chiefly subependymally, and in the cerebellar white matter. A spongy alteration has been described in the white matter of the pons and medulla oblongata as well (Tripier et al. 1981). Differential diagnosis must include triethyltin poisoning. Premature and newborn infants with desquamative skin changes are especially affected. It is unclear whether hexachlorophene itself can cause death, since infants so treated are already at particular risk due to their immaturity (Powell and Lampert 1977).

17.4.4.2 Lindane

Lindane (γ-hexachlorocyclohexane = HCH) is primarily an *insecticide*. In medicine, it is applied externally to treat *scabies* and *pediculosis*. Overdose – both by massive cutaneous resorption and oral ingestion – can cause acute intoxication with *mydriasis*, *hyperglycemia*, *cyanosis*, *respiratory distress* as well as clouding of *consciousness*, *generalized seizures*, and *cardiac arrest*. Chronic intoxication leads to *neuropsychiatric deficits*. *Morphologically*, the picture includes among other things extensive *necrosis of the small blood vessels* in the lungs, kidneys, and brain (Velvart and Moeschlin 1980).

17.4.5 Methyl Alcohol (Methanol)

Source. Methyl alcohol is a colorless, combustible liquid that smells somewhat like spirit of wine and has a not unpleasant taste. It is used as *antifreeze in the cooling systems of gasoline engines*, and as a *solvent for paints*, *glues*, *cleaning agents*, etc. Methyl alcohol is ingested because it is mistaken for ethanol or as an additive to home-distilled spirits. During the prohibition era in the United States, methyl alcohol was used as an alcohol substitute. Inhalation and percutaneous application have also been described. Doses as low as 10 ml can cause severe intoxication, 30–100 ml can be lethal.

Morphology. The morphology of the affected brain is characterized by two kinds of changes, symmetrical necroses characteristic of methanol, and nonspecific diffuse or disseminated findings. The latter

include hyperemia and edema (Schmidt 1946; Orthner 1949), with perivascular hemorrhagic necrosis, and (hemorrhagic) leukoencephalopathy (Fig. 17.4) (Menne 1938; Henze et al. 1986; Phang et al. 1988). Although selective vulnerability exists in almost all neuropathological conditions, methanol is a striking example of the principle that a generalized insult, in this case a circulating toxin that reaches all CNS tissue via the blood, nevertheless causes damage in highly specific regions. Intriguingly specific to methanol, if death occurs slowly, the bilateral necroses are seen in three regions of the CNS. *First*, there is necrosis of the putamen (Fig. 17.4a) with late cystic changes (Erlanson et al. 1965); and *second*, there is visual damage and retinal ganglion cell necrosis, which was long thought to be due to direct ganglion cell toxicity in the retina (McLean et al. 1980). But methanol blindness is now known to be due to symmetrical areas of softening in the retro-orbital portion of the optic nerve. The nerve cell destruction in the retinal ganglion cell layer is thus merely secondary to the axonal destruction in the optic nerve (Sharpe et al. 1982), as are changes in the lateral geniculate body, the white matter, and spinal cord (Kolkmann and Volk 1976). A *third* area of symmetrical necrosis in addition to the optic nerves and putamena is the pontine tegmentum, visible on MR imaging as well as neuropathologically (Gaul et al. 1995). Why methanol should cause symmetrical necrosis in these three regions of the CNS remains a mystery, but its NMDA antagonist properties (Lovinger et al. 1989) seem not to correlate and thus cannot explain the remarkable regional localization of brain damage due to methanol.

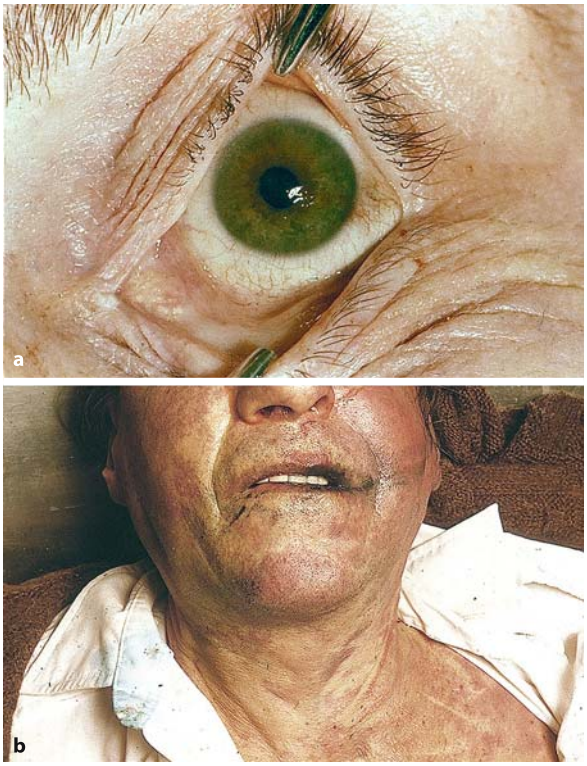

Fig. 17.5a, b. Parathion intoxication. The clinical feature and autopsy findings are commonly characterized by an extreme myosis (**a**) and/or blue-colored stain around the mouth on the clothes (**b**)

17.4.6 Organophosphorus Compounds

Source. Phosphate esters are used as *pesticides*. Poisonings are generally either accidental or suicidal, and are rarely associated with homicide. This large family of compounds have also been used militarily as nerve agents.

Pathogenesis. Phosphate esters of different types are potent inhibitors of cholinesterase and acetyl cholinesterase, some acting directly (dichlorvos), others indirectly. Parathion (E 605), for example, is metabolized in the body to paraoxon (E 600), which is toxic, whereas parathion itself is not (Reiner and Lotti 1993). Organophosphate insecticide has been shown to cause persistent impairment of cholinergic synaptic function (Slotkin et al. 2001), especially in the mammalian striatum.

Clinical Features. (For review see Murphy 1986; Lotti 2000.) Acute poisoning is characterized by anxiety, confusion, tremor, ataxia, coma, convulsions, muscular weakness, fasciculation, and respiratory depression. Further symptoms are miosis, salivation, abdominal cramps, and diarrhea. The symptoms occur within 10 min to 2 h; death is caused by central respiratory arrest. Small doses and less toxic agents cause an axonal neuropathy.

Morphology. At autopsy commonly an extreme miosis is conspicuous (Fig. 17.5a), and often a blue-colored stain – a warning color in parathion solutions – is visible around the mouth and/or on the clothes (Fig. 17.5b). In the brain, only hyperemia and edema are seen (Oehmichen et al. 1983). Histochemical detection of acetylcholinesterase allows demonstration of this enzyme's inhibition in the putamen (Fig. 17.6a, b), in muscles and in the myenteric plexus of the intestines (Fig. 17.6c, d; cf. Table 17.3) as could be demonstrated by Oehmichen and Besserer (1982). An inhibitory effect was dose-dependent (Table 17.3). An inhibition of non-specific esterase is also demonstrable in monocytes of the peripheral blood (Oehmichen et al. 1984). If intoxication is survived due, for example, to intensive medical therapy, the brain may exhibit signs of systemic circulatory collapse in the form of changes seen in global ischemia.

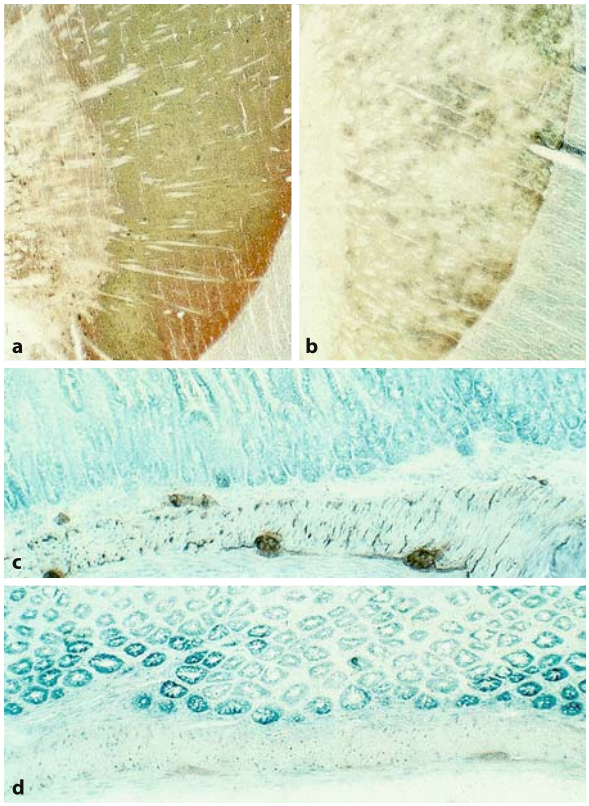

Fig. 17.6a–d. Parathion intoxication. In animal experiments (Oehmichen and Besserer 1982) reduced acetylcholinesterase activity is demonstrable in the putamen (**a** normal staining; **b** state after poisoning) and the myenteric plexus of the intestine (**c** normal activity, **d** state after poisoning) [**a–d** acetylcholine esterase histochemistry according to El-Badawi and Schenk (1967); magnification **a–d** ×100]

17.4.7 Toxic Oil

In the spring of 1981, Spain experienced an epidemic attributed to the consumption of rapeseed oil containing *oleyl-anilide* (Philen and Posada 1993). Symptoms included atypical pneumonia, myalgias, and eosinophilia. The clinical picture was dominated by neurological symptoms, mainly muscle weakness, peripheral neuropathy, and respiratory insufficiency.

Soldiers in France suffered poisoning when machine gun cooling oil was mistakenly used as cooking oil. The toxic agent was the extremely poisonous *tricresyl-phosphate*. Shortly after ingestion nausea, vomiting, diarrhea, and convulsions occurred. After 15–20 days, paralytic symptoms were noted, which subsequently increased before finally receding (*Neue Züricher Zeitung* 2000, July 29/30, p. 29).

Morphology. The early phase of intoxication is characterized by endomyseal inflammation of the skeletal musculature, and the infiltrates gradually but continually diminish. This is followed by severe fascicular neurogenic muscular atrophy with round cell infiltrates surrounding venules and capillaries. Biopsy samples of the sural nerve consistently show perineurial fibrosis. Focal loss or degeneration of individual axons is observed, as is an occasional myelin breakdown (Ricoy et al. 1983).

17.5 Nerve Agents

A number of chemical warfare agents were developed during the Second World War: in England *diisopropyl fluorophosphate (DFP)*, in Germany, *tabun*, which is 10 times as toxic. Since 1945, *sarin*, which is 5–10 times as toxic as tabun, has been developed (for review see Lee 2003) and more recently pinacolyl ester (*soman*), which is itself 5–10 times as toxic as sarin. All of these agents belong to the family of organophosphorus compounds (Schrader 1963). Absorption occurs via the skin and respiratory tract. *Clinically*, the first conspicuous symptoms are respiratory distress and miosis; these are followed by convulsions, which can transform into status epilepticus. These agents of chemical warfare are at present very difficult or even impossible to detect by chemical analytical techniques due to the extremely small concentrations in the body. But inhibition of cholinesterase is demonstrable, which explains the pathophysiological effect.

Sarin recently made world headlines when it was used in an attack by the Aum sect (1995) on the Tokyo subway, leaving 12 people dead. A gas attack in Matsumoto in 1994, which killed 4 people, was apparently carried out by the same sect (Okudera et al. 1997; Okumura et al. 1998; Yokoyama et al. 1998). Sarin was first used in war during the Iran–Iraq conflict in the 1980s (Brown and Brix 1998). Animal studies on the effectivity of sarin have recently been reported (Spencer et al. 2000). After intravenous application of sarin-like organophosphorus agents, the brain showed an increase in tyrosine phosphorylation of several proteins in the cytosol fraction as well as an activation of c-jun *N*-terminal kinase (JNK) and slight activation of mitogen-activated protein kinase (MAPK). The activation of these enzymes may be related to the high toxicity of these nerve agents.

Table 17.3. Dose dependence of the inhibitory effect of paraoxone and parathion on acetylcholinesterase activity in intestines, muscles, and brain. Experimental study in mice and semiquantitative analysis. Source: Oehmichen and Besserer 1982

Dose: mouse	Survival time (min)	AChE activity in:		
		Intestine	Muscle	Brain
Paraoxone				
0.2 mg/kg	15[a]	+++	++	++
	30[a]	+++	++	++
0.7 mg/kg	15[a]	+	+	+
	30[a]	+/–	++	+
	60[a]	+	+	–
1.4 mg/kg	15[b]	–	–	–
2.1 mg/kg	13[b]	+/–	+	–
Parathion				
1 g/kg	43[b]	–	++	+/–
5 g/kg	50[a]	–	+	–
10 g/kg	30[a]	–	+	–
20 g/kg	20[b]	–	+	–

[a] Result checked in two decapitated mice
[b] Died spontaneously

17.6 Drugs and Pharmaceutical Products

17.6.1 Sedatives, Hypnotics and Analgesics

The medications in this group (*barbiturates*, *benzodiazepines*, *bromine*, *methaqualone*, *pyrazolon derivatives*, *salicylic acid derivatives*, etc.) all affect the CNS, but they do not have a primary neurotoxic effect that causes morphological changes. They all, however, can induce secondary systemic hypoxia via a central respiratory paralysis, which, in turn, triggers morphological destruction of parts of the brain as a consequence of generalized cardiorespiratory failure. The detailed description of each of these neurotoxic agents is beyond the scope of this text, and, therefore, comments will be limited to a few representative substances.

The synthetic drug MPTP (*N*-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine) was developed in the 1970s. It is illegally combined with heroin for use as a narcotic. This drug can lead to a *Parkinson-like syndrome*, caused by drug-induced neuronal loss in the substantia nigra and in the striatum. MPTP is involved in the metabolism of catecholaminergic neurons. Inhibition of the monoamine oxidase B enzyme leads to the accumulation of a toxic metabolite, which is stored in the cell.

Phenytoin (diphenylhydantoin) is used today after decades as a successful anti-epileptic. *Clinically* chronic overdose induces tremor, ataxia, diplopia as well as dizziness and vomiting. These symptoms are reversible. *Morphologically* an overdose can lead to atrophy of the cerebellar cortex (Dam 1972) with depletion of Purkinje and granule cells plus gliosis in the molecular layer. *Pathogenetically* it was discussed for a long time whether the injury is caused by hypoxia-induced convulsions alone. Nowadays it is thought that diphenylhydantoin has a primary neurotoxic effect (Volk et al. 1986).

Tryptophan (Eosinophilic Myalgia). L-Tryptophan is applied to treat depression, sleep disorders, premenstrual syndrome, and in drug-withdrawal therapy. In 1989, it was reported to induce severe myalgia and eosinophilia together with numerous other symptoms (facial edema/swelling, sclerodermatitis-like skin changes, myopathy, pulmonary manifestations, etc. – Bulpitt et al. 1990). The predominant adverse effect however is a polyneuropathy.

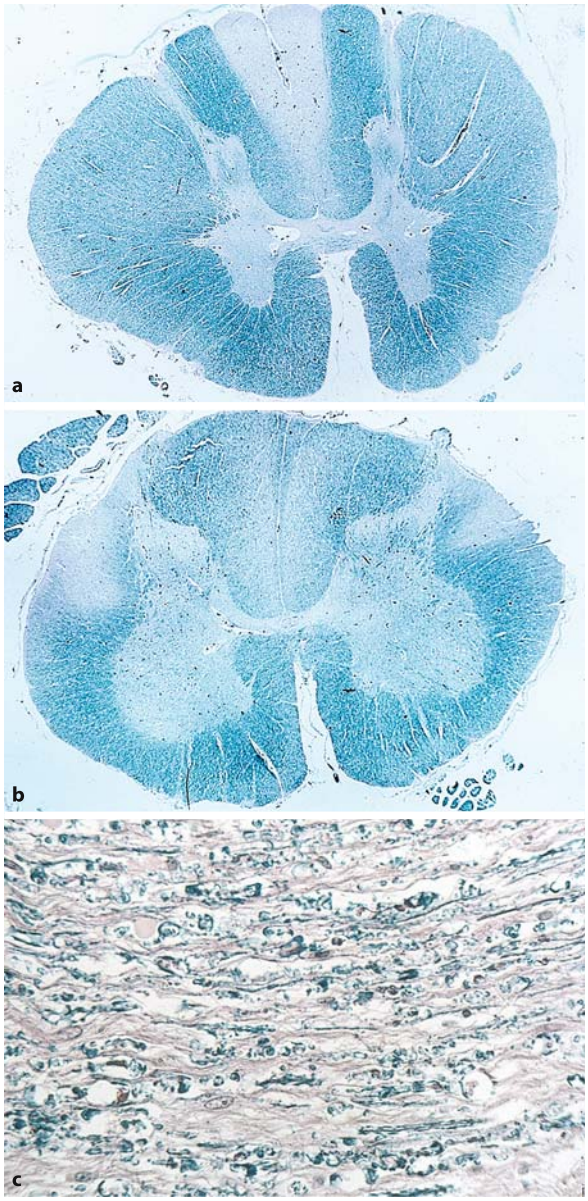

Fig. 17.7a–c. Clioquinol intoxication called subacute myelo-optic neuropathy (*SMON*). Chronic treatment of diarrhea by clioquinol leads to demyelination of the posterior white columns (**a**), the anterior and lateral funiculi of the spinal cord (**b**) and the optic nerve (**c**). (**a, b** Luxol fast blue; **c:** silver stain; magnification **a, b** ×50; **c** ×500). The figures were kindly provided by Professor Dr. Yoshio Narita, Tokyo

17.6.2 Antiprotozoal Agents

17.6.2.1 Chloroquine

Source. Drugs containing chloroquine (sulfate) are lysosomotropic and used for their anti-inflammatory effect in treatment of *rheumatoid arthritis* and for their antiprotozoal effect as *antimalarials*. Chloroquine's amphophilic nature gives it a membrane stabilizing effect. Chronic use however is associated with numerous side-effects – which chloroquine shares with other amphophilic substances, such as *tricyclic neuroleptics* (phenothiazines), *cholesterol synthesis inhibitors*, the appetite suppressant *chlorphentermine*, and the cardiovascular agent *perhexiline* (Klinghard 1976; Drenckhahn and Lüllmann-Rauch 1979) – such as skin changes, muscle degeneration, muscular dystrophy, and epileptiform convulsions.

Clinical Features. Retinopathy and polyneuropathy are sometimes seen. In acute intoxication, exogenous psychosis with the psychogenic symptoms – paranoia, aggressiveness, depression, confusion – are observed together with compulsive behavior and phobias. No deaths have been reported.

Morphology. The morphology is characterized by neurolipidosis. The nerve cells – mainly the spinal ganglia – contain membranous multilamellar bodies or lamellar or hexagonally arranged crystalloid inclusions (Klinghard 1976). The picture resembles GM_2 gangliosidosis and/or neurovisceral ceroid lipofuscinosis.

17.6.2.2 Clioquinol

Source. Clioquinol is used to treat *diarrhea caused by amoebae*, *lambliae*, and *shigellosae*. In Japan, chronic use in the treatment of diarrhea induced signs of a *subacute myelo-optic neuropathy syndrome (SMON)* (Mamoli et al. 1975; Shigematsu and Yanagawa 1978). This disease occurred in epidemic proportions.

Clinical Features. The most salient symptoms are reduced vision, spinal ataxia, signs of a pyramidal tract lesion and sensorimotor deficits, together with bladder insufficiency.

Pathogenesis. There is a distal axonopathy confined to the CNS (Schaumburg and Spencer 1980) thought to be caused by impaired axonal transport (Thomas et al. 1984).

Morphology. The morphological picture is dominated by edematous alterations in the cerebrum and cerebellum with gliosis. Foci of demyelination are evident in the optic nerve, the posterior white columns as well as in the anterior and lateral funiculi of the spinal cord (Fig. 17.7).

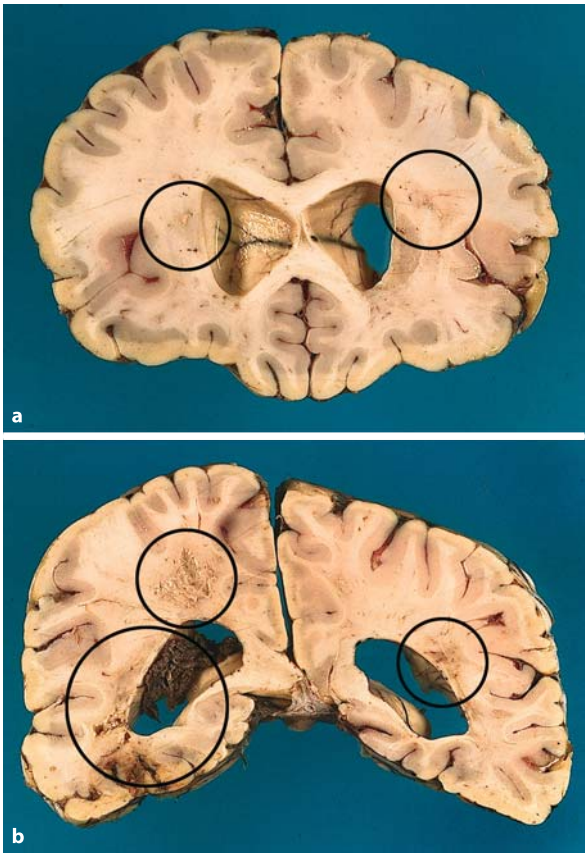

Fig. 17.8a, b. Necrotizing leukoencephalopathy, as a morphologic marker of an intrathecal methotrexate application

17.6.3 Cytostatics and Antituberculous Agents

Many cytostatic agents, such as cyclohexyl-1-nitrosourea (CCNU) or bischloroethyl nitrosourea (BCNU) as well as selected antituberculous agents, for example isoniazid, can cause CNS injury by a vascular mechanism (Omojola et al. 1982) but we concentrate here on agents damaging the brain by a mechanism directly acting on the nervous parenchyma.

17.6.3.1 Methotrexate

Source. Methotrexate is a folic acid antagonist used as a cytostatic, especially in the treatment of leukemias. For this purpose, methotrexate is applied intrathecally in combination with cranial and craniospinal radiotherapy. This combined treatment can cause neuronal injury. Intravenous application of methotrexate alone has a neurotoxic effect in sufficiently high doses.

Clinical Features. The following clinical features have been described: acute myelopathy, subacute myelopathy and chronic leukoencephalopathy. Acute signs of transient confusion, lethargy, and headache have also been reported. Chronic administration may induce fatigue, irritability, ataxia, and confusion. Spasticity has also been occasionally observed.

Morphology. Intrathecal or intraventricular methotrexate treatment is known to cause a necrotizing leukoencephalopathy located mainly periventricularly, but which also occurs multifocally with coagulation necrosis (Shapiro et al. 1973) and axon swelling (Fig. 17.8). Intrathecal application combined with radiotherapy is associated with demyelination alone or in combination with disseminated necrosis, especially in the centrum semiovale (Rubinstein et al. 1975; Robain et al. 1984). It is striking that there is no significant cellular reaction.

The neurotoxic effect is especially conspicuous under the conditions of pregnancy which may cause a cytostatic embryopathy. The characteristic morphologic feature is systemic hypoxia-like damage of the entire brain (microcephaly, hydrocephalus, hypoxic changes of the cortex) associated with malformation of the skull (Fig. 17.9).

17.6.3.2 Vincristine, Vinblastine

The intrathecal or intraventricular application of vincristine or vinblastine is not allowed. In single reported cases, accidental injection into these compartments has occurred and leads to death (Slyter et al. 1980). Both vincristine and vinblastine inhibit mitosis by causing metaphase arrest. Their ability to simultaneously bind tubulin and block its polymerization into microtubules (Prakash and Timasheff 1992) inhibits axoplasmic transport (Chan et al. 1980), which in turn leads to aggregation of the microtubules within the axon.

Clinical Features. The clinically dominant feature is a sensorimotor peripheral neuropathy, especially associated with vincristine.

Morphology. The predominant signs are axonal degeneration with proliferation of neurotubules and neurofilaments. Only intrathecal application is known to produce primary cell irritation with marked aggregation of neurofilaments (Slyter et al. 1980). There is rapid onset of fatal encephalomyelopathy with diffuse necrosis of CNS tissue (Fig. 17.10) in contact with cerebrospinal fluid (Wisniewski et al. 1968; Williams et al. 1983).

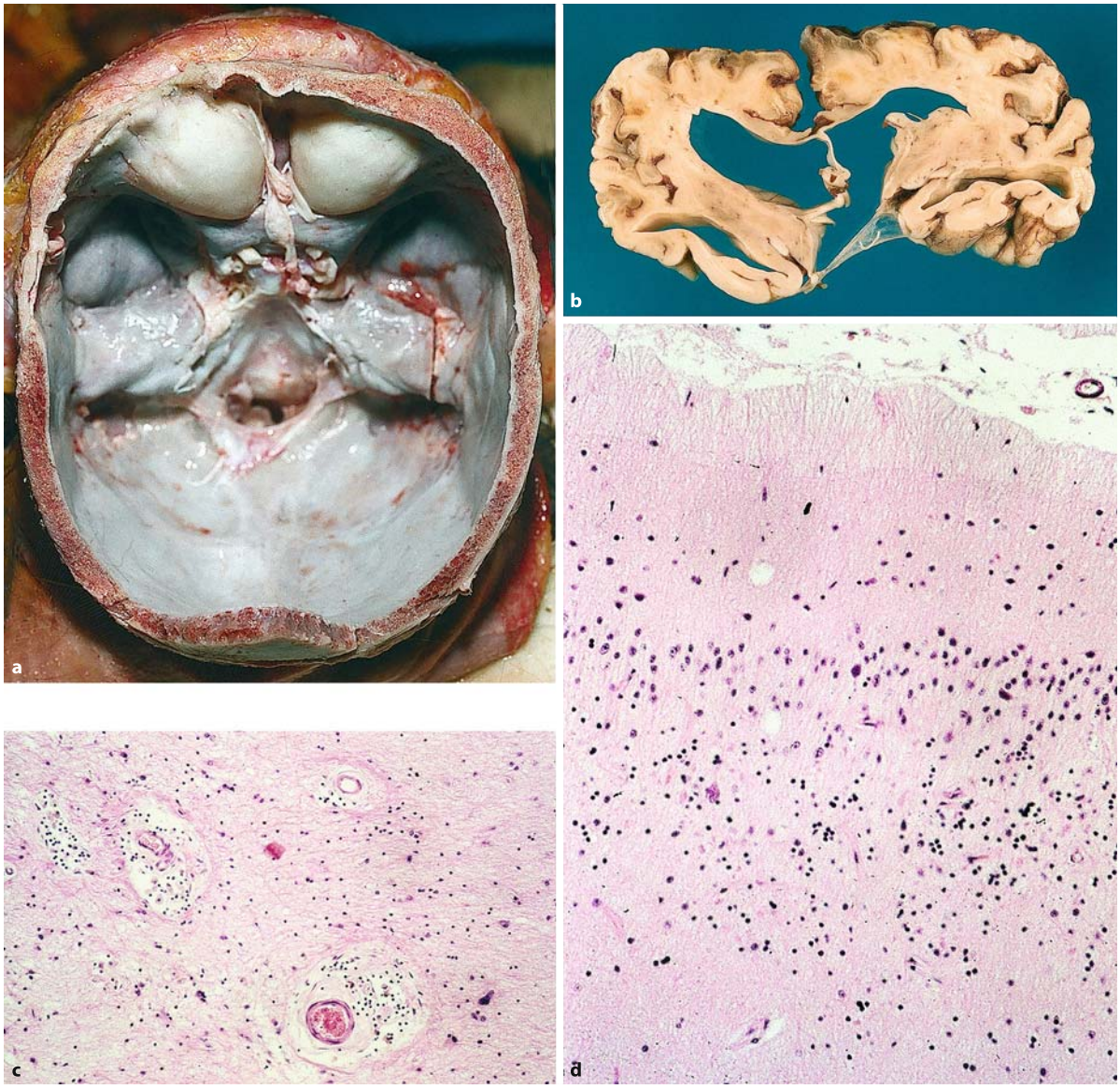

Fig. 17.9a–d. Cytostatic embryopathy. **a** Malformation of the base of the skull; **b** extreme hydrocephalus and cortical atrophy with lamellated structure; **c, d** loss of neurons, glial reaction and widening of the perivascular spaces in a 7-year-old child (**c, d** H&E; **c** magnification ×50; **d** magnification ×200)

17.6.3.3 Isoniazid

During the treatment of tuberculosis isoniazid, i.e. isonicotinic acid hydracide (=INH), produce peripheral neuropathies. PNS demyelination obviously is secondary to axonal degeneration. In experimental animals the CNS may be additionally effected. The morphology is characterized by spongy changes in the white matter and resemble those in TET intoxication.

17.7 Biological Toxins

17.7.1 Plants

Among poisonous plants, *mushrooms* are the most important. *Clinically*, mushroom poisoning sometimes produces gastrointestinal, sometimes CNS symptoms, although *morphological findings* in the CNS are as yet unknown. The differential diagnosis

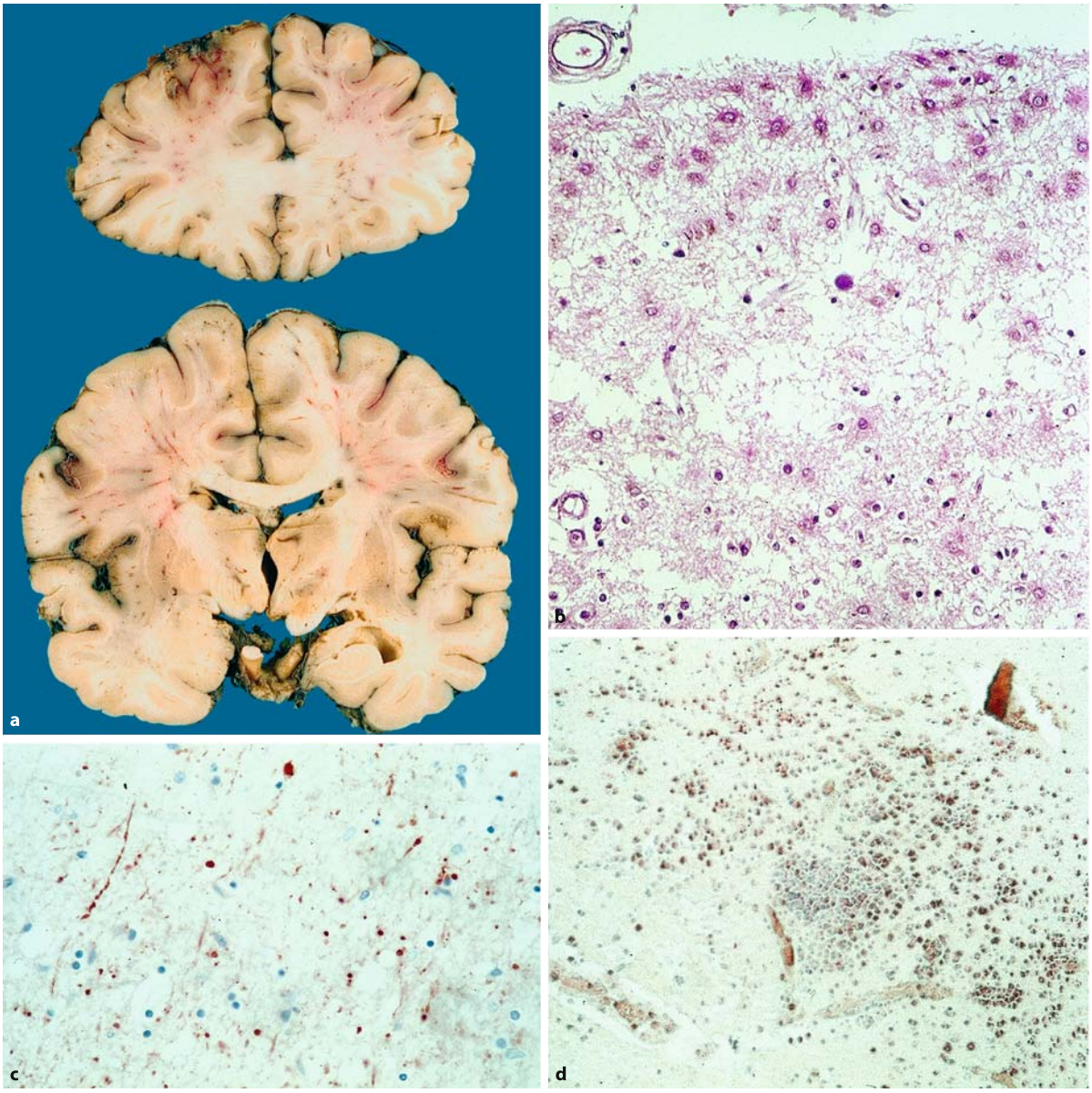

Fig. 17.10a–d. Vincristine intoxication. **a** Macroscopically cortical atrophy is visible; **b** microscopically the neurons and dendrites of the cortex, the basal ganglia and thalamic nuclei are lost, associated with a conspicuous glial reaction (**b** H&E, magnification ×500); **c** a loss of dendrites in the cortical structures (MAP reactivity) and **d** an increase of axonal balls (β-APP reactivity) are demonstrable (magnification **c, d** ×500)

is discussed by Flammer (1980). Reference is made to three different types of mushroom:

Amanita muscaria is capable of inducing a pantherina syndrome within only a few minutes to 2 h after consumption. The symptoms include fatigue, giddiness, dizziness, clouding of consciousness or even unconsciousness. Victims appear to be slowed down; they sometimes feel euphoric, indifferent and relaxed as though in a narcotic state. Death can occur within 15–24 h from circulatory collapse.

Amanita phalloides (Death Cup) initially (within 6–24 h) causes gastrointestinal disturbances with considerable loss of water and oliguria, followed by symptoms of acute liver dystrophy. The biological effect is characterized by a reduction of the contractility of structural proteins, as evidenced by, for example, the inhibition of mitosis.

Inocybes or *clitocybes* induce a muscarinic syndrome with marked perspiration, hypersalivation and lacrimation, hyperthermia, slow pulse, miotic pupils and impaired vision appearing within a few minutes to 1 h following ingestion. The differential diagnosis must include phosphate ester-induced intoxication.

In 1987, many inhabitants of Canada became ill after eating commercially grown shellfish. The acute symptoms were headache, seizures, hemiparesis, ophthalmoplegia, and abnormalities of arousal ranging from agitation to coma. Chronically, neuropsychological testing several months later revealed that 12 of the patients had severe anterograde-memory deficits, with relative preservation of other cognitive functions. Clinical and electromyographic evidence of pure motor or sensorimotor neuronopathy or axonopathy was found in 11 patients. Positron-emission tomography of four patients showed decreased glucose metabolism in the medial temporal lobes. A few victims exhibited temporal lobe epilepsy (Cendes et al. 1995). The illness was caused by domoic acid, a potently excitotoxic amino acid released by the single-cell alga *Nitzschia pungens* and which was found to be present in large amounts in the shellfish (Perl et al. 1990; Teitelbaum et al. 1990). Neuropathological studies in the four patients who died after mussel-induced intoxication demonstrated neuronal necrosis and loss, predominantly in the CA3 and CA1 hippocampus and amygdala (Carpenter 1990; Teitelbaum et al. 1990).

17.7.2 Animals

Poisoning can also be caused by animal toxins, which can induce CNS symptoms (Mebs 2002) for which, however, no neuropathological equivalents have yet been found.

Among *snakes* (snake venom) in Germany, the most important are the *European viper* and the *aspis viper*, whose poison contains toxalbumins; i.e., hemolysins, neurotoxins, coagulins, proteases, and other enzymes. The clinical sequelae are severe pain at the site of penetration and rapid spread of edema and discoloration. This is followed by symptoms of shock and progressive signs of a hemorrhagic tendency with bloody vomiting, bloody diarrhea, sinking blood pressure, and hemolysis. Other snake venoms may cause necrotizing myopathy and neuromuscular transmission syndrome.

Poisonous *fishes* include the *puffer* and the *blowfish* (for review see Schaper et al. 2002). The puffer's poison (tetrodotoxin) is found mainly in its bile and liver, that of the *blowfish* in the ovaries. The poison affects the sodium–potassium pump in the cell membrane and leads to an acute disruption of neuronal function with paralysis, coma, and death. Specific morphological changes have not been described.

The *Black widow (Latrodectus mactans)* is the only dangerous *spider* native to both Central Europe and North America. Its bite releases a neurotoxin, the so-called α-latrotoxin, which binds to the presynaptic membrane, which then becomes permeable to Ca^{2+} ions. The influx of calcium leads to a release of transmitters (Lazdunski et al. 1986) from cholinergic as well as adrenergic peripheral nerve endings. The blood–brain barrier is not breached. Clinical symptoms appear 10–15 min following a bite and disappear spontaneously after 12–24 h. The most predominant symptom is exquisite pain resulting from generalized muscle spasms. In addition, autonomic as well as psychological symptoms appear (Rehm et al. 1988).

Members of the order *Hymenoptera* (*bees*, *wasps*, *hornets* and *fire ants*) are also potentially dangerous. Their toxins often cause anaphylactic reactions. Primary neurotoxic effects are rare, bee venom apparently representing an exception in being capable of causing a peripheral neuropathy in some victims (Saida et al. 1977).

17.7.3 Microorganisms

Chief among toxin-producing microorganisms are the anaerobic spore-forming bacilli (*Clostridium botulinum*, *Clostridium tetani*), which produce potentially life-threatening neurotoxins. While the diphtheria toxin is, of course, of general significant importance, anthrax has recently become known as a potent biological toxin being a specific weapon of terrorism.

17.7.3.1 Botulinum Toxin

Source. *Clostridium botulinum* synthesizes a toxin which is inactivated at 80°C. It is incorporated with food or through skin wounds. The botulinus toxin binds to the peripheral cholinergic, presynaptic nerve ending and blocks the release of acetylcholine (neuromuscular blockade) (Ochs 1992). *Clinically*, the toxin has a delayed onset of action. The main symptoms are headache, dizziness, prominent cranial nerve palsies, and descending paralysis. *Morphological* changes have not been described.

17.7.3.2 Tetanospasmin

Under anaerobic conditions, *Clostridium tetani* produces the toxin tetanospasmin, which becomes inert at 65°C. If the toxin reaches the blood, it induces toxemia. The *clinical picture* is characterized by nausea, irritability, headache, and spasms of the facial muscles (risus sardonicus). Death occurs from shock or respiratory insufficiency.

Pathogenetically the toxin attaches to presynaptic terminals of cholinergic synapses (Price et al. 1975a, b), from which the toxin travels in a retrograde man-

ner as far as the anterior horns of the spinal cord (Walsh et al. 1982). *Morphologically* all changes are non-specific. The cytoplasmic vacuoles in the motor cells of the anterior horn are regarded as characteristic (Müller and Jeschke 1970).

17.7.3.3 Diphtheria Toxin

The non-sporulating *Corynebacterium diphtheriae* generates a toxin that binds stereospecifically to membrane receptors and is transported by endocytosis into the interior of the cell (Walsh et al. 1982). *Clinically* the picture is that of a peripheral neuropathy, in some cases with progressive paralysis of the Guillain–Barré type. *Morphologically* there is destruction of myelin mainly of the peripheral nerves with relatively well preserved axons and no signs of inflammation – chiefly in the spinal ganglia of the posterior roots (Fisher and Adams 1956; Kaplan 1980; MacGregor 1995).

17.7.3.4 Anthrax

Anthrax is an acute infectious disease caused by the spore-forming bacterium *Bacillus anthracis*. Anthrax can occur in humans when they are exposed to infected animals or tissue from infected animals. Anthrax lethal toxin is the principal virulence factor associated with lethal pathologies following infection with *Bacillus anthracis* (McAllister et al. 2003). Recently, anthrax is best known as a biological weapon (Inglesby et al. 1999). There are three types of anthrax transmission and clinical features (Dixon et al. 1999):

1. Cutaneous transmission, with bacterium entering through a cut or abrasion on the skin. Skin infection begins as a raised itchy bump that resembles an insect bite, which develops into a painless ulcer with a characteristic black necrotic area in the center.
2. Several days after inhalational transmission, victims develop symptoms that may progress to severe breathing problems and shock. Inhalation anthrax is usually fatal.
3. Intestinal transmission may follow the consumption of contaminated meat (food poisoning) and is characterized by an acute inflammation of the intestinal tract. Intestinal anthrax results in death in 25 – 60% of cases.

Clinical and Neuropathological Manifestation. Anthrax bacillus has been implicated in a wide range of infections including abscesses, bacteremia/septicemia, wound and burn infections, ear infections, endocarditis, ophthalmitis, osteomyelitis, peritonitis, and respiratory and urinary tract infections. Most of these occur as secondary or mixed infections or in immunodeficient or otherwise immunocompromised hosts, such as alcoholics and diabetics.

CNS involvement is characterized by a fulminant and rapidly fatal hemorrhagic meningoencephalitis (Meyer 2003). According to Dixon et al. (1999) the most common portal of entry to the leptomeninges is the skin (and inhalation route), from which the organisms can spread to the central nervous system by hematogenous or lymphatic routes. Anthrax meningitis is almost always fatal, with death occurring 1–6 days after the onset of illness.

Gross examination at autopsy reveals extensive hemorrhage of the leptomeninges, which gives them a dark red appearance described as "cardinal's cap" (Abramova et al. 1993). The microscopic findings are consistent with a hemorrhagic meningitis (Tahernia and Hashemi 1972; Martin and Adams 2003), with extensive edema, inflammatory infiltrates, and numerous Gram-positive bacilli in the leptomeninges (Dutz and Kohout 1971; Rangel and Gonzalez 1975).

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Alcohol, Organic Solvents, and Aerosols 18

18.1 Epidemiology

In the Federal Republic of Germany, 4.5 million people are estimated to be alcohol dependent and about 40,000 alcohol-related deaths occur annually (Trojan 1980; Petersson et al. 1982). Among individuals ≥16 years of age, 2–7% of the population are alcoholics, 16–47% are heavy consumers of alcohol, whereas only 6–14% abstain entirely or "almost" entirely from alcohol (Trojan 1980). The heaviest consumers of alcohol are males aged 30–49 years (Feuerlein and Küfner 1977).

Mortality studies in Norway have demonstrated an excess mortality of 113% for alcohol-dependent persons relative to the general population of Norway (Sundby 1967). The principal causes of alcohol-related death were determined by Schmidt and de Lint (1972): these include cirrhosis of the liver, cancer of the stomach and the upper digestive tract, apoplexy, suicide, and accidents. The following statistics also apply:

1. The mortality rate of alcoholics is 2.5–4 times greater than that of the general population (Garfield 1981; Taylor et al. 1983; Lithell et al. 1987).
2. The total annual mortality per 1,000 alcoholics was 25.9, but was only 8.8 for drug users (Barr et al. 1984).
3. Prospective studies by Petersson and colleagues (1982) showed that 3 years after examination of 10,000 males aged 46–48 years, 199 had died, 61 (30.7%) of alcohol-related causes.
4. The relative proportion of alcohol deaths documented in Institutes of Forensic Pathology is 0.6–22% (Kringsholm 1976; Wiese et al. 1990).
5. The percentage of deaths whose cause could not be determined is twice as high for alcoholics as for control cases (Hansen and Simonsen 1991).

Alcoholism usually occurs sporadically. But family, twin, and adoption studies have convincingly demonstrated that genes play an important role in the development of alcohol dependence (for review see Dick and Foroud 2003), accounting for approximately 50–60%. Furthermore, there is evidence of genetic effects on patterns of alcohol use as early as in adolescence, and these effects seem to increase during the course of time (Rose et al. 2001). In spite of these findings the complexity of alcohol-related traits has made the path to specific gene identification arduous. Alcohol dehydrogenase (ADH) genes – in particular ADH class I isoenzyme ADH1B, which is closely linked on chromosome 4q23 (Edenberg and

Bosron 1997), as well as the acetaldehyde dehydrogenase (ALDH) gene, especially the ALDH class II isoenzyme ALDH2 (Harada et al. 1982) – remain the only genes with definitely established contributions to alcohol dependence. The effects of these genes seem to be additive, with ALDH2 having a stronger effect. Subsequent studies have reported reduced rates of the ADH1B and/or ALDH2 allele among alcoholics in Asian populations (Chen et al. 2001).

18.2 Metabolism, Kinetics, and Causes of Death

Alcohol is absorbed through the gastrointestinal tract and diffuses into the circulatory system (for review see Goodman et al. 2001). There are three *pathways of alcohol metabolism* (for review see Matsumoto and Fukui 2002):

1. *Alcohol dehydrogenase* (ADH: EC 1.1.1.1): oxidizes alcohol to acetaldehyde, which in turn is oxidized by acetaldehyde dehydrogenase to acetic acid. The ADH family consists of numerous isoenzymes (von Wartburg et al. 1964; Hines et al. 2001). The rate of alcohol metabolism is determined by the type and activities of the enzymes present in a given individual. In the Mongoloid race – compared to the Caucasian race – up to 90% of the population possesses an atypical ADH associated with a low tolerance for alcohol (Agarwal and Goedde 1995).
   ADH is located mainly in the liver, but it is also present in other organs, such as the central nervous system (CNS). Whereas ADH can be induced (Raskin and Sokoloff 1968; so-called adaptive acceleration of catabolic metabolism – cf. Topel 1984), acetaldehyde dehydrogenase is limited in its adaptability. An increase in the alcohol dose, therefore, leads to an accumulation of acetaldehyde in the blood, which is much more toxic than alcohol.
2. The *microsomal oxidizing systems* (MEOS; Ohnischi and Lieber 1977) or microsomal mixed-function oxidases (Gilman and Abraham 2001): the activity of this oxidative system is stimulated not only by alcohol but also by some medications, e.g., barbiturates.
3. *Catalase* (Keilin and Hartree 1936).
4. *Conjugation with glucuronic acid* (Besserer and Schmidt 1983): items 3 and 4 account for a negligible percentage of alcohol metabolism when compared to ADH and MEOS.

The *elimination* of alcohol from the body (mainly via the liver) is largely a function of time (zero-order kinetics) and not exponential. The mean rate is 15 (mg/dl)/h (Mallach 1987; Schmidt 1988). Alcohol diffuses throughout the brain, where its levels are proportional to the blood alcohol concentration (BAC); in total the cerebrum: Agapejev et al. (1992); in the occipital lobe and cerebellum: Moore et al. (1997).

Acetaldehyde is the main *toxic factor* (Pratt et al. 1990). Since this metabolite can penetrate the blood–brain barrier only at very high blood concentrations (Hunt 1996), the question arises as to how elevated acetaldehyde levels come to be present in brain tissue even in cases with low blood alcohol levels. A particular isoform of ADH has been demonstrated in the brain, the activity of which is inducible – only in the hemispheres, and not in the brain stem – (Raskin and Sokoloff 1974 – cf. Rout 1992); moreover, in the brain, further catalase activity (Cohen et al. 1980; Zimatkin and Lindros 1996) generates acetaldehyde as a metabolite (Smith et al. 1997). A similar situation holds true for MEOS, which can also be demonstrated in brain tissue (Zimatkin and Dietrich 1997). The accumulation of locally produced acetaldehyde can, therefore, be explained by the presence of local dehydrogenase (Spivak et al. 1987; Zimatkin et al. 1998).

Besides ethanol, alcoholic beverages (wine, beer, cognac, whiskey, etc.) contain alcoholic congeners, so-called fusel alcohols, in concentrations that are characteristic for each type of beverage. Fusel alcohols are byproducts of the fermentation process and include methanol, 1- and 2-propanol, 1- and 2-butanol, isobutanol, and amylalcohol (Bonte 1987). Most of them are toxic and account for the post-intoxication "hangover" effect. Detection and quantification of fusel alcohol is used in forensic practice to demonstrate the type of alcoholic beverage consumed, especially if "after drinks" are claimed. Alcohol, acetaldehyde, and fusel alcohols have a toxic effect on numerous *organ systems*, the chief target organs being the liver and cardiovascular system (Altura and Altura 1987). They simultaneously target organs of the gastrointestinal tract and the pancreas (for review see Oehmichen et al. 1992; Singer and Teyssen 2001).

Recent investigations give evidence of a *gender-dependent difference in brain metabolism* of alcohol (Wang et al. 2003). Since alcohol decreases glucose metabolism in the human brain in a pattern that is consistent with its facilitation of GABA-ergic neurotransmission, the differences could be demonstrated with positron emission tomography. The magnitude of the alcohol-induced decrease of the whole-brain metabolism was significantly larger in male than in female subjects. This phenomenon correlates with studies which documented a greater behavioral effect of alcohol in female subjects than in male subjects.

Death can occur with alcohol without evident organic disease, however. The following types of cases can be differentiated:

1. Alcohol can be an additional, possibly contributing factor, in an acute lethal event involving physical or chemical trauma (blow, fall, stab, traffic accident, hypothermia) and/or reflex mechanisms (bolus, drowning) and/or disease-induced processes (coronary thrombosis, rupture of an aneurysm at the base of the brain, etc. – Weston 1980). This class of events includes combined drug and/or pharmacological and alcohol intoxication (Geldmacher von Mallinckrodt et al. 1976; King 1982).
2. Acute death of an alcoholic can occur without acute alcohol intoxication, but in conjunction with chronic organic changes which explain the death sufficiently (e.g., hemorrhage of esophageal varices, hepatic coma, etc.).
3. Acute death may be due to acute alcohol intoxication in individuals with no known history of alcohol abuse.
4. Acute death may be due to acute alcohol intoxication in individuals with a history of alcohol abuse.
5. Acute death of an alcoholic may occur during alcohol intoxication with observable chronic organic changes, but of a type that would not explain the death. The possible causes of death in these cases include asystole caused by bradyarrhythmia secondary to alcoholic cardiomyopathy or organic brain paroxysm.
6. Acute death may be a result of chronic alcohol consumption and stroke. The relative risk of stroke of chronic alcoholics was recently evaluated by Reynolds et al. (2003): compared to abstainers, consumption of more than 60 g alcohol per day was associated with an increased relative risk of total stroke, while consumption of less than 12 g/day was associated with a reduced relative risk of total stroke, and consumption of 12–24 g/day was associated with a reduced relative risk of ischemic stroke (not hemorrhagic stroke).

Acute alcohol poisoning is lethal at a BAC of between 180 mg/dl (1.8‰) and 670 mg/dl (6.7‰) (Kaye and Haag 1957; cf. Mallach et al. 1980). BACs of this magnitude cause (central) respiratory arrest and consecutive cardiac arrest secondary to hypoxemia and diminished venous reflux (Polaczek-Kornecki et al. 1972). Alcoholics are often discovered dead, however for no discernible reason without highly toxic BACs (Copeland 1985).

18.3 Pharmacology

The effects of alcohol can be divided into three phases: stimulation, disinhibition, and inhibition. At the cellular level, ethanol's lipophilic and hydrophobic properties affect neuronal membranes, changing the composition of the membranous lipids by, for example, membrane liquefaction (Kurella and Genkina 1989; Gustavsson 1990); membrane liquefaction is accompanied by a hypnotic effect.

The pharmacological effect of ethanol is highly complex and cannot be explained by a simple model. Alcohol influences not only membranes, but also membrane-bound proteins, i.e., both neurotransmitters and receptors (Eue and Kemper 1992). Low alcohol levels increase the turnover of noradrenaline, higher levels reduce it, and they also inhibit the cholinergic and GABA-ergic transmitter systems (Hörtnagl and Hanin 1992). The functional changes are apparently caused by glutamate receptors in the hippocampus, cortex, striatum, and thalamus (Foster and Wong 1987), the *N*-methyl-D-aspartate (NMDA) receptor being the most important. Acute exposure to alcohol inhibits the NMDA receptor response, chronic exposure leads to an adaptive hypersensitivity in the sense of dependence and tolerance (Rudolph et al. 1997).

Simultaneously, receptors of various transmitters influence the transmission of neurotransmitters by cyclic AMP and cyclic GMP. In the brain, nitric oxide (NO) metabolites are released; they are present in elevated levels in the cerebrospinal fluid of alcoholics (Neiman and Benthin 1997). Nitric oxide itself is released by excessive glutamate stimulation of the NMDA receptors (Lancaster 1992).

Alcohol is also known (Riley and Walker 1978) to influence the synthesis, release, and metabolism of endogenous opiates. In rats, met-enkephalin and β-endorphin levels increase following acute alcohol consumption, whereas chronic alcohol consumption reduces their levels; alcohol influences the binding of opiates to their receptors (overview see Feuerlein 1989). Application of the opioid antagonist naltrexone can significantly reduce the alcohol uptake of rats (Franck et al. 1988), suggesting that the central δ-opioid receptor modifies voluntary alcohol consumption in rats.

The effects of ethanol are mediated by an activation of γ-aminobutyric acid ($GABA_A$) receptors, release of opioid peptides, release of dopamine, inhibition of glutamate receptors, and interaction with serotonin systems (Anton 1996). The depressant actions of ethanol in the brain are related to its interaction with NMDA and the benzodiazepine/GABA receptor complex (Weight et al. 1992). The hypothermic effects of ethanol have complex interactions with other drugs, which differ in their interaction from those affecting motor behavior (Maickel and Nash 1986).

18.4 Clinical Features

18.4.1 Acute Intoxication

Acute alcohol poisoning is psychopathologically characterized by simple "drunkenness," which can be divided into three stages (Witter 1972):

1. Mild inebriation (BAC = 0.5–1.5‰ = 10.8–32.5 mmol/l = 50–150 mg/dl): general psychopathological disinhibition, decrease in psychomotor performance, impaired coordination, impaired driving ability – caused by involvement of polysynaptic neuronal connections in the reticular formation of the brain stem, the cerebral cortex, and the cerebellum (Klemm 1979).
2. Moderate inebriation (BAC: 1.5–2.5‰ = 32.5–54.2 mmol/l = 150–250 mg/dl): euphoria or aggressive irritability, diminished capacity for self-criticism, satisfying of instinctual drives.
3. Severe inebriation (BAC: >2.5‰ = 54.2 mmol/l = 250 mg/dl): impaired consciousness, poor judgment, disorientation, visual and/or auditory and/or tactile, and/or olfactory hallucinations (illusionary misinterpretation in a given situation), inexplicable fear, agitation, signs of functional impairment of the vestibular organ(s) and cerebellum such as nystagmus, double vision, speech disturbances, ataxia, hypotension, hypothermia, etc.

As mentioned above, *lethal intoxication* can occur at BAC of about 180–670 mg/dl, with a peak at values of 450–500 mg/dl (Poikolainen 1984; Johnson 1985; Kubo et al. 1991). Extremely rare by contrast are observations of BAC exceeding 500 mg/dl, for example of 800 mg/dl (Hammond et al. 1973; Lindblad and Olsson 1976; Püschel et al. 1978).

How can the phenomenon of *tolerance* be explained at the molecular level? If alcohol does indeed lead to an acute increase in the permeability of the membrane lipids, then it may be possible for the neuronal membranes to become resistant to this effect (Chin and Goldstein 1977; Harris et al. 1984). Of at least equal importance is alcohol's affect on the receptor system regulating the ion canals, especially the Cl^- and Ca^{2+} channels. Alcohol reduces depolarization-induced Ca^{2+} flow into neuronal cells. Adaptation to this effect would mean that the number of Ca^{2+} channels in the cell membrane would increase (Hudspith et al. 1987; Rubin 1987). Withdrawal from alcohol itself leads to impairment of neuronal function, above all to overshooting neuronal activity.

18.4.2 Chronic Intoxication (Alcoholism)

Chronic alcohol abuse can be defined by the following criteria (Feuerlein 1989):

1. Abnormal drinking behavior
2. Alcohol-induced somatic damage
3. Alcohol-induced psychosocial damage
4. Development of tolerance and withdrawal syndrome (physical dependence)
5. Withdrawal syndrome at the subjective level (psychic dependence)

Chronic alcoholics have long been characterized exclusively – and essentially – by drinking behavior and associated changes in social behavior. Clinical symptoms usually occur later. Even in the preclinical stages, however, reduced cerebral metabolism (Volkow et al. 1992) and EMG changes are often evident as precursors of polyneuropathy (D'Amour and Butterworth 1994).

Clinical data imply that relapse and craving for alcohol can be induced through different mechanisms (Spanagel 2002, 2003):

- A first pathway may induce alcohol craving and relapse through the mood-enhancing, positive reinforcing effects of alcohol consumption. This pathway seems to involve opioidergic systems in the ventral striatum. The role of the dopaminergic system may lie in the direction of attention towards reward-indicating stimuli, while the induction of euphoria and positive mood states may be mediated by opioidergic systems (Spanagel and Weiss 1999; Olive et al. 2001). Associative learning may, in turn, transform positive mood states and previously neutral environmental stimuli into alcohol-associated ones that acquire positive motivational salience and induce reward craving.
- A second pathway may induce alcohol craving and relapse by negative motivational states, including conditional withdrawal and stress. This pathway seems to involve the glutamatergic system and the corticotrophin-releasing hormone (CRH) system (Spanagel 2002). Chronic alcohol intake leads to compensatory neurotransmission, and increased CRH release leads to a state of hyperexcitability, which becomes manifest as craving, anxiety, seizures, and autonomic dysregulation (Spanagel and Bienkowski 2002).

The neurological deficits are characterized by the following clinical picture:

1. *Alcoholic encephalopathy*: this picture is associated with dementia and inner and outer brain atrophy (mainly of the frontal and temporal lobes), cerebellar atrophy, and alcoholic epilepsy. There

is evidence that light-to-moderate alcohol consumption is associated with a reduced risk of dementia in individuals aged 55 years or older (Ruitenberg et al. 2002).

2. *Wernicke–Korsakoff syndrome*: a small proportion of alcoholics suffer from this disease, which progressively develops – in variable order – with the following symptoms:
   - Oculomotor paralysis with pupillary disturbances and uncertain gait
   - Slight symptoms of delirium
   - Korsakoff's psychosis with loss of long-term memory, decrease in spontaneity, confabulation and poor concentration.
3. *Delirium and hallucinosis*: in combination with – but also independently of – the aforementioned disturbances, delirious states can also occur (Böning and Holzbach 1987), including hallucinosis (Glass 1989a, b) with paresthesias and/or tactile hallucinations. Finally, schizophrenia-like psychoses can also develop.
4. *Convulsive disorders*: organic brain seizures (grand mal) have been seen in 7.8% (Wilkinson et al. 1971) and 5–35% of alcoholics (Meyer and Forst 1977). They can occur after episodes of excessive alcohol intake or during withdrawal (Bartolomei et al. 1997). In some cases, however the convulsive disorder is associated with the cerebral sequelae of cranio-cerebral trauma incidental to alcoholism.
5. *Withdrawal symptoms*: studies of the cellular and molecular actions of acute ethanol exposure suggest effects that reduce synaptic excitation (Aguayo 1990). Removal of ethanol after chronic exposure leads to "hyperexcitability" (Walker and Zornetzer 1974) of the CNS. In the most extreme cases tonic/clonic seizures of pre-convulsive states are observed during withdrawal from chronic ethanol abuse (for review see Crabbe et al. 1990; Lovinger 1993).

Acute alcohol withdrawal can produce the following symptoms (Gross et al. 1972):

- Disturbances of *perception/cognition* (attributable to cortical structures): nausea, tinnitus, visual impairment, paresthesias, optic, acoustic or tactile hallucinations, motor restlessness.
- *Autonomic disturbances* (attributable to the limbic system): tremor, profuse sweating, depression, anxiety.
- Disturbances attributable to the *brain stem*: disturbed consciousness, gait disorders, etc.
- *Seizures* (see above).
- *Delirium tremens* (Taylor and Lewis 1993): this clinical picture is defined (ICD 10) as an acute, temporary, generalized organic disease of the central nervous system with impairment of consciousness and vigilance. It is associated with increased mortality, especially in older patients (Trzepacz et al. 1985). The pathogenesis has not yet been satisfactorily explained. It may well be caused by a generalized metabolic disturbance combined with cardiovascular disorders. Contributing factors may include magnesium deficiency and respiratory alkalosis (secondary to hyperventilation; Victor 1977) and/or an increase in acetylcholine and/or the activity of the entire cholinergic system (Ital and Fink 1966; Taylor and Lewis 1993). Only a few pathological–anatomical studies are available: they show non-specific changes and/or lesions typical of alcoholism in general (cf. Ikeda et al. 1993).

18.5 Neuropathology

18.5.1 Acute Intoxication

The neuropathology following acute alcohol intake is non-specific and characterized by brain edema and congestion. The pathomechanical course is explained by a primary toxic central respiratory paralysis or arrest, which leads to acute right heart failure (Oehmichen et al. 1992). The congestion of the brain can additionally be explained by a vasomotor paralysis, which may be caused by an accumulation of acetate in the brain (Schwartz et al. 1993). The sequelae in addition to the congestion include perivascular extravasation, especially periventricularly. Neuronal changes are usually absent. Although a recent experimental study (Phillips et al. 1997) could not demonstrate a disturbance of the blood–brain barrier, empirical measurements demonstrated an increase in brain volume (Powell et al. 1980; Harper 1982).

Of paramount importance in this regard is the consistent observation of massive perifocal edema secondary to combined brain trauma and acute alcohol intoxication (Persson and Rosengren 1977; Jurkovich et al. 1993; Zink et al. 1993). The prognosis in such cases however does not appear to be noticeably worsened, as has been shown in clinical (Kelly et al. 1995) and experimental (Kelly et al. 2000) studies.

18.5.2 Chronic Intoxication

Neuropathological investigations carried out in a comprehensive study (Skullerud et al. 1991; cf. Torvik 1987) of 127 cases of chronic alcoholism found

alcohol-related findings in 50% of cases: 14% Wernicke encephalopathy; 37% cerebellar atrophy; two cases of central pontine myelinolysis; one case of hepatic encephalopathy. These changes were evenly distributed between males and females (Harper et al. 1990; Mann et al. 1992). Moreover, there is clear evidence today that the central nervous system of females may be more susceptible than that of males to neuronal damage during alcohol intoxication and during withdrawal from long-term ethanol exposure (Prendergast et al. 2000; Hommer et al. 2001; Pfefferbaum et al. 2001).

An analysis of alcohol-specific brain damage was recently published by Harper (1998; see also Gass and Hennerici 1999), who describes the following primary alcohol-toxic sequelae:

1. Injury to the cerebral white matter with interior and exterior brain atrophy.
2. Nerve cell loss in the cerebral cortex, the hypothalamus, and cerebellum [but not in the hippocampus – cf. Harding et al. (1997); in contrast to Bengochea and Gonzalo (1990) and Franke et al. (1996)].
3. Dendritic and synaptic damage together with receptor and transmitter-induced changes as the early equivalents of functional and cognitive deficits.

   Cell death as well as astrocytic death may be enhanced by inflammatory mediators (Valles et al. 2004). Chronic ethanol treatment of rats stimulates glial cells, upregulating the production and expression of inflammatory mediators (iNOS, COX-2, IL-1β) in the brain, and activating signalling pathways and transcription factors involved in inflammatory damage and cell death.

These changes occur to varying degrees, and are usually observed in combination, with the combinations observed differing from patient to patient. The clinical result can be a dementia and ataxic-motor disturbances. The symptoms are not always identical.

Apparently, the pattern of neuropathological findings is aggravated by an associated thiamine deficit (vitamin B_1 – comp. pp. 606 f), including for example neuronal changes in the cerebral cortex (Kril and Homewood 1993) with widespread sparing of the noradrenergic neurons (Baker et al. 1994) and injury of the cerebral white matter (Langlais and Zhang 1997). Animal studies have demonstrated damage to synapses in the stratum lucidum of the CA3 region (Lundqvist et al. 1994), and loss of the hippocampal granule cell layer and pyramidal cell layer, primarily in the CA3 region, as well as an astrocytic reaction (Franke et al. 1996). The described Hirano bodies, which occur in the CA1 region of the hippocampus, must be regarded as non-specific (Laas and Hagel 1994).

It should be noted that some of the functional and morphological deficits are *reversible with withdrawal treatment*. This is especially true of the so-called atrophy, which is thought to be caused by alcohol-toxic dehydration. Rehydration, regeneration or elevated corticoid levels during withdrawal treatment – in some cases – have been reported to have produced "normalization." Detailed studies taking into account the literature have excluded phenomena such as dehydration (Harper et al. 1988) and changes in the corticoid levels as influencing factors (Mann 1992). Moreover, functional reversibility can additionally be explained by a partial regeneration in the sense of fresh dendritic arborization, rearborization and the formation of new synapses (Riley and Walker 1978), which can apparently occur within 2 weeks (Mann 1992).

Referring to the different patterns of *injury*, Peiffer (1989) distinguishes neuronotropic, gliovasotropic, and myelinotropic damage to the brain from polyneuropathy and myopathy. This morphological classification can include non-specific alcohol-induced changes and particular clinical syndromes in combination with localized and tissue-specific structural changes.

18.5.2.1 Diffuse Brain Alterations

Cortical and subcortical white matter damage is due to thiamine deficiency as well as to direct toxic effects of alcohol (Langlais and Zhang 1997). Atrophy of the cortex and white matter (Fig. 18.1) can be observed by CT, macroscopically as well as microscopically. This results in a mean loss in brain mass of 1.43–1.35 kg in males (Harper and Kril 1993). The extent of atrophy has been shown (Harding et al. 1996) to be dependent upon the amount of alcohol consumed and the duration of alcohol dependence. Atrophy is based on a reduction of cortical neurons (Fig. 18.1a, b) and of the prefrontal cerebral white matter (Kril et al. 1997) (Fig. 18.1c–e), as well as – especially – the corpus callosum (Fig. 18.1c) (Harper and Kril 1988). The cerebral white matter is usually more vulnerable than the gray matter (Hansen et al. 1991), especially the subcortical white matter. The atrophic process partly is reversible, however (see above) (Pfefferbaum et al. 1995; Trabert et al. 1995). A recent study (Pfefferbaum et al. 2002) on the effect of alcohol abuse on white matter brain macrostructure provided evidence of a correlation between a higher life-time level of alcohol consumption and smaller volumes and prolonged transverse relaxation time in the pons; an overall deficit in white matter macrostructural size is observed in alcoholic women.

A loss of neuronal elements in the cerebral cortex is seen mostly in patients with Wernicke–Korsakoff syndrome (see below) (Kril et al. 1997). Harper et al.

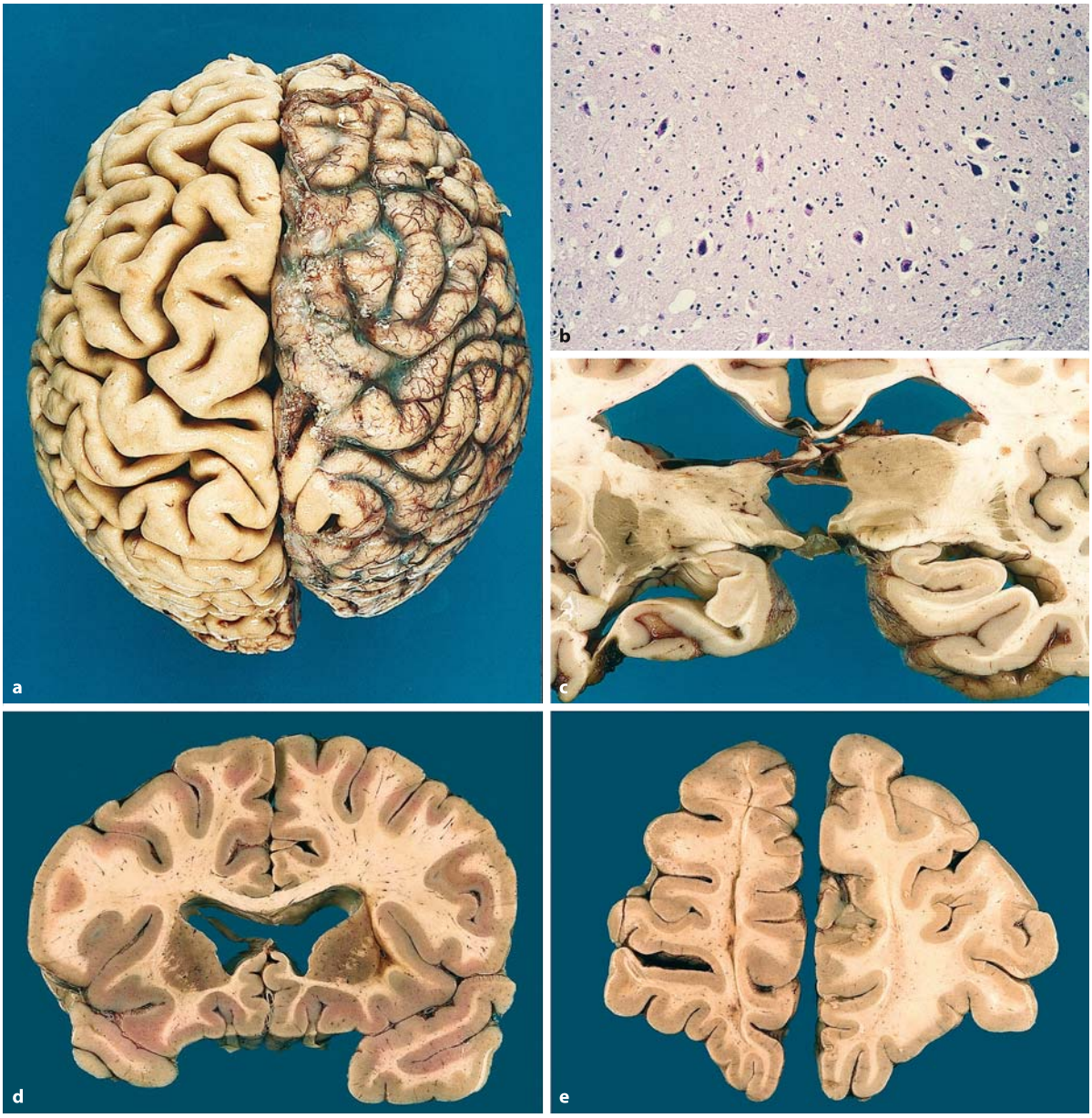

Fig. 18.1a–e. Chronic alcohol intoxication. **a** Cortical atrophy; **b** the atrophy is caused by a decline in nerve cell density and secondary gliosis (H&E, magnification ×200); **c** atrophic mammillary bodies are seen associated with an extreme hydrocephalus internus and a reduction of the corpus callosum; **d** subcortical white matter atrophy, which results in an interior atrophy, **e** rarely associated with macroscopic visible bilateral cystic white matter involvement

(1987) observed a loss of neurons in the frontal cortex (Moselhy et al. 2001) chiefly involving the large pyramidal cells (Harper and Kril 1989). There is also a reduction in the number of dendritic branches in the third cortical nerve cell layer (Harper and Corbett 1990) and a decrease in the number of dendritic spines in the fifth cortical nerve cell layer (Ferrer et al. 1986).

A decline in nerve cell density is seen, especially a loss of vasopressin-immunoreactive neurons in the magnocellular hypothalamus, supraoptic nucleus, and paraventricular nucleus (Harding et al. 1996; Harper et al. 1997). On the other hand, secondary gliosis has only been observed in a few cases (Harper et al. 1997). The Alzheimer's type I and II astrocytes observed in the thalamus and striatum are less a direct indication of chronic alcoholism than of the accompanying impairment of liver function with subsequent brain involvement in the sense of hepato-cerebral degeneration (p. 611).

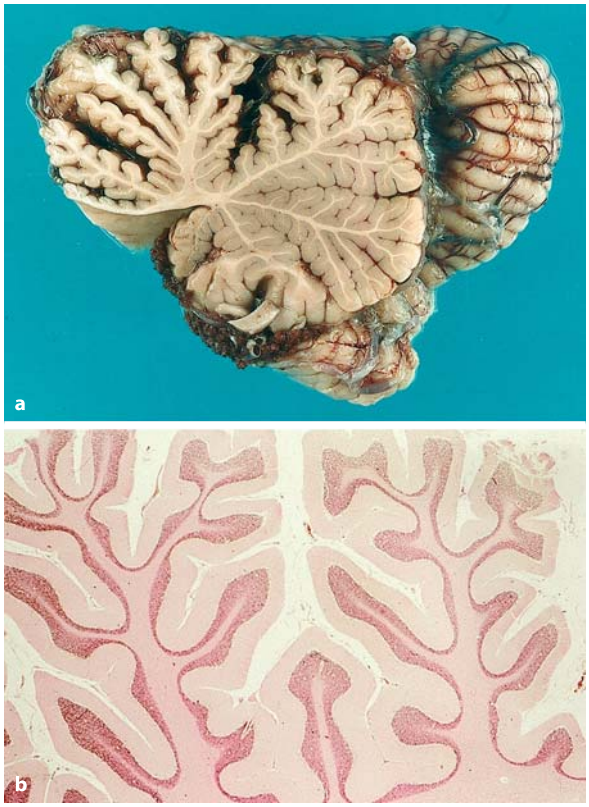

Fig. 18.2a, b. Chronic alcohol intoxication. An early alteration is the cortical atrophy of the superior cerebellar vermis, which is macroscopically (**a**) and microscopically (**b**) visible, associated with an atrophy of the molecular layer and a decline of Purkinje cells

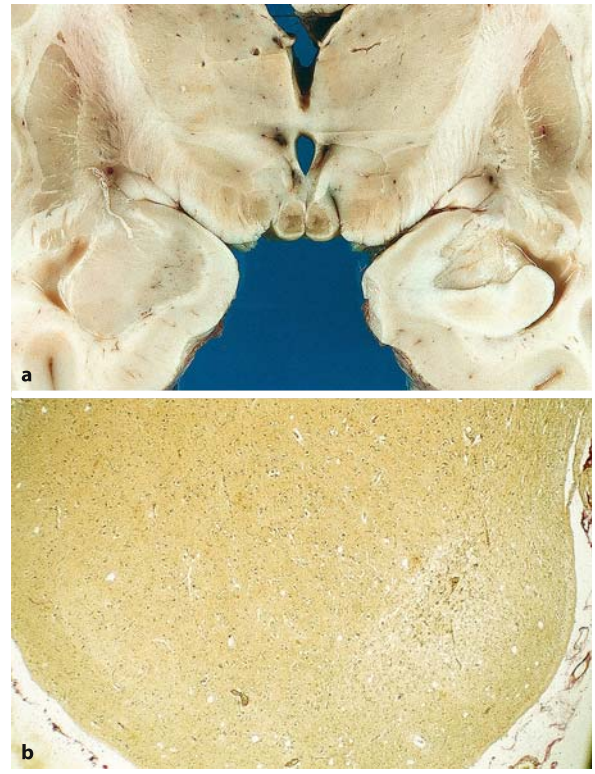

Fig. 18.3a, b. Wernicke–Korsakoff syndrome. Brownish-colored siderin-positive mammillary bodies (old hemorrhages) are seen as well as acute periventricular hemorrhages

18.5.2.2 Cerebellar Atrophy

Cerebral computer tomography (CCT) confirmed cerebellar atrophy in about 40% of chronic alcoholics (Haan 1986). *Pathological-anatomical* atrophy was found in 26.8% of alcoholics (Torvik et al. 1982), with shrinking mainly of the anterior superior cerebellar vermis. The atrophy was caused by a reduction in cerebellar white matter (Harding et al. 1998) and of the molecular layer (stratum moleculare) of the cerebellar vermis and a drop in Purkinje cell density (Karhunen et al. 1994) as well as reactive proliferation of astrocytes, the Bergmann glia (Fig. 18.2). The total number and density of Purkinje cells declines, apparently a dose-dependent phenomenon (Karhunen et al. 1994). A decrease in dendritic arborization has also been shown (Ferrer et al. 1984). Cerebellar atrophy is expressed *clinically* in ataxia and impaired coordination, mainly of the lower extremities. Thiamine deficiency is thought to be the chief cause of the cerebellar atrophy (cf. Adams 1976), resulting from malnutrition and a daily ethanol intake of more than 140 g over 10 years, which were independently associated with the development of cerebellar shrinkage (Nicolás et al. 2000).

18.5.2.3 Wernicke–Korsakoff Syndrome

Whereas the clinical symptoms of somnolence, ataxia, and ophthalmoplegia can be attributed to the *Wernicke syndrome*, the *Korsakoff psychosis* is characterized mainly by amnesia, disorientation, and suggestibility with confabulation. Neither of the two syndromes is a distinct entity since the transitions between them are fluid both clinically and pathologically. Both types of changes must be attributed to alcohol intoxication in combination with a thiamine deficiency (Butterworth 1989; Laforenza et al. 1990), as well as activation of microglia and astroglia (Todd and Butterworth 1999). An acute course must be distinguished from a more chronic course.

The *acute course* is characterized by disorientation, confusion, and autonomic deficits and has a poor prognosis. Both macroscopically and microscopically new, sometimes non-reactive capillary hemorrhages can be demonstrated; they are located mainly in the mammillary bodies, but also in the paraventricular nuclei, especially the supraoptic nu-

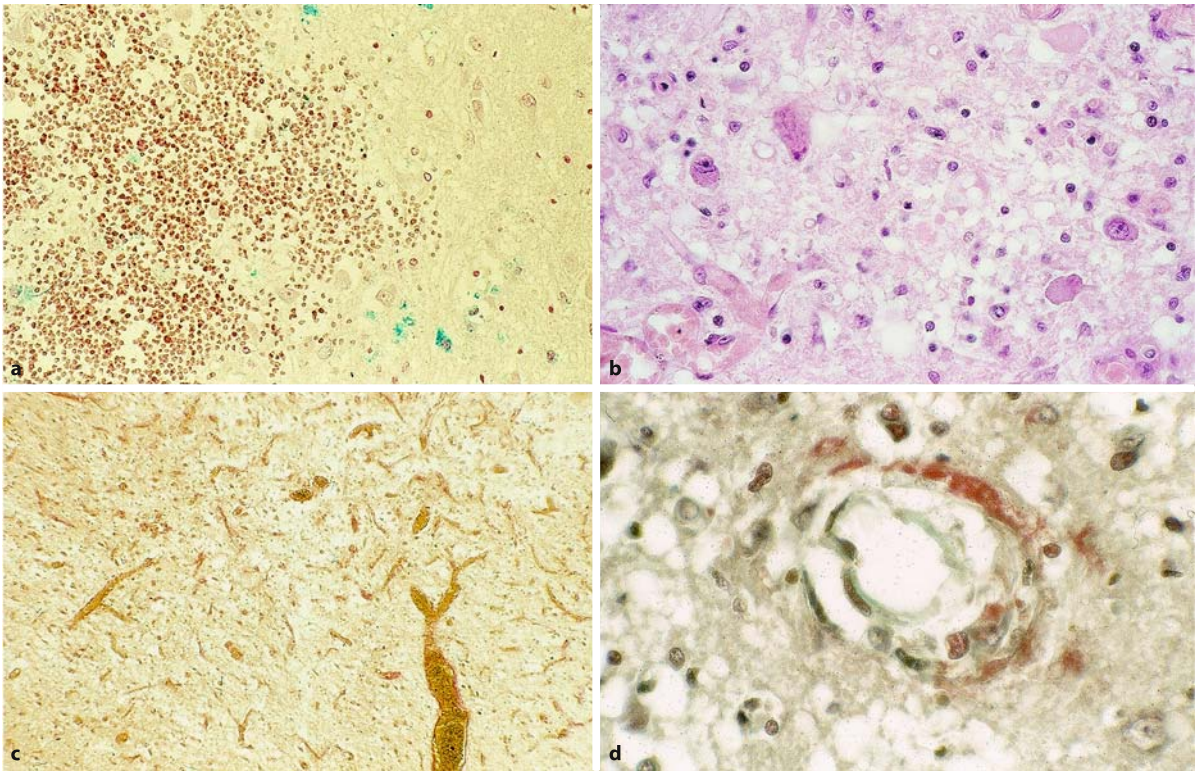

Fig. 18.4a–d. Wernicke–Korsakoff Syndrome. Microscopically the mammillary bodies are characterized by hemorrhages of different age, a spongy desintegration (**a**), an intense vascularization and astrogliosis (**b, c**), as well as fibrinoid degeneration of arterioles and capillaries with morphologically intact neurons (**d**) (**a, c** van Gieson stain; **b** Prussian blue reaction; **c** trichrome stain; magnification **a** ×100, **b** ×500, **c** ×50, **d** ×1000)

cleus and quadrigeminal plate (Colmant 1965). The acute course is rare.

The *chronic course* exhibits both of the aforementioned clinical pictures (Wernicke's syndrome, Korsakoff psychosis). Morphologically the following changes are encountered.

The gross appearance is dominated by atrophic, brownish *mammillary bodies* (Fig. 18.3) and *periventricular hemorrhages* (Fig. 18.4a) of varying age at the level of the third and fourth ventricles and the aqueduct. Histology reveals astrogliosis and capillary proliferation (Fig. 18.4c) plus siderophages (Fig. 18.4a) and spongy disintegration of the neuropil and demyelination as well. The vascular changes include angiectasis, looping, and swelling of endothelium as well as fibrinoid degeneration (Fig. 18.4d) selectively affecting arterioles and capillaries (Okeda et al. 1995). The neuronal elements remain largely intact and only occasionally exhibit swelling with chromatolysis. A large proportion of cases also have neuronal changes in the thalamic nucleus (53–100%, Harper and Butterworth 1997, especially in the mediodorsal and anterior principal nuclei), including perineuronal vacuoles and degenerating neurons, some with eosinophilic cell change and cytoplasmic vacuolization (Olney 1990; Meldrum and Garthwaite 1991). All of these morphological phenomena have been reproduced experimentally by reductions in thiamine intake. In chronic alcoholics, they are explained by impaired intestinal absorption caused by alcoholic gastroenteritis.

18.5.2.4 Central Pontine Myelinolysis

The primary cause of this disorder does not appear to be specifically alcohol induced but caused by a secondary electrolyte disturbance (pp. 610 f) in the sense of hyponatremia (Endo et al. 1981), and especially the rapid clinical correction of an existing hyponatremia (Kleinschmidt-DeMasters and Norenberg 1981; Illowski and Laureno 1993). A combination with other factors has also been discussed (Bratzke and Neumann 1989; Mundle et al. 1999).

The main morphological feature of central pontine myelinosis is a glial-myelinolytic process, seen mainly in the rostral central cerebellar peduncle. Macroscopically it is characterized by clearly demarcated symmetrical demyelination of the central pontine segments, mainly in the raphe (Fig. 18.5). Microscopically there is a selective demyelination process involving neurons and axons with oligodendrocyte

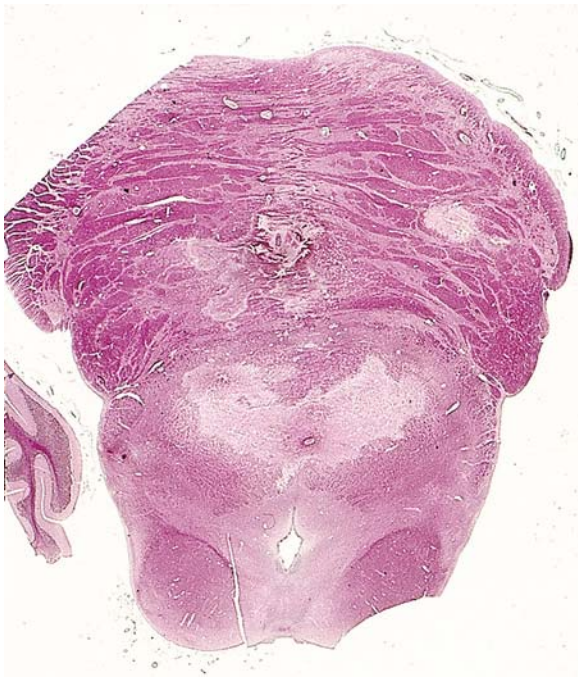

Fig. 18.5. Central pontine myelinolysis. Demyelination in the center of the pons, characterized by a spongiform degeneration, axonal swelling, and increase of macrophages

loss. Macrophage proliferation is combined with the spongy disintegration.

The clinical picture is dominated by pseudobulbar paralytic symptoms such as dysphagia, dysarthria, and paralysis of deglutition. The picture can progress to decerebrate rigidity (Berlet et al. 1983). With increased awareness, the causal diagnosis is now made more often clinically, and with computed tomography and magnetic resonance imaging.

18.5.2.5 Marchiafava–Bignami Syndrome

This is an exceptionally rare disease seen nearly exclusively in male alcoholics, especially Italian red wine drinkers but also in Japanese drinkers of rice wine (sake) (Brion 1976; Kohler et al. 2000). Macroscopically there is a gray discoloration of the corpus callosum caused by local demyelination, with disintegration of the white matter resembling that encountered in central pontine myelinolysis. Microscopically there is demyelination of the corpus callosum with spread to the deep frontoparietal cerebral white matter (see Fig. 18.1c–e).

18.5.2.6 Pellagra

A deficiency of nicotinic acid (vitamin B_6) or of its precursor tryptophan, which may be the result of alcohol-caused malnutrition, can cause dementia. Primarily there is a degeneration of cortical motoneurons (and basal ganglia), cerebellar nuclei, and anterior horn cells of the spinal cord (see below). The clinical features are marked by depression, fatigue, loss of concentration, confusion, hallucination, and optic nerve atrophy (Harper and Butterworth 1997; Gass and Hennerici 1999).

18.5.2.7 Alcoholic Myelopathy

Only isolated case reports have been published (Wieser 1965; Sage et al. 1984). The clinical picture is characterized by spastic paralysis and cystoplegia. Liver damage is almost universal and could, in itself, be etiologic. Sage et al. (1984), however, describe cases without liver damage or vitamin deficiency, so that a primary alcoholic effect can be assumed. In addition to chronic alcoholic intoxication, the main cause is a vitamin B_{12} and niacin deficiency. Degeneration of the anterior horn cells appears, which could also – or additionally – represent the sequelae of progressive Wallerian degeneration in primary peripheral neuropathy (Victor et al. 1989).

18.5.2.8 Neuropathy of the Autonomic Nervous System

Detailed studies have found that 5 of 30 chronic alcoholics suffer from an isolated parasympathetic neuropathy and, in 6 cases, a combined parasympath etic–sympathetic neuropathy was found (Barter and Tanner 1987; cf. also Johnson and Robinson 1988). Morphologically, there was a significant decline in the density of myelinated nerve fibers in the distal portion of the vagal nerve, together with axonal degeneration and changes associated with "dying-back" (Walsh and McLeod 1970). Sudden unexpected death in alcoholics with known symptoms of Wernicke–Korsakoff has been observed in combination with an autonomic neuropathy (Johnson and Robinson 1988).

18.5.2.9 Neuropathy/Polyneuropathy

The morphology characterized by widespread symmetric axonal involvement in conjunction with sensory and motor symptoms. The disorder corresponds to the pattern of distal axonopathy, where axonal changes primarily involve the distal tract of the longest fibers with the largest diameter of the lower limbs, and, to a lesser degree, the upper limbs (Fig. 18.6a, b – Pinelli 1985).

Alcoholic neuropathy is one of the most common consequences of chronic alcoholism. Although only 9% of 1030 hospitalized alcoholics had clinical

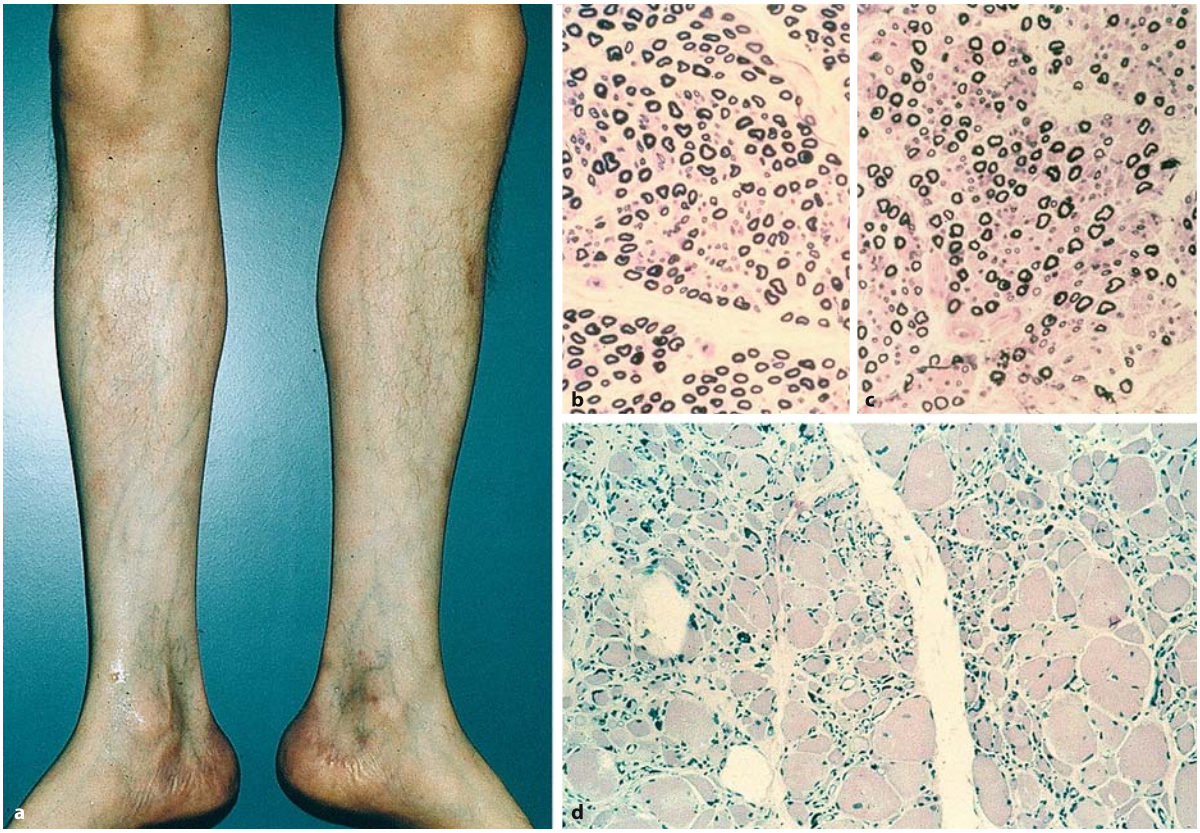

Fig. 18.6a–d. Alcoholic neuropathy and myopathy. **a** Macroscopically chronic alcohol intoxication often is characterized by a muscle atrophy of the distal type; **b** microscopically, in comparison with the normal density of axons in the sural nerve, **c** a decline of axons is demonstrable; **d** moreover, a typical distribution of atrophic muscle fibers is seen, which is associated with a neurogenic muscle atrophy (symmetric atrophy of small groups of fibers of the lower leg muscles). (**b–d** Semithin sections; magnification ×1000). The figures **b–d** were kindly provided by Professor Dr. H. Wiethölter, Stuttgart

symptoms of polyneuropathy (Victor et al. 1971), 93% of them exhibited electromyographic changes (D'Amour et al. 1991; D'Amour and Butterworth 1994). This phenomenon was recently stated by Vittadini et al. (2001) who found polyneuropathies especially in wine-drinkers.

18.5.2.10 Myopathy

Alcoholic myopathy is found in about 46% of outpatients (Urbano-Marquez et al. 1989) and 60% of hospitalized patients (Martin et al. 1985). It is apparently partly caused by the direct toxic effect of alcohol, and, in part, by neuropathic atrophy.

Acute muscle fiber necrosis can arise in the form of rhabdomyolysis (Haller and Knochel 1984), which chiefly affects the proximal muscles of the extremities (symmetric, asymmetric or focal – for review see Charness et al. 1989). Type I fibers appear to be selectively vulnerable. Subjectively, patients complain of pain in addition to impaired motor function. Chronic intoxication can lead above all to atrophy of type II fibers. The muscle weakness and atrophy predominate (Fig. 18.6a, d) (Haller and Knochel 1984; Martin et al. 1985). Pathologic change is not uniformly distributed throughout the muscle, but is more marked in some areas than in others. Atrophic fibers may be seen in some specimens as a group of smaller fibers surrounded by relatively normal-sized fibers. The small group atrophy is characteristic of denervation. Large group atrophy is caused by the direct toxic effect of alcohol. Perturbations in protein metabolism are central to the effects on muscle and account for the reductions in muscle mass and fiber diameter. Further biochemical mechanisms, including carbohydrate as well as lipid metabolism, ethanol-mediated insulin resistance, metabolic disturbances due to alcoholic cirrhosis, etc., are discussed by Preedy et al. (2001).

18.5.2.11 Secondary Pathologic Alterations

Specific alcohol-induced changes of the brain are discussed below; the following secondary pathologi-

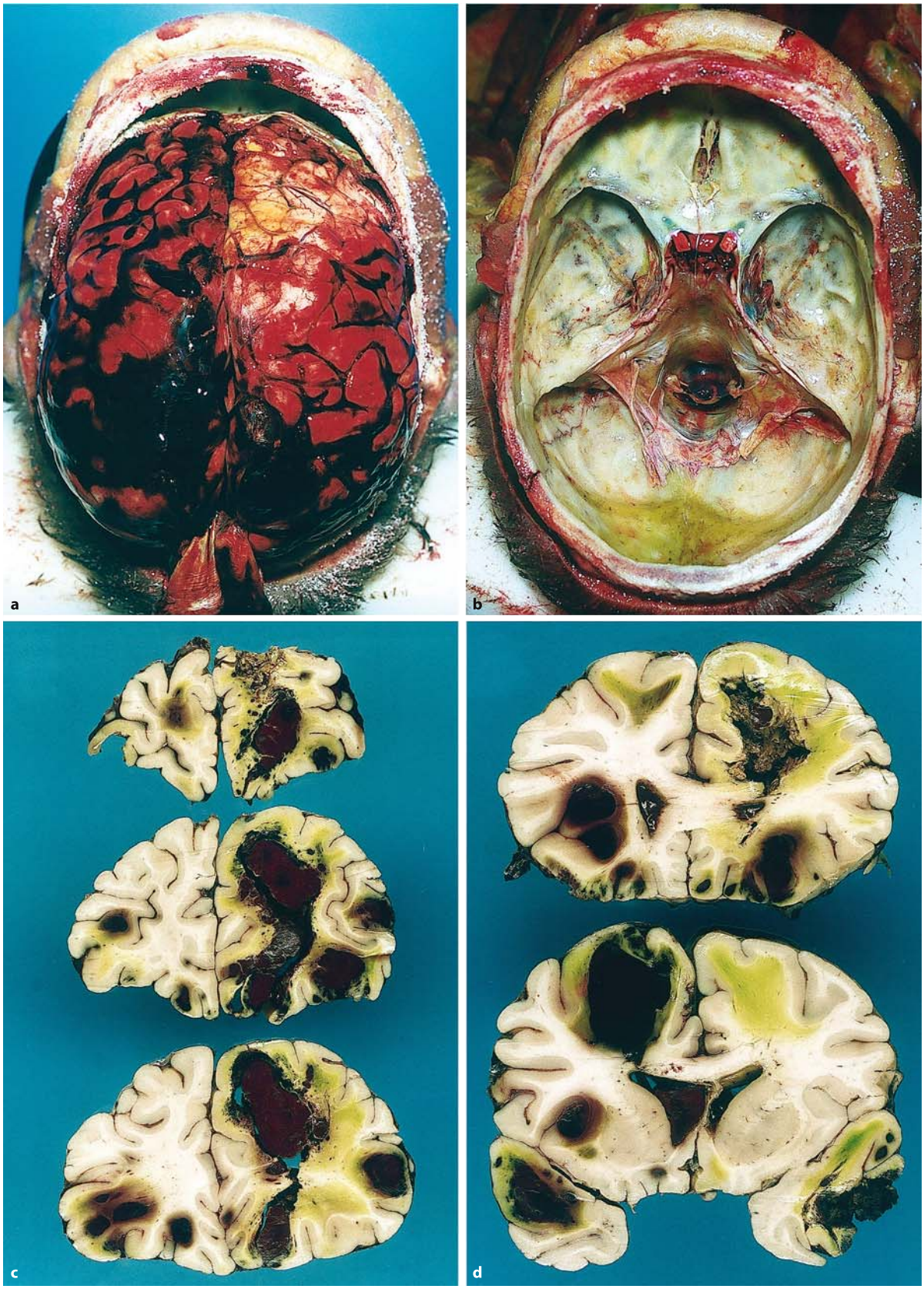

Fig. 18.7a–d. Secondary cerebral involvement in chronic alcohol intoxication. Intracranial bleeding caused by associated coagulation involvement and minor MBI: **a, b** subdural hemorrhage; **c, d** multiple intracranial hemorrhages

cal *processes* pose an increased risk to chronic alcoholics:

1. Mechanically induced brain damage can be caused by alcohol-induced motor impairment and/or by the milieu (Rönty et al. 1993).
2. Vascular injury, especially stroke, is more common in alcoholics. They usually involve ischemic necrosis, not hemorrhagic infarction (Gorelick 1989; Hansagi et al. 1995).
3. Intracranial bleeding, especially subdural hemorrhages (Fig. 18.7a, b) and intracerebral hemorrhages (Fig. 18.7c, d) is seen secondary to elevated blood pressure and impaired liver function with coagulation disorders (Monforte et al. 1990).
4. Thiamine (vitamin B_1) deficiency is caused by poor nutrition, insufficient absorption, and/or diminished phosphorylation of the coenzyme thiamine pyrophosphate (TPP). The activity of the TPP-dependent pyruvate dehydrogenase is significantly depressed in the cerebellar vermis of alcoholic patients (Butterworth et al. 1993).
5. A proliferation of Alzheimer type II astrocytes is induced by liver cirrhosis (hepatic encephalopathy) in the putamen: this type of astrocyte is characterized by PAS and glycogen granules inside a large, pale, vacuolated nucleus and a dense nuclear membrane. In severe cases, there can also be a proliferation of Alzheimer type I astrocytes with large, lobulated nuclei and distinct nucleoli (Diemer 1978). Because treatment usually interrupts the disease, nowadays mostly type II astrocytes are characteristically seen in hepatic encephalopathy. Both Alzheimer type II and type I astrocytes result from elevated levels of ammonia in the blood (Haschek and Rousseaux 1998). The astrocytes also contain elevated levels of glutamine synthetase, which converts glutamate to glutamine by incorporation of ammonia.

18.5.2.12 Disulfiram Treatment

Disulfiram is an inhibitor of aldehyde dehydrogenase (ALDH), which is used as an active agent in the management of maintaining abstinence. Administration of oral tablets (250 or 500 mg) induces a five- to tenfold increase in blood acetaldehyde concentrations.

Disulfiram induces facial flushing, throbbing headache, anxiety, abdominal pain, nausea, vomiting, sweating, thirst, chest pain, tachycardia, etc. This response, of course, does not depend solely on disulfiram's inhibition of ALDH and the consequent accumulation of high levels of acetaldehyde (Hald and Jacobsen 1948). It is also in large part due to an additional neurotoxic effect of disulfiram itself. Among other symptoms described are fatigue, restlessness, tremor, as well as psychosis and Parkinsonism. Moreover, a neuropathy of the distal axonopathy type, which begins within a few months after initiation of therapy, has been described, and a few instances of extrapyramidal symptoms associated with bilateral lesions of lentiform nuclei have been reported (Vaccari et al. 1998). Disulfiram appears to be a primary Schwann cell toxicant (Tonkin et al. 2000). Specific morphological alterations in intoxicated patients are not described.

18.6 Alcoholic Fetopathy and Embryopathy

Alcohol can also be especially cytotoxic and neurotoxic to embryos and fetuses, since alcohol penetrates the blood–placental barrier and because the enzyme system of the fetus or embryo is still undeveloped (West et al. 1990). The impact is multifarious. Moreover, physical dependence begins from the time of intrauterine intoxication.

Among the reported sequelae are intrauterine hypotrophy, craniofacial dysmorphy, and extracranial skeletal malformation (Clarren and Smith 1978; Majewski 1979; Streissguth et al. 1980; Rosett and Weiner 1984). The brain is subject to neuronal migration inhibition with neuroglial heterotopia and internal hydrocephalus. Extensive experimental studies describe, above all, migration inhibition in the cerebellum (Volk 1980).

Wisniewski et al. (1983) (see also Archibald et al. 2001) list the following neuropathological changes caused by alcoholic fetopathy and embryopathy (Fig. 18.8):

- Microcephaly
- Hydrocephalus
- Cerebellar malformations, especially of the cerebellar vermis
- Abnormalities (agenesis) of the corpus callosum and the anterior commissure
- Disproportionality and reduced basal ganglia volume
- Hypoplasia of the optic nerve and globe of the eye (microphthalmia)
- Loss or deficiency of retinal ganglion cells
- Meningeal glioneuronal heterotopia
- Neuronal microdysplasia

It is now known that alcohol – at least in animals – can cause massive intrauterine cell death; this nerve cell death is apparently caused by the blockade of the NMDA receptors on the one hand and activation of the GABA receptor on the other (Ikonomidou et al. 2000).

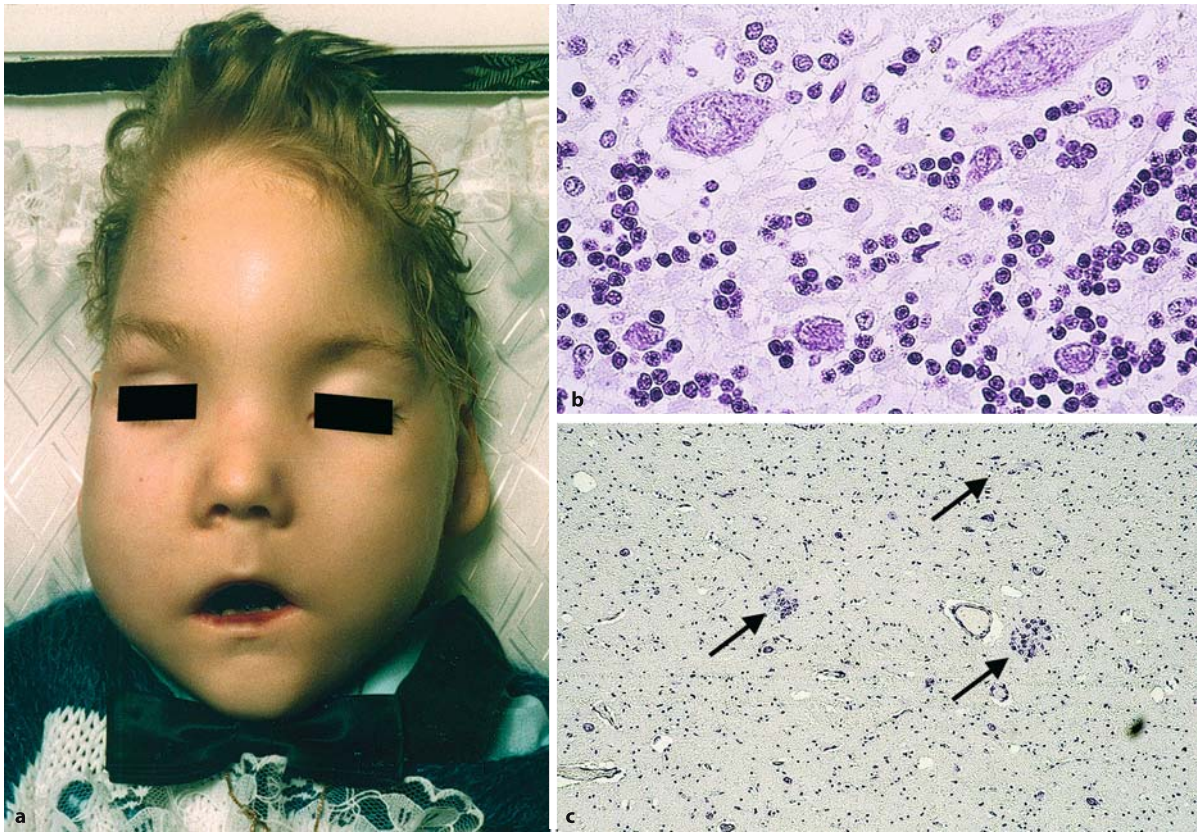

Fig. 18.8a–c. Fetal alcohol syndrome, which is characterized by craniofacial dysmorphy (**a**), microcephaly and hydrocephalus as well as retarded migration of Purkinje cells in the cerebellar cortex = heterotopia (**b**) and microdysgenesis of the pallidum (**b, c** Nissl stain; magnification **b** ×1,000; **c** ×300)

18.7 Organic Solvents and Aerosol

A wide variety of lipophilic solvents are used for so-called sniffing, including spot removers, nail polish remover, gasoline (benzene), hair sprays, deodorants, etc. Table 18.1 offers a list of these substances (Karch 2001). Inhalation of these organic solvents and aerosols, possibly using a plastic bag placed over the head, produces a "high" similar to that engendered by narcotics. They are also sexually stimulating, which accounts for death due to asphyxia during autoerotic manipulation.

Inhalation of solvents can induce a psycho-organic syndrome followed by encephaloneuropathy with personality changes, and dementia with impaired memory and intelligence and emotional disturbances (Rosenberg et al. 1988; Pryor 1990). A few cases of accidental poisoning and its consequences have been reported after accidental inhalation at the workplace.

Neuropathology. The literature contains only a few autopsy reports describing the neuropathological changes of such poisoning. The main finding in cases of chronic abuse is *extensive demyelination* (Escobar and Aruffo 1980; Rosenberg et al. 1988). Kornfeld et al. (1994) describe three cases with severe, but spotty loss of myelin, but with relatively mild axonal loss and gliosis. PAS-positive macrophages were present in all three cases. Moreover, toxic *neuropathies* with demyelination have been described.

Further pathologic-anatomic findings include glomerulonephritis and acute cardiac death. The forensic neuropathologist must always bear in mind that death in these cases can result from systemic and cerebral ischemia as a consequence of cardiac toxicity.

Table 18.1. List of lipophilic solvents for "sniffing." Source: Karch 2001

Aerosol propellants (air fresheners, deodorant spray, hair spray)
Dimethyl ether
Butane
Halogenated fluorocarbons
Bromochlorodifluoromethane (in fire extinguishers)
Carbon tetrachloride
Ethyl chloride
Perchloroethylene
Trichloroethylene
Gas fuels (disposable cigarette lighters)
Propane
Butane
Liquid petroleum gas
Chlorinated solvents (commercial dry cleaning/degreasing agents)
Carbon tetrachloride
Dichloromethane
Methanol
Tetrachloroethylene
Toluene
Solvents from adhesives (also paints, nail polish, varnish remover)
Acetone
Butane
Cyclohexanone
Toluene
Xylene

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Illegal Drugs and Drug Dependence 19

19.1 Epidemiological and Social Data

Alcoholism and the dependency on drugs are "diseases" as any others. In addition to acute and chronic alcohol intoxication, the most common form of lethal poisoning encountered in the forensic laboratory is acute intoxication caused by illicit drugs. Consumption of these drugs is increasing and poses major social, psychological, medical, and forensic problems both in the United States and in Western Europe. The increasing number of deaths among young and chronic addicts is of particular concern and has caused much public debate. Associated with the rise in consumption is an increase in prostitution and in the number of crimes against property and violent crimes committed by addicts to obtain money to finance their habits.

Drugs of abuse are able to elicit compulsive drug-seeking behaviors upon repeated administration, which ultimately leads to the phenomenon of addiction. Evidence indicates that the susceptibility to develop addiction is influenced by sources of reinforcement, variable neuroadaptive mechanisms, and neurochemical changes that together lead to altered homeostasis of the brain reward system. Addiction is hypothesized to be a cycle of progressive dysregulation of the brain reward system that results in compulsive use and loss of control over drug taking and the initiation of behaviors associated with drug seeking (Koob et al. 1998; Koob and Le Moal 2001). The view that addiction represents a pathological state of reward provides an approach to identifying the factors that contribute to vulnerability, addiction, and relapse in genetic animal models (Laakso et al. 2002).

Although each type of drug will be described individually below, most drug addicts today consume more than one type of drug, i.e., they will take any drug that has an effect on the central nervous system (CNS): stimulants such as cocaine, amphetamines; sedatives such as alcohol, codeine, morphine, barbiturates, benzodiazepines, etc.; and hallucinogens such as lysergic acid diethylamide (LSD), mescaline and numerous other substances (Geschwinde 1998;

Karch 2001). Substances used in substitution therapy such as methadone and dihydrocodeine (DHC) also have considerable toxic potential and drug addicts consume these substances in highly toxic doses. Particularly the combination of these substances with other drugs – including alcohol – can be fatal.

Since in neuropathology only the final condition is assessed, in the individual case it is hardly possible to differentiate which toxic substance caused which morphological changes. Animal studies are of little help in this regard since chronic abuse with such high dosages of toxic substances cannot be created even experimentally, as a rule. In addition the drug scene itself has an influence on the health of street users and can create secondary effects: intravenous injection of suspensions containing insoluble particulate substances, for example, or infections caused by needle sharing, malnutrition, and/or the antisocial milieu together with immunodeficiencies secondary to drug consumption. HIV infection is an ever-present possibility.

In forensic-neuropathological practice, therefore, the morphological feature is usually a mixed sequela produced by numerous factors. Nevertheless, we will attempt to present the functional and pathological changes regarded as typical for each toxic agent.

19.2 Cannabis

Preparations from *cannabis species* have been used since antiquity, not only as psychotropic drugs but also in the treatment of a number of ailments. Over 60 cannabinoid compounds are present in hemp. "Marijuana" is made from the tops and leaves of the hemp plant; "hash" from resins covering the flowers and leaves of female plants (Brust 1999). The main active component Δ^9-tetrahydrocannabinol (THC) produces most of its effects on the CNS by interacting with specific cannabinoid receptors on neurons (CB_1-receptors). Under normal circumstances, these receptors are thought to be one element of a neurotransmitter system that controls neuronal excitability. Other components of this putative signaling system include cannabinoids that are found naturally in the body, as well as cellular mechanisms by which these "endocannabinoids" are synthesized, transported, and metabolized (Piomelli et al. 2000 – for review see Christie and Vaughan 2001).

Cannabis has been considered an entry drug on the path to "hard" drugs and for this reason is prohibited by law in most Western countries. An inhaled dose of at least 2 mg and an oral dose of at least 10 mg THC is assumed to be the normal dosage. The target organ is the CNS.

Effect. Marijuana and hash are smoked or consumed orally. After a few "hits," the smoker feels relaxed and euphoric, his conscious processes and orientation remaining largely unaffected. After even low or medium doses however a mild stupor can occur.

Among the psychophysical effects are impaired temporal and spatial orientation, cognitive abilities, vision, motor function (ataxia), and circulation. In acute intoxication, e.g., driving ability is impaired. At the same time, there is a reduction in spontaneity and a certain apathy. At high doses, some individuals experience illusions or hallucinations.

The "high" *peaks* after about 15–40 min (smoking) or 30–120 min (oral application), and lasts for up to 2–6 h. The *half-life* of THC in blood plasma is 1–4 days; in extreme cases, metabolites of THC can be demonstrated in blood for more than 10–20 days. The urine of chronic users contains traces of cannabinoids (mainly the glucuronide of THC-COOH) for as long as 1–2 months.

After prolonged use, a certain psychic tolerance to THC can develop. It is still controversial whether chronic THC consumption can lead to *mental abnormalities* (Weinrieb and O'Brien 1993). The most often discussed abnormality is an "anti-motivated syndrome" characterized by apathy and flat affect, decreased attentiveness, and impaired short-term memory (Hollister 1967). Frequent cannabis use in teenage girls predicts later depression and anxiety, with daily users carrying the highest risk (Patton et al. 2002). Given recent increasing levels of cannabis use, measured reduction of frequent and heavy recreational use seems warranted. Moreover, evidence establishes a clear link between the use of cannabis and psychiatric illness, i.e., psychosis (Arseneault et al. 2002; Zammit et al. 2002). Recent studies have also found links between the use of marijuana and depression (Hall and Degenhardt 2000; McKay and Tennant 2000; Bovasso 2001; Rey et al. 2002).

Morphologically evident permanent injury of the CNS has not been described (Ray et al. 1979). THC may be powerfully neuroprotective, reducing ischemic neuronal necrosis (Louw et al. 2000) in spite of an increase in brain temperature (Perron et al. 2001).

19.3 Hallucinogens and Entactogens

Hallucinogens are substances which are commonly associated with hallucinosis. Entactogens are substances which generate a sense of "the touch within," i.e., a substance that affects individual physical sensations of touch. Hallucinogens and entactogens not only affect a person's emotional state – they can also induce deep psychological changes. These com-

pounds include substances that can alter sensory impressions and/or lead partly to sensory hallucinations. Hollister (1967) describes the following common features:

1. Changes in mood and perception dominate
2. Minimal memory or intellectual impairment
3. No association with stupor or excessive agitation
4. Minimal side-effects on the autonomic nervous system
5. Craving and addiction do not occur

Chemically the following three groups of hallucinogens can be differentiated:

1. Phenylalkylamines (mescaline)
2. Indole alkylamines (LSD)
3. Substituted amphetamines [3,4-methylenedioxmethamphetamine (MDMA), 3,4-methylenedioxyethamphetamine (MDEA) – without hallucinogenic, but entactogenic effects – cf. Thomasius 2000].

Deaths relating to these compounds are extremely rare compared to heroin-induced deaths. However, the danger exists that the number will increase in the foreseeable future due to the increasing use of these substances. In central Europe meanwhile the preferred drugs are synthetic agents such as MDMA and MDEA.

19.3.1 Mescaline

Mescaline is obtained from cacti native from southwestern North America and from the peyote plant. Mescaline was already being produced synthetically at the turn of the last century (1900). However, the main source of mescaline today is the peyote plant. An oral dose exceeding 700 mg has a *toxic effect on the liver*. The hallucinatory effect occurs after metabolism, i.e., after the mescaline has bound to endogenous proteins. The *half-life* of mescaline is about 6 h. The highest concentrations occur in the liver and kidneys, the lowest in the brain, where after 30 min mescaline can no longer be detected. About 2% of the ingested mescaline penetrates the blood–brain barrier. The hallucinatory effect begins within 1–2 h and lasts for 8–12 h. In an accidental death attributed to a mescaline-induced state of confusion, the following concentrations were found: blood 9.7 µg/l, urine 1,163 µg/l (Reynolds and Jindrich 1985). Morphological alterations of the brain are not known.

19.3.2 Lysergic Acid Diethylamide (LSD)

LSD was first synthesized in 1938 by Albert Hoffmann. Today LSD is taken at "rave" parties as an alternative to MDMA, almost exclusively in small – non-toxic – doses. The resulting levels in urine range over 2–3 µg/l; i.e., near the limit of detection. However, the metabolite's levels (2-oxo-3-hydroxy-LSD) are comparably high. A single standard street dose today is 20–80 µg (Nelson and Foltz 1992). LSD has an estimated half-life of 2.5 h. Clinical symptoms are similar to those produced by mescaline. From 1960 to 1980, numerous cases of acute panic reactions, flashbacks, and homicides were described (Klepfisz and Racy 1973), but today these phenomena are no longer observed. Only a few deaths from LSD toxicity have been reported. No specific neuropathological features are known.

19.3.3 Amphetamine Substitutes

Amphetamine substitutes are summed up by the term "designer drugs" and are generally taken in tablet form (e.g., "ecstasy"), and are often used to enhance performance. The drugs have both amphetamine-like and entactogenic properties. The main consumers of designer drugs are young people who want to make social contacts and dance through the night in discos. Eighty-one deaths related to taking ecstasy in people aged 15–24 years during the period 1997–2000 in England and Wales were evaluated (Schifano et al. 2003). Results of toxicological examination were made available in 75 cases; MDMA was present in 68 (91%), MDEA in 7 (9%), and opiates or opioids in 44 (59%) of these cases. In 26 (38%) cases, one or more drugs had been prescribed to the deceased patient. Those substances are neurotoxic by selective inhibition of monoamine oxidase A (MAO-A; Scorza et al. 1997), and by the induction of acute hypertension.

19.3.3.1 MDMA (3,4-methylenedioxmethamphetamine)

The half-life of MDMA (*synonyms*: *MDM*, *Eve*, *Ecstasy*) is about 8 h. In dogs, the LD_{50} is 8–23 mg/kg, in Rhesus monkeys 17–28 mg/kg, after intravenous administration. Following oral intake of 50 mg, a concentration of 105 µg/l could be detected in the blood of an adult man after 2 h. Blood levels had declined to 5.1 µg/l at 24 h. MDMA can still be detected in the blood after 3 days (Verebey et al. 1988). In cases of lethal intoxication, blood levels of up to 1,260 µg/l have

been observed (Bedford et al. 1992). The blood levels of living and dead users overlap. The clinical picture is characterized by hyperpyrexia, seizures, disseminated intravascular coagulation, rhabdomyolysis, and renal failure. In isolated cases (for review see Balmelli et al. 2001) the intake of fluids after MDMA ingestion may lead to potentially fatal hypervolemic hypotonic hyponatremia with cerebral edema.

MDMA acts on the CNS by increasing the release of serotonin and catecholamines and preventing reuptake (Abbott and Concar 1992). Clinically, chronic users are liable to develop paranoid psychoses (McGuire et al. 1994; McCann et al. 2000; Ricaurte et al. 2002), seizures, stroke, and various neurocognitive deficits as a result of neurotoxic lesions (Thomasius 2000). In animal experiments using non-human primates the cerebral serotonin terminals were selectively destroyed in neocortex, striatum and hippocampus, and axonal injury could be demonstrated (Insel et al. 1989; Ricaurte et al. 1992, 2000). As demonstrated in mice by Colado et al. (2001), production of specific radicals might be possible by MDMA metabolites reacting in turn with nitric ions.

Neuropathological findings in human beings, in contrast, have not been published. A recent study gives evidence of the immunohistochemical reactivity of nearly all neurons and axons of the cerebrum and cerebellum with antibodies to MDMA and MDEA – in two cases (DeLetter et al. 2003). The pathophysiological significance of this reaction pattern is still unknown and the diagnostic relevance has to be reexamined.

MDMA seems to have a selective neurotoxic effect on the serotonergic system (Battaglia et al. 1988). Neurochemical investigations and functional neuroimaging studies in humans suggest alterations of central nervous functions after ecstasy use lasting weeks to months (Obrocki et al. 2001). Moreover, pathologic-anatomic evidence of hyperthermia, rhabdomyolysis, renal failure, and disseminated intravascular coagulation as well as hepatopathy including acute yellow hepatic dystrophy have been described (Campkin and Davies 1992).

19.3.3.2 MDEA (3,4-methylenedioxyethamphetamine)

This drug is a close relative of MDMA (*Synonym*: *Eve*, *Ecstasy*) with similar psychophysical and pathological effects, kinetics, and concentrations. It is a true "designer drug" synthesized when MDMA was prohibited.

19.3.4 Other Agents

A large number of natural and synthetic hallucinogens are known, e.g., psilocybin, 2,5-dimethoxy-4-methylamphetamine (DOM), and phencyclidine. Neither acute nor chronic intoxication by most of these substances causes neuropathological changes. Clinically and pathologically they are comparable in their effects to the aforementioned hallucinogens.

Phencyclidine (*PCP*), a dissociative anesthetic and widely abused psychotomimetic drug, and related agents (MK-801, tiletamine, and ketamine) have an apparent neurotoxic effect, which has heretofore been overlooked: these drugs induce acute pathomorphological changes in specific populations of brain neurons when administered subcutaneously to adult rats in relatively low doses (Olney et al. 1989). It is unlikely, however, that similar lesions appear in the human brain.

19.4 Narcotics: Opium and Opioids

19.4.1 Basic Principles

19.4.1.1 Epidemiology

Most deaths due to chronic illicit drug abuse involve the consumption of opiates. The increase in the number of drug deaths in Europe and the USA is due mainly to the increase in the number of intravenous drug addicts. At present, the annual number of drug-related deaths is approximately 2,000 in Germany (Deutsches Bundeskriminalamt – cf. Oehmichen 1997) and 5,000 in the USA (Drug Abuse Warning Network). As there is no international agreement on the definition of a drug-induced death, the epidemiological data of different countries are not comparable. The German statistics include deaths classified according to the following criteria (Oehmichen and Staak 1988):

1. Direct toxic effect of the drug or its metabolites (accidental or suicidal overdose).
2. Direct toxic effect of adulterants or extraneous substances injected along with the drug.
3. Infections as a complication of the drug culture life-style including needle sharing or depressed immune function (Novick et al. 1989).
4. Death of a drug addict due to causes having no direct connection with drug consumption.

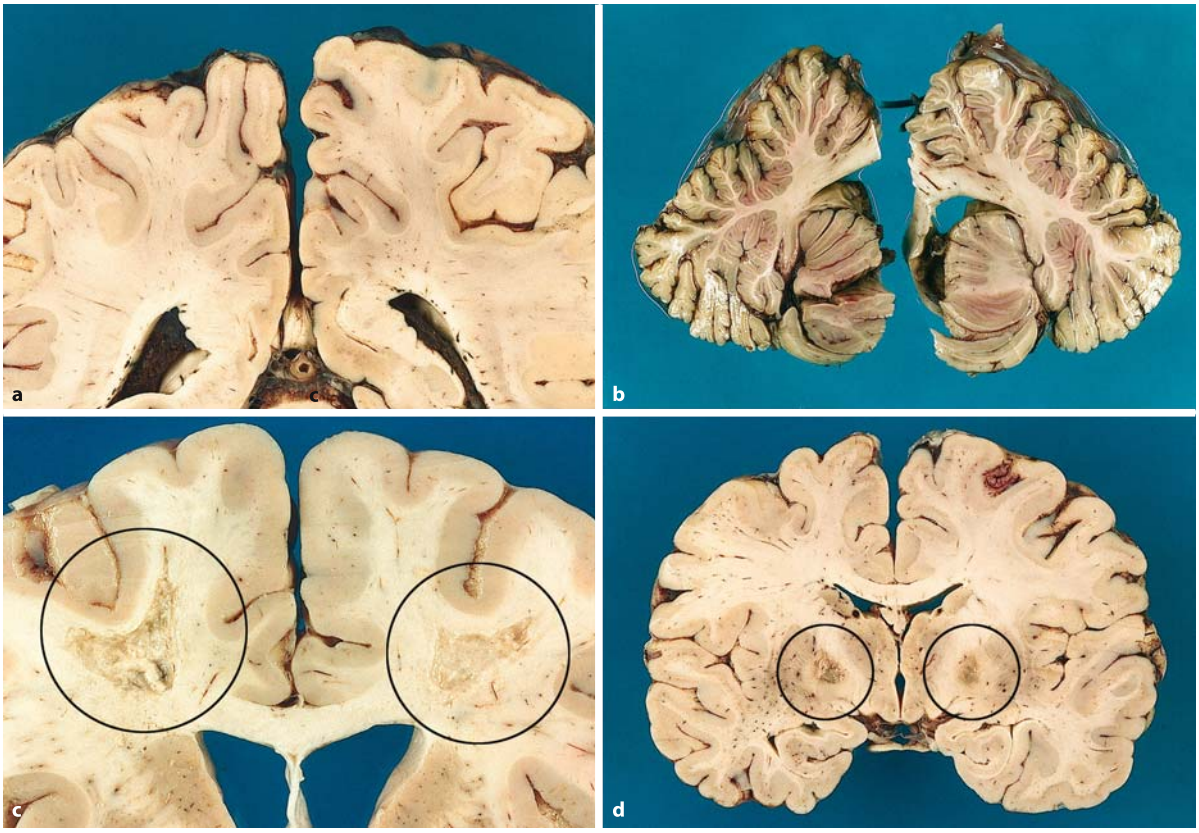

Fig. 19.1a–d. Ischemic encephalopathy in chronic drug addicts. **a** Cerebral cortical atrophy in a 20-year-old man who survived an acute drug intoxication for <5 h. **b** Cerebellar atrophy; **c** bilateral white matter softening as an indication of demyelination; **d** bilateral pallidum necroses

19.4.1.2 Pathophysiology

The effective mechanism is explained by binding to specific opiate receptors on neurons of the CNS. Several different receptors have been described which are normally targeted by endogenous opioids (endorphins). The similarity in chemical structure of the exogenous morphine derivatives allows them to bind to (and possibly block) the neural receptors, thereby inhibiting, for example, the function of the endorphin system. This appears to hinder the release of acetylcholine and depolarization of the neurons (Dominiak 1992). At the same time, the effectiveness of dopamine is enhanced, since the propagation of inhibiting signals from neighboring neurons is also prevented. This leads to the typical phenomena of euphoria and addiction. The addiction itself is caused by the memory of the nerve cells for the positive reinforcement of the experienced "high," which is in turn due to the release of dopamine.

All narcotics have their target organ in the CNS, where they also inhibit the respiratory centers. An overdose causes a primary central respiratory arrest possibly with maintained heart action. The result is massive congestion of blood in all organs secondary to the relative right ventricular insufficiency, which is aggravated by pharmacological paralysis of the vessels and by a hypoxia-induced reduction in vascular tone.

19.4.1.3 Neuropathology

In acute death resulting from heroin consumption, there is *congestion*, *perivascular hemorrhages*, and *cerebral edema* (Richter et al. 1973; Oehmichen et al. 1996). If an antidote is given (naloxone) or if artificial respiration is performed, the patient can survive without any signs of neurotoxic injury.

Overdose victims with longer survival times, but who do not receive the above-mentioned therapies or whose therapy is applied too late, exhibit all the signs of *generalized circulatory failure*, i.e., cortical atrophy of the cerebrum (Fig. 19.1a) and the cerebellum (Fig. 19.1b). Sometimes there are *patches of demyelination* (Fig. 19.1c) producing a picture resembling that of the intermittent form of CO poisoning (Sudo 1968). The sequelae will be a so-called ischemic encephalopathy (Makrigeorgi-Butera et al.

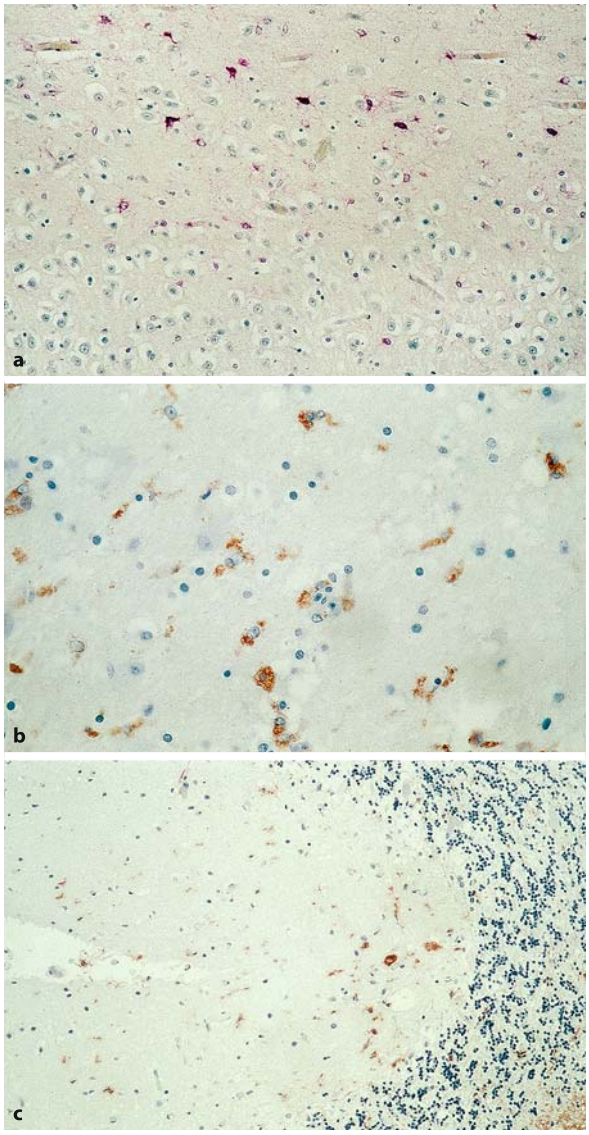

Fig. 19.2a–c. Reactive alterations indicating a relapsing ischemia. Focal increase of astrocytes (**a**) and microglia (**b**) in the hippocampal cortex; **c** loss of Purkinje cells and microglial activation (**a** GFAP; **b, c** CD68; magnification **a** ×300; **b** ×1,000; **c** ×500)

1996; Oehmichen et al. 1996). Some cases additionally are characterized by a bilateral *pallidum necrosis* (Anderson and Skullerud 1999) (Fig. 19.1d) similar to that described in CO poisoning.

Chronic intravenous drug addicts, whose death is not caused by an acute overdose or late, unsuccessful resuscitation, almost always exhibit numerous secondary injuries caused by repeated phases of ischemia. In the brain, there is a focal increase of astrocytes and microglia (Fig. 19.2a, b), which is especially conspicuous in the hippocampal formation and which is sometimes accompanied by selective and segmental nerve loss in the CA1 region of the hippocampus (Ammon's horn) and in the Purkinje cell layer or in both areas (Oehmichen et al. 1996) (cf. Fig. 19.3). A total of about 26% of 162 fatal cases of drug abuse expressed a distinct neuronal loss in the cerebellar cortex (Purkinje cell layer) and in the CA1 region of the hippocampal area. The number of cases with reactive cortical changes, i.e., focal astrocytic and/or microglial reaction, gave an indication of about 90% of dead chronic intravenous drug addicts with relapsing transient ischemia (Oehmichen et al. 1996 – see Fig. 19.4).

In addition to these rather non-specific sequelae, some heroin addicts also show a *transverse myelopathy* (Stodieck 1983; Kishorekumar et al. 1985). This usually involves flaccid paralysis, which sometimes may be reversible. A morphological equivalent is present only in the rarest of cases: localized distention of the cervical region of the spinal cord, as demonstrated by a myelogram – non-specific necroses of the gray matter or necrotizing vasculitis. The occurrence of relapses after temporary withdrawal is striking, which some authors think points to an allergic pathogenesis.

A special form of injury is the occurrence of a *leukoencephalopathy*, usually observed in the white matter of the cerebrum and, occasionally, also in the cerebellum (Ropper and Blair 2003) (Fig. 19.1c). This is observed mainly following inhalation of heroin pyrolysate and is reported almost exclusively in Europe (Poulet-Perez et al. 1992; Oehmichen et al. 1996; Rizzuto et al. 1997). The pathological features are characterized by a more diffuse or spongiform demyelination and patchy necrosis involving the globus pallidus and the cerebral and cerebellar hemispheric white matter. The putative pathogenetic mechanisms are anoxic damage to small vessels, cerebral edema, acidosis and edema, and severe hypoxic injury (see also Karch 2001).

In isolated cases, *transverse myelitis* has been described, but the incidence of this disorder seems to be decreasing (Karch 2001). The myelitis may be the result of a thromboembolic syndrome, an inflammatory vascular disease or a toxic manifestation due to some contaminants injected along with the heroin.

Moreover, *peripheral neuropathy* has been described associated with non-sterile injections, elevated compartment pressure, or trauma (Sheehan and Jabre 1995). Occasional reports of *stroke* and *polyarteritis*-like disorders have been published.

Finally, it must be pointed out that some of the most common – and fatal – late complications seen in intravenous dope addicts are *hepatitis B*, *C* and *HIV infections*, which can be manifested in many different forms (pp. 593 ff).

The following are the most important narcotics.

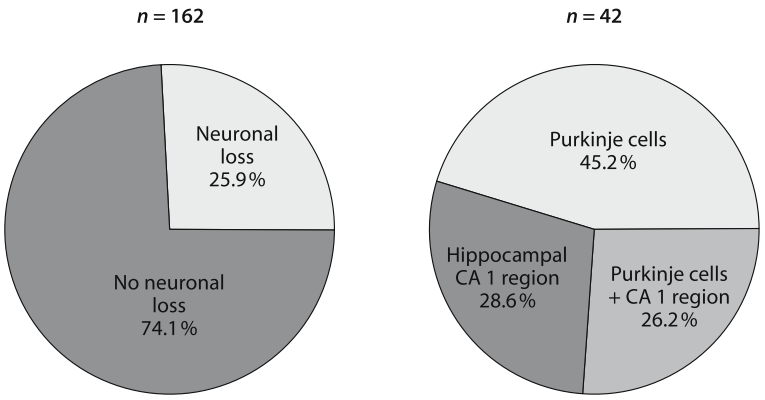

Fig. 19.3a, b. Frequency of neuronal loss in chronic intravenous drug addicts is demonstrated in about 26% of 162 cases: **a** either in the cerebellar cortex or the hippocampal CA1 region or in both the areas (**b**) (cf. Oehmichen et al. 1996)

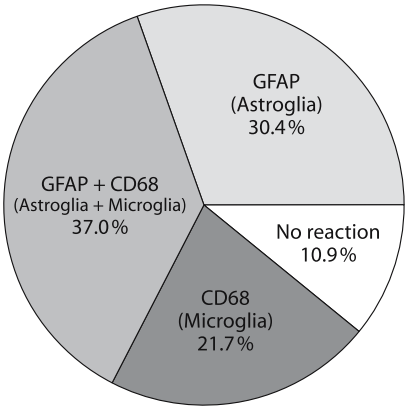

Fig. 19.4. Frequency of reactive alterations in the hippocampal area of chronic intravenous drug addicts (n=46) as an indication of a repeated ischemic state for a prolonged period which was demonstrable in 90% of the cases (cf. Oehmichen et al. 1996)

19.4.2 Morphine

Morphine is administered intravenously, subcutaneously, orally, rectally, intranasally, and by inhalation. Pure morphine is predominantly applied in clinical practice to treat pain.

The *pharmacokinetics* of morphine depends on the route of administration. Morphine is metabolized by conjugation with glucuronic acid to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). The half-life of intravenous morphine is 1.7 h. The half-life of the glucuronide metabolites by contrast is 3.9±1.5 h for M3G and 2.6±0.69 h for M6G (Osborne et al. 1990).

It is striking that 6-acetylmorphine is present in the cerebrospinal fluid (CSF) and brain in much higher levels than in other organs (concentration – blood: 11.3 ng/ml; CSF: 58 ng/ml; brain: 158 ng/ml – Goldberger et al. 1994). The lethal dosage depends on individual tolerance.

The period of survival following the last morphine intake can be estimated based on the relationship between morphine levels in the cerebellum and medulla oblongata: cases with short survival times and acute deaths have higher concentrations in the cerebellum than in the medulla oblongata, whereas for cases with longer survival times the reverse is true (Vycudilik 1988).

19.4.3 Heroin

Heroin is produced synthetically. In the body, heroin can be demonstrated for a maximum of 15 min and is metabolized into 6-monoacetylmorphine (6-MAM). This in turn is metabolized into morphine and finally to glucuronides (M3G and M6G).

The lethal dosage depends on individual tolerance and – in part – on the environmental circumstances. While concentrations of free morphine in cases of lethal overdose vary widely (from 50 µg/l to 1500 µg/l), it is now assumed generally that blood levels below 100 µg/l are mostly survived, whereas levels exceeding 100 µg/l are potentially lethal (Recker 1998; Meissner et al. 2002). Fatalities at lower blood levels point to other factors contributing to the death: very low tolerance because of acute drug withdrawal, simultaneous consumption of other drugs such as alcohol, or dihydrocodeine, or accompanying illnesses such as respiratory infection (Koch 2002).

19.4.4 Codeine

Codeine is a naturally occurring alkaloid found in opium, which is metabolized to morphine. Its half-life is 2.4–3.2 h. The therapeutic dosage as an antitussive is 30–50 mg/day (maximum 100 mg/day). Codeine has a slight sedative effect and is mildly analgesic. Codeine is used by drug addicts as a substitute and during therapeutic withdrawal periods

at doses of 300–400 mg/day, i.e., 5–10 capsules. The maximum effect is reached after 1–2 h, the effect lasts for 4–6 h. Chronic users develop tolerance. Specific neuropathological alterations are not known.

19.4.5 Dihydrocodeine (DHC)

DHC is also an anti-tussive taken at doses ranging over 10–30 mg/day. The potential for addiction is somewhat greater than for codeine. This substance otherwise behaves like codeine.

19.4.6 Methadone

Methadone is synthetically produced. D-Methadone is to be distinguished from the enantiomer L-methadone, levomethadone (L-methadone = polamiden). Since the early 1960s, methadone has been used in heroin withdrawal therapy in the USA. In Germany today DL-methadone-HCl as well as Polamidon is administered orally in withdrawal therapy. The standard single dose is 7.5 mg, the daily dose 30–50 mg, depending on the tolerance of the individual addict; in some cases as much as 180–260 mg/day is needed to block the opiate receptors (Walton et al. 1978).

Numerous lethal methadone poisonings have been reported. Usually heroin and/or DHC is detected in addition to methadone. Fatal blood levels in cases of isolated lethal methadone poisoning range from 200 µg/l (Worm et al. 1993) to 1,000 µg/l (Worm et al. 1993) and 260–2,500 µg/l (Drummer et al. 1992). Blood levels in methadone maintenance patients range 20–308 µg/l (Lorimer and Schmid 1992).

Under controlled oral intake of methadone and abstinence from all other drugs (when compliance is good), methadone therapy has a high success rate with a low risk of intoxication. In contrast, intravenous application of methadone in combination with heroin, barbiturates, amphetamines or alcohol entails a high risk of fatal intoxication.

19.4.7 Other Narcotic Agents

Other substances with effects similar to those of methadone are propoxyphene, fentanyl, and hydromorphone. These substances are used much less often and then only as substitute drugs.

19.5 Stimulants

19.5.1 Cocaine

Cocaine is obtained from the Bolivian coca plant. The ancient inhabitants of Bolivia knew of the narcotic effect of cocaine, and even today many of their descendants continue the habit of chewing coca leaves. In Western populations, cocaine is taken mainly by snorting, smoking or intravenous injection.

Cocaine is said to increase the risk of homicide, suicide, and violent death in general. In fact, the majority of cocaine-related deaths are a consequence of taking too much cocaine for too long (Karch 1999). In large American cities, most cocaine-related deaths (roughly 60%) are a direct consequence of chronic cocaine toxicity. Homicides account for another 20%. Suicide is the mode of death in <10% of cases where cocaine is detected, and in those cases the presence of cocaine, or cocaine metabolites, is usually an incidental finding (Tardiff et al. 1989). Of course, isolated cases of suicidal overdoses have been reported (Sperry and Sweeney 1989), but most documented cases of massive overdose involve drug smugglers with a ruptured packet of cocaine in their intestines (Wetli and Mittelmann 1981).

Metabolism. Cocaine has a half-life in humans of 0.5–1.5 h (Jatlow 1988). It is rapidly metabolized into ecgonine methyl ester (EME) and benzoylecgonine (BZE). Only a small percentage of cocaine is excreted unchanged in the urine (Ramcharitar et al. 1995). Cocaine metabolites have a much longer half-life: EME of about 4 h, BZE of almost 6 h after ingestion.

Because cocaine is more stable in the brain's lipid-rich environment than in postmortem blood, brain cocaine levels are a better indication of levels at the time of death (Hernandez et al. 1994). Being lipophilic, cocaine easily crosses the blood–brain barrier, BZE only with difficulty (Misra et al. 1975). The striatum has the highest density of cocaine receptors in the brain. Cocaine levels in the brain are 4–10 times higher than those in plasma when measured 0.5–2 h after administration of the drug (Spiehler and Reed 1985; Benuck et al. 1989).

Pathophysiology. Cocaine disrupts catecholamine metabolism and prevents the reuptake of neurotransmitters such as dopamine, noradrenaline, adrenaline, and serotonin (White 1998). Additional adrenaline is released from the adrenals (Knuepfer and Branch 1992). Large doses of cocaine will result in continuous seizure activity (Campbell 1988) and affect temperature regulation (hyperthermia effect).

Increasing α-adrenergic stimulation of vascular smooth muscle causes vasoconstriction and ischemia. Simultaneous stimulation of α- and β-receptors is associated with increased oxygen demand.

Robinson et al. (2001) could demonstrate that repeated treatment with psychostimulant drugs, such as cocaine, amphetamine, or nicotine, produces long-lasting increases in dendritic branching and spine density in some brain regions (nucleus accumbens, pyramidal cells in the parietal cortex, hippocampus). These changes may be related to the development of behavioral sensitization and the compulsive pattern of drug-seeking behavior (Kolb et al. 2003).

Pathology. External markers of cocaine use may include perforated nasal septum and crack keratitis. Moreover, the histopathology is comparable with morphologic alterations in catecholamine intoxication: contraction band necrosis of cardiomyocytes (Oehmichen et al. 1990; Karch 2001). Pulmonary edema is the principal finding at autopsy (Karch 1991). Although sudden death may be a fatal consequence of cocaine abuse, it is not sufficiently explained pathophysiologically, even though numerous hypotheses exist (Karch 2001).

Neuropathology. In only a few cases there were findings in the brain, especially cerebrovascular complications (Levine et al. 1991): cerebral infarction as a consequence of vasoconstriction (Konzen et al. 1995), cerebral vasculitis with transmural infiltration by leukocytes and/or mononuclear inflammatory cells (Fredericks et al. 1991), subarachnoid and intracerebral hemorrhages (Daras et al. 1994) (see also p. 573), seizures (Derlet and Albertson 1989; Brust 1993), and movement disorders (Brust 1993, Daras et al. 1994). In experimental toxicology an acute astroglial response (GFAP upregulation, increase of astrocytes, their cell size and shape complexity) could be demonstrated in mouse dentate gyrus (Fattore et al. 2002).

19.5.2 Cocaine Freebase: Crack

Mixing cocaine-hydrochloride with alkaline substances such as sodium or ammonium bicarbonate or baking powder plus water produces the freebase of cocaine, the acute psychophysical effect of which exceeds even that of cocaine hydrochloride. Crack is usually smoked. When freebase cocaine is smoked, peak blood levels approach those obtained by intravenous application and are rapidly attained. However, the high lasts no longer than 30 min (Foltin et al. 1988; Foltin and Fischman 1991) and is followed by a phase of depression ("crash"), which the abuser often combats by renewed inhalation of crack.

The pathological findings correspond to the findings following cocaine abuse.

19.5.3 Amphetamine and Methamphetamine (Speed)

These substances are produced synthetically. They are chemically related and produce similar effects.

Pharmacokinetics. Both agents can be swallowed, injected, smoked or "snorted," oral intake being most common. Orally applied DL-methamphetamine has a mean plasma half-life of 11.1 h, peak levels being reached after about 3 h (Cook et al. 1992); the half-life after injection is 1.2 h. Up to 45% of methamphetamine is excreted unchanged in the urine, 4–7% is *N*-demethylated to form amphetamine.

Pathophysiology. Both substances affect synapses by preventing the reuptake of catecholamines and they induce transmitter release. Blood levels do not correlate with the degree of impairment because of variations in tolerance. When measuring the levels of methamphetamine and those of its metabolite amphetamine in autopsied brain regions of human users, only slight regional differences were observed. There is a heterogeneous distribution; no preferential retention in dopamine-rich brain areas was observed (Kalasinski et al. 2001). Moreover, methamphetamine can induce neurotoxicity, which is associated with reactive oxygen and nitrogen species and their contribution to neuronal death via necrosis and/or apoptosis (for review see Davidson et al. 2001).

Clinical Correlation. Functional brain disturbances give rise to, for example, psychotic symptoms, apparently caused by the affinity of amphetamines for sigma receptors (Itzhak and Stein 1990). Amphetamine abuse can also cause personality changes, the abuser becoming restless, tense and fearful, partly paranoid, but not disoriented. Some abusers suffer auditory, tactile, and visual hallucinations.

These substances have a strong stimulating effect on the CNS. The peripheral sympathomimetic effects include vasoconstriction, elevated blood pressure, accelerated pulse and dilation of the upper airways as well as dryness of the mucous membranes of mouth and nose. Depending on dosage, mydriasis, hypertonia, tonicity of the smooth muscles and increased sexual drive also occur. Both agents are anorectics. Users experience a subjective feeling of increased powers of concentration and thinking and enhanced self-confidence unaccompanied by an objective improvement in performance.

Pathology. Methamphetamines (as well as MDMA and cocaine) apparently affect the temperature center in the brain stem: they are known to cause hyperthermia (Käferstein and Sticht 2000), which can lead to rhabdomyolysis and renal failure and thus to death. Methamphetamines also damage the cardiovascular system and chronic abuse can be fatal because of a stimulant-related cardiomyopathy.

In the brain, amphetamine or methamphetamine in rare cases can cause hemorrhagic and ischemic strokes. About 50 cases have been described in the literature. Sometimes the cause is a necrotizing vasculitis (Citron et al. 1970), sometimes preexisting arteriovenous malformations. In general, the hyperdynamic circulation and increased cerebral blood flow with amphetamine (Berntman et al. 1978) can cause intracerebral hemorrhage (McGee et al 2004). Thus, although specific parenchymal patterns of brain degeneration have been described with different drugs in animal models (Ellison and Switzer 1993), it is as well to remember that most effects in humans are generalized, non-specific cardiovascular effects. Amphetamine itself, however, may be toxic to dopamine terminals within the brain (Krasnova et al. 2001), and the cytokine interleukin-6 may play a role in methamphetamine neurotoxicity (Ladenheim et al. 2000).

Recent postmortem studies reported that chronic amphetamine users of unknown abuse intensity show long-term losses in dopamine and 5-hydroxytryptamine function in the caudate nucleus (most striking loss) and the putamen (Wilson et al. 1996).

19.5.4 Caffeine

Caffeine is the most widely used stimulant in the world. Numerous beverages and some medications are common sources of caffeine. Its spectrum of effects, its toxicity, and its chemical structure all resemble those of *theophylline*. A conspicuous finding in rat experiments is that, although both substances were present in nearly all tissues in about the same concentrations, the brain caffeine levels are about 25% higher than theophylline levels (Ståhle et al. 1992).

Pharmacokinetics. In adults, the half-life of caffeine is 3–7.5 h, in infants it is much longer, being 82 h shortly after birth, and 14.4 h at age 3–4.5 months.

Effects. Caffeine's effects are dose dependent and vary widely at low doses. The effective mechanism involves inhibition of phosphodiesterase, excessive intake being accompanied by signs of sympathetic stimulation. Plasma catecholamine levels are thought to rise due to increased release of catecholamine from the adrenal medulla (Benowitz et al. 1982). More recent studies, however, have cast doubt on these assumptions (Cameron et al. 1990). Caffeine has a direct effect on cardiac myocytes (increase of myocardial contractility and release of calcium ions from the sarcoplasmic reticulum), cerebral blood flow (which decreases), and on systolic blood pressure (which increases – Cameron et al. 1990).

Toxicity. A few case reports have been published of high doses of caffeine (plasma levels 79–1,560 mg/l, cf. Mrvos et al. 1989) causing lethal cardiac arrhythmia together with pulmonary edema and visceral congestion. Specific morphological changes due to caffeine have not been described. Such changes may occur if caffeine is ingested together with some other β-antagonists, such as low doses of isoproterenol (myocardial necrosis).

The few published human autopsy reports describe non-specific alterations at most. No specific lesions of the brain could be observed (Bryant 1981). Animals studies show that caffeine augments hippocampal necrosis due to electroshock seizures (Enns et al. 1996), but in ischemia acute and chronic effects of caffeine appear to differ, with acute caffeine augmenting but chronic caffeine mitigating ischemic neuronal damage (Sutherland et al. 1991).

19.5.5 Ephedrine

Ephedrine is a natural product obtained from a species belonging to the genus "*Ephedra*" of the "Ephedracea" family. It is structurally similar to adrenaline and noradrenaline, but is chemically stable and effective when taken orally. Ephedrine produces an indirect sympathomimetic effect, which ranges between that of adrenaline and noradrenaline. Ephedrine releases noradrenaline from the storage granules of the sympathetic nerve endings and inhibits the reuptake of noradrenaline from the synaptic gap. Since ephedrine can pass the blood–brain barrier, it has a stimulating effect not only on the peripheral, but also on the central nervous system.

Chronic consumption can produce psychological dependence similar to that associated with amphetamines. Exogenous psychoses (cerebral stimulant psychoses), which are accompanied by schizophrenia-like symptoms and resemble alcoholic delirium, have also been described. Paranoid reactions predominate.

19.5.6 Khat

Khat is used in East Africa and in Yemen as a psychostimulant. When chewed, khat leads to activation

of the sympathetic nervous system, which in turn causes a rise in blood pressure, body temperature, and respiratory rate with variable effects on heart rate.

The early literature described cerebral hemorrhages, myocardial ischemia, and pulmonary edema (Halbach 1972). Animal experiments have shown that khat releases dopamine and hinders uptake of dopamine.

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Pediatric Neuropathology V

Basic Principles

20

The developing brain's liability to insult from impact, asphyxia, and exposure to chemicals and drugs is well known. This vulnerability is based on (and characterized by) phenomena associated with the proliferation of neurons and glial cells, the migration of neurons, the differentiation of neurons and glial cells, including synaptogenesis, gliogenesis and myelination, as well as with apoptosis as a form of programmed cell death (Barone et al. 2000). The brain of the fetus, the infant, and the toddler differs chemically, structurally, and thus also functionally and biomechanically from the adult brain. Its size and mass depend on its developmental age. The infant brain consists of >90% water, the adult brain only 76% (Davison and Dobbing 1966; Blinkov and Glezer 1968). Unlike the adult brain, the infant brain is not held together by an extensive network of myelinated nerves; its essence is its fluidity. Beginning in the womb, normal development of the nervous system requires that the concomitant and coordinated ontogeny of proliferation, migration, differentiation, etc. as well as a specific reactivity to different impacts occur in a temporally and regionally dependent manner. For these and related reasons a separate section is presented dealing with the unique problems associated with forensic pediatric neuropathology. The developmental phases depicted in Fig. 20.1 (Vorhees 1986) apply to the classification of the gestational age used here.

20.1 Epidemiology

The forensic pediatric neuropathologist must distinguish deaths occurring in the perinatal phase from postnatal deaths.

20.1.1 Injuries During the Perinatal Period

The perinatal period shortly before and after birth is delimited as a phase beginning with the completion of the 28th week of gestation and is variously defined as ending 1–4 weeks after birth. The literature offers numerous surveys on perinatal mortality rates. The comparison of their findings, however, is often difficult due to differences in the definitions applied and in the objective of the authors (Golding 1993). Moreover, the perinatal mortality rate in a given country reflects the quality of medical care available to its citizens. Industrially developed nations have a perinatal mortality rate of about 4–7 per 1000 live births (Guyer et al. 1999). The principal causes of stillbirth deaths in these countries are as follows (Hovatta et al. 1983 – necropsy classification):

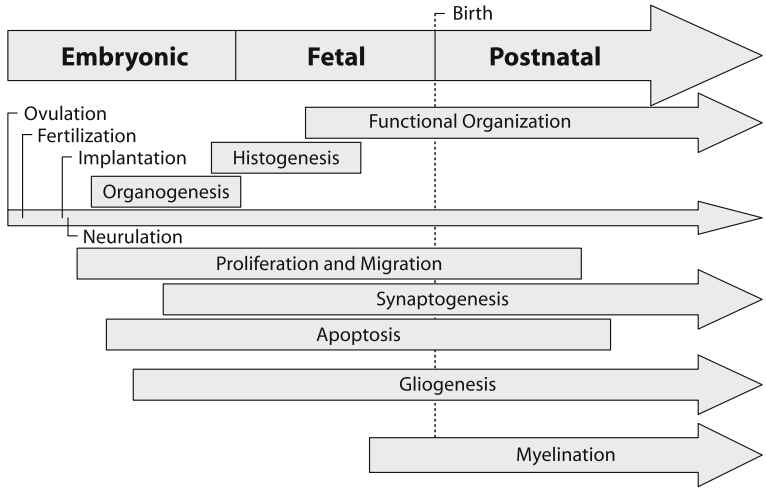

Fig. 20.1. Developmental periods (*upper panel*) and developmental processes of organogenesis and histogenesis of the central nervous system (source: Vorhees 1986)

- Asphyxia, as demonstrated by meconium aspiration, petechiae on serous membranes and intracerebral hemorrhages: 38.3%
- Major malformation: 16.9%
- Severe erythroblastosis fetalis: 0.8%
- No cause found: 1.2%
- Maceration only, without a demonstrable cause of death: 42.8%

The morphologic picture of inflammatory infiltrations (inflammatory and reparative tissue reaction) in developing human CNS was investigated by Damska et al. (2004). Morphological feature of inflammatory reaction in the immature CNS develop in the second half of pregnancy. The final localization in fully mature inflammatory reactions is prolonged in time. It was found that numerous granulocytes appear in bacterial infections, but not in aseptic lesions of the brain. The changes depend on the character of the injurious factor and the level of maturation of the CNS. The topography of maturing brain lesions due to infectious and anoxic/ischemic damage was similar and the lesions were localized most often in the periventricular white matter.

20.1.2 Acquired Postnatal Injury

Among the causes of brain injury occurring after birth, i.e., during the early postnatal period, are traumatic events, bleeding, anoxia, infections, brain tumors, and other malignant disorders. A review of morbidity and mortality to the age of 14 years revealed a cumulative incidence of serious mechanically induced brain injury (MBI) of 235 per 100,000 in a Finnish population (Rantakallio and Wendt 1985). This is comparable with a total incidence of acquired brain injuries of 175–200 per 100,000 in the population of the USA reported by Kraus and McArthur (1996). Epidemiological data from the USA, Germany, and other western countries (e.g., Sweden – Emanuelson and Wendt 1997) reveal similar statistics: in Germany, about 100,000 cases of MBI are documented each year, half of the victims being under 25 years old, 15% are children 5 years of age or younger (Mayer 1998 – *Dtsch Ärztebl* 94:C2516). In the USA, the estimated annual incidence of MBI per 100,000 population ranges from 193 to 367 (Kraus et al. 1986; Tullous et al. 1992).

20.2 Developmental Neuroanatomy

It would exceed the limits of the present volume to offer a detailed description of CNS development in the infant. The reader is referred to the relevant monographs, in particular that of Feess-Higgins and Larroche (1987). Instead, only a short review is intended. Though we cannot describe the functional development of the nervous system in early infancy, it will be important to know the relation of neurologic findings in preterm infants reaching term age in comparison to infants of gestational age at birth. Preterm infants examined at term were more hyperexcitable and tended to have less flexor tone in the limbs and less extensor tone in the neck in the sitting posture (Mercuri et al. 2003).

20.2.1 The Coverings

The *scalp* of the newborn and child is thinner than that of the adult, contains less fat tissue, and is more elastic, but is more susceptible to blunt impacts and to tearing forces. Erythema and pressure marks are relatively uncommon, making it easy to overlook the

Table 20.1. Head circumferences of children. Sources: Altman and Dittmer 1962; Prader and Budliger 1977; Dekaban 1977

Age	Head circumference (cm)	
	Males	Females
Birth	35.3 (33.5–37.0)	34.7 (33.4–36.0)
0.25 years	40.9 (39.2–42.1)	40.0 (38.5–41.7)
0.5 years	43.9 (42.7–45.4)	42.8 (41.4–44.5)
0.75 years	46.0 (44.5–47.1)	44.6 (43.2–46.3)
1 year	47.3 (45.5–48.4)	45.8 (44.3–47.7)
1.25 years	48.0 (46.3–49.2)	46.5 (44.9–48.4)
1.5 years	48.7 (47.0–49.9)	47.1 (45.5–49.0)
2 years	49.7 (48.0–51.0)	48.1 (46.4–50.1)
2.5 years	50.2 (48.5–51.6)	48.8 (47.0–50.8)
3 years	50.4 (48.9–51.9)	49.3 (47.5–51.1)

effects of blunt force impact by external macroscopic inspection alone (i.e., without autopsy). A special type of injury seen in the newborn infant is massive *subgaleal hematoma*, sometimes associated with skull fractures. The time-dependent morphological alterations of subcutaneous or subgaleal hematomas may differ from that of comparable injuries in adults (Gonzales et al. 1954; Wilson 1977).

The neonatal *skull* is characterized by open sutures between the cartilaginous bone plates. Because the cartilaginous skull, especially the cranial vault, ossifies only gradually over the first 2 years of life, the infant skull retains an enormous elasticity. The circumference of the head/skull increases with that of the brain (Fig. 20.2, Table 20.1) and thus is dependent upon age. The fontanels close at different ages (Peacock 1986):

- The posterior fontanel: 2nd postnatal month
- The anterior fontanel: between the 7th and 19th postnatal months (90% of the cases – Aisenson 1950)

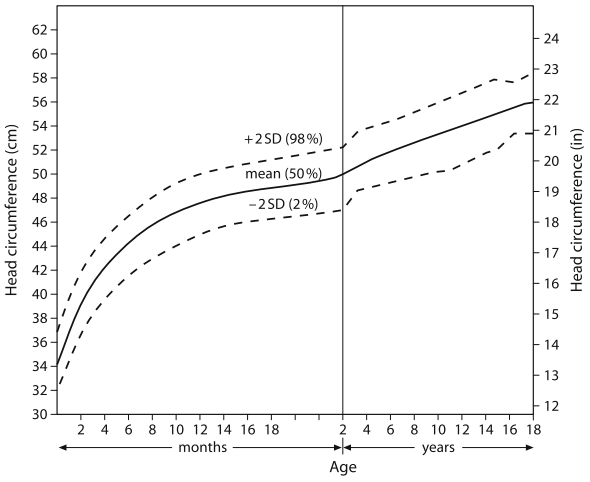

Fig. 20.2. Head circumference of boys. Source: Nellhaus 1968

The neonatal *dura* has a structure (Friede 1989) distinct from that of the adult meningeal membrane. The arachnoid granulations do not attain their final form until adulthood, nor do the bridging veins, which display an age-related difference in elasticity (Yamashima and Friede 1984; Friede 1989). A comparative prospective study has shown that so-called subdural neomembranes unassociated with MBI or different types of delivery are common in infants (Rogers et al. 1998).

The outer surface of the *arachnoid membrane* is fused with the inner surface of the dura mater in a manner which confers scant cohesion at the interface layer, the dura separating easily from the arachnoid. Upon disruption of the interface layers, some cells remain on the surface of the arachnoid and some on the dura mater. Proliferation of these residual cells produces neomembranes. Stretching and tearing of the bridging veins are partly responsible for subdural hemorrhages, the walls of bridging veins in infants being particularly thin (Friede 1989). Moreover, in children the dura tends to develop hygroma or is involved in the process of growing skull fractures as well as leptomeningeal cysts (see below).

Table 20.2. Brain mass before birth in relation to gestational age. Sources: Gruenwald and Minh 1960; Schulz et al. 1962; Guihard-Costa and Larroche 1990

Gestational age (weeks)	Gruenwald and Minh (1960)		Schulz et al (1962)		Guihard-Costa and Larroche (1990)	
	N	Brain mass (g)	N	Brain mass (g)	N	Brain mass (g)
14–15					2	15±1
16–17					3	21±1
18–19					10	37±8
20			5	45		
20–21					15	52±7
22–23					9	75±17
23±2	317	70±18				
24			24	112 ±36		
24–25					15	101±18
26±0	311	107±27				
26–27					21	130±17
27±5	295	143±34				
28			47	169±46		
28–29					18	169±19
29±0	217	174±38				
30 – 31					21	203±25
31±3	167	219±52				
32			70	283±52		
32±4	148	247±51				
32–33					13	234±28
34±6	140	281±56				
34–35					14	280±28
36			62	354±70		
36±4	124	308±49				
36–37					6	325±40
38±0	120	339±50				
38–39					10	391±41
39±2	138	362±48				
40			64	409±60		
40±0	144	380±55				
40±4	133	395±53				
40±4	106	411±55				
40±6	57	413±55				
40–41					17	409±37
41±4	31	420±62				
41±2	15	415±38				

20.2.2 The Brain

Due in part to differences in anatomical proportions and relative brain masses, the pathological and clinical features of brain injury in infants and children differ from those in adults. The infant brain comprises 15% of total body mass at birth, compared to 2% in the adult. The immature brain grows rapidly, reaching 75% of adult brain mass within 2 years and over 90% of adult brain mass by age 6 (Friede 1989).

The mass of the childhood brain depends on the stage of development, both before (Table 20.2) and after (Table 20.3) birth. The brain's *rapid expansion* in the time just preceding and after birth reflects the ongoing maturational process, including a proliferation of connections among neurons that facilitates neuronal function and contributes to structural complexity. This growth in size is accompanied by a decline in the *water content* of the cortex and white matter from 87% and 89%, respectively, at birth, to 85% and 77% during the first decade of life. The adult norms of 83% and 69% are gradually attained late in the second decade (Katzman and Pappius 1973).

Development of the *cerebral cortical surface* proceeds gradually from the flat lissencephalic brain of the fetus to the adult pattern of sulci and gyri. The gyral formation does not develop until the 18th week of gestation (Fig. 21.4). Primary fissures appear between weeks 18 and 28. Opercularization of the Sylvian fossa and the Rolandic sulcus begins at week 20, the superior temporal sulci are set between weeks 24 and 28. The schedule of these changes is invariable. The cortical surface area of the newborn brain measures approximately 700 cm^2, 61% of which is intrasulcal (Hesdorffer and Scammon 1935; Scammon and Hesdorffer 1935) compared to the adult figure of about 43%, which is reached by the second year of life. The surface area more than doubles postnatally, to reach the adult value of approximately 1,600 cm^2. During early embryogenesis (5th–6th weeks) the hemispheric wall consists of an inner and a superficial germinal layer plus a cellular zone (the "Randschleier"). The maturation of *cortical layering* is accompanied by a decrease in the packing density of nerve cells. This is a universal feature of maturation of gray matter attributable to an increase in the volume of neuropil, mainly due to dendritic growth and the ramification of afferent processes.

The criteria of cortical maturation include *the development of dendrites* and the degree of their specialization (Purpura 1975). The shape and length of the dendritic spines in particular reflect the extent of cortical maturation: long, thin spines indicate immaturity; stubby, mushroom-like spines indicate advanced maturity.

Table 20.3. Brain mass after birth and its age-related variability. Source: Boyd 1952

Age	Brain mass (g)	
	Male	Female
Newborn	353	347
0–0.25 years	435	411
0.25–0.5 years	600	534
0.5–0.75 years	877	726
0.75–1.0 years		
1–2 years	971	894
2–3 years	1076	1012
3–4 years	1179	1076
4–5 years	1290	1156
5–6 years	1275	1206
6–7 years	1313	1225
7–8 years	1338	1265
8–9 years	1294	1208
9–10 years	1360	1226
10–11 years	1378	1247
11–12 years	1348	1259
12–13 years	1383	1256
13–14 years	1382	1243
14–15 years	1356	1318
15–16 years	1407	1271
16–17 years	1419	1300
17–18 years	1409	1254
18–19 years	1426	1312
19–20 years	1430	1294

Another clear marker of neuronal maturation, synaptophysin as demonstrated by immunohistochemistry, obviously depends on the increase in the number of *synaptic connections* of the neurons. It may therefore be an indicator of presynaptic readiness in specific regions of the brain and spinal cord. CNS tissue of 8- and 10-week-old fetuses shows no immunoreactivity for synaptophysin in any part. At 12 to 14 weeks of gestation, the ventral horns of the spinal cord and the molecular layer (lamina I) of the cerebral neocortex express synaptophysin, while other areas exhibit a different time dependency (Sarnat and Born 1999). It is assumed that mental retardation will be the result of defects in synaptic structure and function (Chechlacz and Gleeson 2003).

The *expression of superoxide dismutase* (SOD) and *nitric oxide synthase* (NOS) in the developing brain is important for understanding early neuronal development. As demonstrated by Takikawa et al. (2001), neuronal NOS can be detected only at 28 and 33 weeks of gestation in the cerebrum and at 15, 18, and 23 weeks of gestation in the brain stem. Nitric oxide (NO) probably contributes to neuronal differentiation and is cytotoxic in large quantities due to its reaction with superoxide anions. These data suggest that SOD serves as a scavenger of superoxide anions at an early developmental stage in preparation for stage-specific expression of neuronal NOS for a potential differentiation role and to avoid NO cytotoxicity. The results of Folkerth et al. (2004) indicate that a developmental „mismatch" in the sequential antioxidant enzyme cascade likely contributes to the vulnerability of free radical toxicity of the immature cerebral white matter due to ischemia/reperfusion, particularly between 24 and 32 gestational weeks.

Up to the 30th week of gestation, the *germinal layer* (matrix cells) of the lateral ventricles forms a subependymal sheet of tightly packed immature cells lining the entire ventricular wall. After that the layer begins to thin out. The cerebral *white matter* grows at a slower rate than the cortex during fetal development, but postnatally it continues to grow long after the gray matter has attained its definitive volume. The onset of function in a neuron probably correlates well with its acquisition of a *myelin sheath*. The spinal anterior root is one of the nerve structures that begins to be myelinated at the earliest stage – at around 16 weeks – of fetal life, whereas myelination of the pyramidal tract begins just before birth and is completed at around 2 years of age (for a timetable of myelogenetic cycles, see Yakovlev and Lecours 1967; Peacock 1986).

Cortical growth subsides by the second year of life. Although most of the brain has been myelinated by the second year of life (Norton 1972), the hemispheric *white matter* continues to grow until after the first decade from continued accumulation of myelinated fibers and an increase in their caliber (Scammon 1932). Between the 6th and 18th postnatal months the white matter is smaller in volume than the almost fully developed, deeply gyrated cortex. Myelination of the structures involved in the highest intellectual functions; i.e., the short intracortical connections of the association areas in the frontal, parietal, and temporal lobes, begins in the third postnatal month and may continue even into the sixth decade.

Differentiating *astrocytes* exhibit changes in their expression of intermediate filament proteins. The radial glia and immature astrocytes are positive for vimentin and negative for glial fibrillary acidic protein (GFAP) (Bignami and Dahl 1976; Voigt 1989). During the first two postnatal weeks, a transition from vimentin to GFAP takes place (Schnitzer et al. 1981; Voigt 1989). Astrocytes in adult brains (of animals) are usually positive for GFAP and negative for vimentin. During the transitional period, both vimentin and GFAP can be co-expressed.

Just before myelin formation begins, there is a massive proliferation of glial cells known as myelination gliosis (Roback and Scherer 1935). Before onset of myelination gliosis, *glial density* of white matter is low. The processes of the radial glia, which extend from the ventricular walls to the pia mater, can be demonstrated by the 12th week of fetal life (Choi 1986); the radial glia also stain for vimentin (Pixley and de Vellis 1984). Sheath formation is associated with metabolic activation of the sheath cells.

Hippocampus. The hippocampal area is selectively vulnerable during development. Development in the CA1 subfield of the rat hippocampus after birth is accompanied by a rapid increase in the number of *N*-methyl-D-aspartate (NMDA) receptor sites. The number of sites is greatest during the second postnatal week, and subsequently declines to the adult level of about 50% by the end of the third postnatal week. These changes are attributed to a proliferation of NMDA sites, rather than to a change in ligand affinity (Tremblay et al. 1988). Though the significance of these changes is unclear, they must have an influence on function and on the morphological sequelae of cerebral ischemia–hypoxia (Taskar 1999).

Cerebellum. The rate of cerebellar growth lags behind that of the cerebral hemispheres until the fifth month of gestation. Early in embryonic life, Purkinje cells form in the alar plate and migrate directly to their definitive cortical sites. The superficial granular layer forms from germinal cells of the rhombic lip, which migrate during early fetal life to the cortical surface and continue to proliferate there long after the periventricular germinal tissue has disappeared (Uzman 1960). The definitive cerebellar granular layer forms from proliferating cells in the superficial granular layer; their descent is guided by the processes of glial cells (Rakic 1971).

Cervical Spine. Due to the scant musculature of the neck and throat, the *cervical spinal column* possesses a relative biomechanical instability. This, in combination with the comparatively heavy head, makes the child liable to certain forms of injury and especially at risk when subjected to certain types of external violence (pp. 493 ff).

20.3 Autopsy Findings

Macroscopic examination of the head and brain should always be preceded by an external examina-

tion of the whole body of the fetus or baby. The following examinations and/or measurements should be carried out (Emery 1989 – modified):

1. A radiograph of the whole body and limbs in standard position, particularly of the head.
2. Measurement of the head – its circumference and its diameters as well as the diameters of the open fontanels – to document the extent of growth or growth retardation.
3. Inspection of the posterior margin of the foramen magnum and preservation of cerebrospinal fluid (Wigglesworth and Husemeyer 1977; Emery 1989; Keeling 1993a): the child is placed face down with the body mass supported on a block. The skin at the back of neck is opened by incision, at the atlanto–occipital junction. A cerebrospinal fluid sample can be conveniently taken at this point with needle and syringe. After dural incision the cervical cord and foramen magnum are exposed. Observation of the cerebellar tonsils can provide information on their downward displacement (herniation syndrome) and/or the presence of Arnold–Chiari malformation, which usually accompanies meningomyelocele.
4. Extraction of vitreous fluid from the eye.

20.3.1 Head and Cranial Contents

In infants up to about 3 months of age the "flower" method of dissection of the head is preferred; in older children the usual method is the same as that for removing the adult brain.

Flower Method. After external inspection of the scalp, face, and neck as well as photographic documentation of the pathology, a coronal incision is made in the scalp starting behind one ear, cutting posterior to the vertex toward the other ear. The incision permits satisfactory reconstruction of the head should further viewing of the body be required; it also imparts a degree of stability should skull bones be retained for examination. The size of the anterior fontanel and width of suture lines are noted. Where there is increased intracranial pressure, particularly of recent origin, the fontanel is tense and bulging and the suture lines may be wider than normal. If there has been long-standing increased intracranial pressure, the anterior fontanel often extends forwards, widely separating the frontal bones along their entire length.

The anterior fontanel is incised parasagittally with a scalpel, taking care not to damage the sagittal sinus. Incisions are extended forward and backward on each side in turn. On each side, the frontoparietal and parieto-occipital suture lines are incised. The frontal and parietal bone flaps can be deflected laterally (like the opening of flowers, see Fig. 25.5) and the surface of the brain inspected on each side in turn (Prahlow et al. 1998). Observe the cerebral gyral pattern: the normal gyral pattern appears uniform. Its increasing complexity with fetal maturity has been well documented by Dorovini-Zis and Dolman (1977).

Next, the head is tipped forwards and laterally and the occipital pole gently lifted with a finger or scalpel handle to inspect the falx and tentorium for hemorrhage and tears. Congestion and focal hemorrhage within the dural folds are common and usually insignificant. The whole of the falx and tentorium can be examined in this way.

The removal of the brain will usually follow techniques used in adults. Under special circumstances as well as for special documentation, removal under water or separate removal of each of the hemispheres may be recommended. Moreover, special attention is paid to the subdural space. In the presence of subdural hematoma (SDH), the disrupted bridging vein must be located – if possible. The bridging veins are attached to the sagittal sinus. Acceleration of the head may lead to stress on these veins which can disrupt and bleed into the subdural space.

After removal, the brain is placed in fixative. After about 14 days, the brain should be examined in detail and described meticulously after external inspection. The mass (and volume) is to be measured, then – depending on the context – the brain is cut in the frontal, transverse or sagittal plane and the findings recorded photographically and by full description. Due to the high water content of the fetal, newborn, and infant brain, the subsequent dehydration process of tissue blocks before routine embedding in paraffin should proceed very slowly, allowing about twice as much time as the dehydration of histological blocks of adult brain tissue.

20.3.2 Cervical Spine

In nearly all cases of MBI in infants and children as well as in cases of suspected physical abuse and – especially – in cases of shaken baby syndrome the removal and examination of the cervical spine including the occipito–cervical junction will be obligatory or at the very least recommended. The removal technique is described elsewhere (p. 89). The demonstration of spinal dural hemorrhages as well as of axonal injury of the spinal cord is of significant importance in providing additional evidence of a traumatic event which may be the cause of death, though there may be no other macroscopic indications.

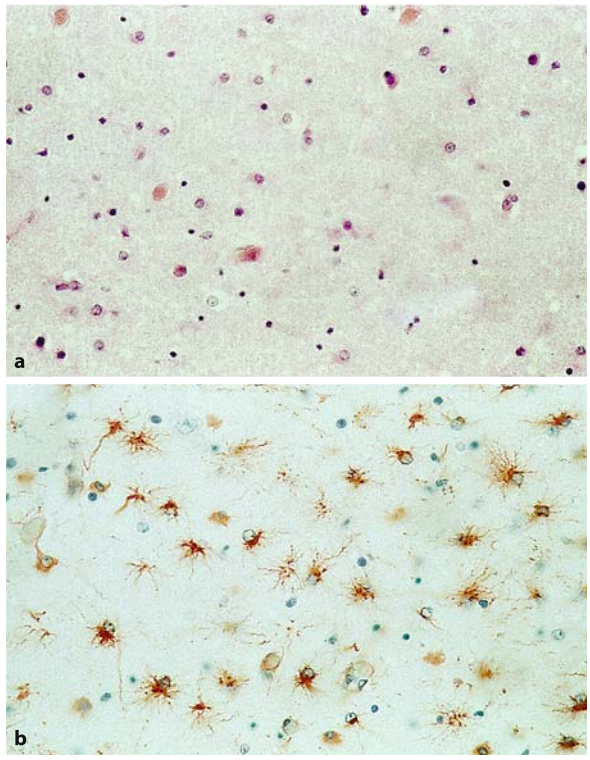

Fig. 20.3a, b. Increased astrocytes in the white matter during the process of myelination (**a** H&E, **b** GFAP reactivity; magnification **a, b** ×300)

20.3.3 Ears and Mastoids

The middle ears and mastoids should be inspected macroscopically and microscopically at all necropsies, as quite surprising results are frequently found. The middle ears and mastoid cavities in the baby can easily be removed using a pair of bone forceps to make the incisions. It is helpful to stabilize the posterior tip of the bone forceps in one of the cranial nerve apertures when making these cuts.

20.3.4 Eyes

It is important to examine the eyes both macroscopically and microscopically as intra-ocular damage consisting of vitreous and retinal hemorrhage, lens opacity, optic nerve damage, retinal detachment, and displaced lens is known to be very common in non-fatal (Friendly 1971; Tomasi and Rosman 1975) and fatal child abuse. Up to 70% of children with subdural hemorrhage also have retinal hemorrhage (Tomasi and Rosman 1975 – see pp. 497 ff). To remove the eyes, the frontal base of the skull should be opened and the eyeballs, or in most cases only the posterior half of the eyeballs, are extracted from the interior of the skull.

20.4 Microscopic Examination: Cell Reaction

The classification and assessment of cellular appearance and cell reactivity depend on knowledge of the normal, i.e., age-dependent, phase of cellular development (prenatal development of cellular reagibility – see p. 408). We have to record the stage-like density of cortical neurons and astrocytes (Fig. 20.3) in the white matter and of neurons in the gray matter. Myelination occurs during the first 2–10 years (see above), etc.

Early fetal *anoxic/ischemic brain injury* may mimic malformation, e.g., polymicrogyria. Peri- or postnatal hypoxia/ischemia injury results in typical morphological changes also found in adults known as hypoxic/ischemic neuronal cell changes and scarring processes. The various types of cell reaction during development of the infant brain are discussed briefly in the following (cf. Friede 1989).

The manifestations of *ischemic neuronal necrosis* during early infancy differ in terms of cell changes and in regional distribution. The neuronal changes include cytoplasmic swelling, chromatolysis, nuclear pyknosis, and occasional karyorrhexis. Pontosubicular neuronal necrosis in particular is characterized by karyorrhexis.

Moreover, immunohistochemical staining for β-amyloid precursor protein (β-APP) is a well established marker for mechanically induced axonal injury in adults (pp. 205 ff). A recent investigation (Reichard et al. 2003) found β-APP-reactive axons in 27 of 28 pediatric autopsies (infants and young children – up to 7 years), which were mainly caused by brain swelling and secondary vascular compromise but also by mechanically induced injury in 19 out of 28 cases.

During the first half of gestation almost no residual *gliosis* is seen, even with massive tissue destruction. Astrocytes develop the capacity to react with proliferation and hypertrophy during the last trimester of gestation, as is evident in the mature newborn‘s response to asphyxia, for example, in the manner of ulegyria or periventricular infarcts. Astrocytic hypertrophy is often less pronounced when compared to the adult brain. Reactive astrocytes have a moderate density of nuclear chromatin and less cytoplasmic hypertrophy, sometimes up to twice that of the nuclear diameter. Using GFAP immunohistochemistry, reactive astrocytosis – in contrast to non-reactive astrocytes – can first be detected at

20 weeks of gestation; *plump gemistocytic astrocytes* are first seen at 23 weeks of gestation (Roessmann and Gambetti 1986a, b). *Metabolic astrocytosis* as a consequence of metabolic diseases is readily detected in infants older than 1 or 2 years (Friede 1989).

Removal of necrotic tissue by *macrophages* occurs in the fetal brain at a time when the astrocytic response is still minimal. The rate of removal appears to be even greater than in the adult. Monocytes found in the circulating fetal blood as early as the fourth week of gestation may emigrate and become extravasated macrophages (or activated microglia). The scavenger function of brain marcophages after hemorrhages are described on p. 429.

The early experimental studies of Spatz (1920) give evidence of the *cell reaction pattern during the developmental stages* and are summarized as follows:

- Liquefaction and dissolution of necrotic tissue is exceptionally rapid in newborns. Organization may be essentially complete after 8 days and the last phagocytes disappear by the 12th day, with a certain dependency on the extent of necrosis.
- Little or no proliferation of „fixed" glial elements occurs during the early fetal stage. No gliomesodermal scars form, organization being carried out mainly by macrophages which disappear rapidly from lesions. The residual cavity forms a smooth-walled porus. The walls of the porus are formed by a thin layer of glial tissue deficient of neurons, but without glial scarring. Glial tissue may persist subpially, forming a thin gliomesodermal membrane.

Moreover, recent data have suggested that recovery from injury in the preterm brain may involve the reactivation of radial glia in the germinal layers (Ganat et al. 2002). In the days after acute or chronic hypoxic/ischemic insult, there is increased cell proliferation in both the subventricular zone and the dentate gyrus, and the "reactive" cells that divide after perinatal hypoxia appear phenotypically to be a type of radial glia (see Vaccarino and Ment 2004).

20.5 Postmortem Biochemistry

Chemical investigations can help establish the cause of death (hypoglycemia, dehydration); they can aid in assessment of the physiological effects underlying anatomic findings at autopsy, and may help to establish the time of death.

It is not the task of forensic neuropathology to delve deeper into the significance of those investigations. The reader is referred to the review of Coe (1989), which among other things provides the range of values for sodium and chloride in vitreous humor for diagnosis of dehydration in newborns, infants, and children.

20.6 Diffuse Cerebral Swelling

The *clinical features* of elevated intracranial pressure in infants are seizures, split sutures, a bulging fontanel, a high-pitched cry, and coma. Brain mass and size are of little use in *neuropathological evaluation* of cerebral swelling due to their wide variability in children (Emery 1989). It is the volume of the brain within its own cavity that matters and the pouting of the brain tissue through the cervical incision is much more important than the mass of the brain. The macroscopic manifestations of increased intracranial pressure are flattening of the gyri, narrowing of the ventricular systems and – rarely – herniation of cerebellar tonsils.

Pathophysiology. The immature brain is thought to respond to severe mechanical load, infection or intoxication differently than the adult brain. Because the cranial vault of the infant is more pliable and elastic, the manifestation of increased intracranial pressure in the newborn differs from that in adults. In infants, the fontanels and the open sutures permit distension of the cranium, thus weakening the force of caudal pressure; secondary midbrain hemorrhages are therefore unknown in the newborn. Moreover, cerebellar herniation and acute tonsillar necrosis are hardly ever seen during the first year of life.

Children appear to be more likely than adults to develop diffuse cerebral swelling. A number of studies have reported its incidence to be two to five times higher in children than in adults (Aldrich et al. 1992; Lang et al. 1994); for example, up to 44% of children exhibit diffuse cerebral swelling after the incidence of severe MBI (Berger et al. 1985). Clinical studies have reported a 50% mortality rate in children with diffuse cerebral swelling (Aldrich et al. 1992); the mortality is even higher in younger children (<4 years), who more frequently develop diffuse swelling (Luerssen et al. 1988). These findings contrast with observations made in animal experiments on cats on early postnatal development showing that the immature brain is less prone to develop edema (Go et al. 1973), which appears to occur independently of a breakdown of the blood–brain barrier (Okuma and Yamada 1978).

Pathology. The morphological features are summarized by Kirkham (2001), and are characteristic of the presence of intracranial pressure (see also Chap. 4, pp. 42 ff):

1. Intracranial hypertension induces a decline in cerebral perfusion pressure, since the latter is the difference between the mean blood pressure and the intracranial pressure. This causes cerebral ischemia, particularly in the marginal zones of the main arterial territories.
2. If supratentorial hypertension is present, i.e., if there are pressure differences between the forebrain compartment and the posterior fossa, a single (uncal herniation) or both temporal lobes may herniate through the tentorium (diencephalic and midbrain/upper pontine herniation syndrome).
3. Sub- or infratentorial pressure may cause the brain to herniate upward through the tentorium of the cerebellum.

Among the possible causes of diffuse brain swelling are hyperemia and edema of the brain.

20.6.1 Hyperemia

Hyperemia (vascular enlargement, congestion) is thought to be a major cause of diffuse cerebral swelling (p. 42) especially in infants and children (Bruce et al. 1979, 1981; Obrist et al. 1979). It is thought that changes in cerebral metabolism can induce impairment of the autoregulatory mechanisms of the cerebral vasculature. Recent findings from experimental studies support the role of hyperemia following the incidence of severe head injury in children: Biagas et al. (1996) were able to demonstrate a delayed increase in cerebral blood flow (CBF) in immature and young rats, but not in adult rats.

Suzuki (1990) studied CBF in 80 normal unanesthetized children. It was shown that CBF in normal children may range from 40 ml/100 g per minute during the first 6 months of life to a peak of 108 ml/100 g per minute at 3–4 years of age, and down to 71 ml/100 g per minute in children aged 9 years. Considering this large range, comparisons of CBF data in children are valid only when small, well-defined age ranges are selected. As Zwienenberg and Muizelaar (1999) could demonstrate, a substantial increase of CBF did not seem to exist. Therefore, hyperemia may not be as common in severe pediatric MBI as previously thought (see also Sharples et al. 1995; Adelson et al. 1997).

20.6.2 Edema

The available recent data do not allow the inference that diffuse cerebral swelling is due in large part to hyperemia. In addition to the aforementioned vascular reactivity and impairment of autoregulatory mechanisms, disruption of the blood–brain barrier seems to be the principle mechanism underlying the increased intracerebral volume, i.e., the development of *vasogenic edema* (see Chap. 4, pp. 44 ff). The blood–brain barrier function is not present at birth but only develops as the child grows. Hyperbilirubinemia at birth is known to cause acute bilirubin encephalopathy (kernicterus), a phenomenon not seen in adults (pp. 452 f, 611). Damage to the blood–brain barrier in conjunction with hyperemia can lead to vasogenic edema, increased osmotic and oncotic gradients contributing to the fluid flux into the extracellular space. The blood–brain barrier can reconstitute within 24 h, although a secondary episode of increased permeability is possible. The edema generally peaks within 24–72 h after the traumatic event.

As already mentioned elsewhere (Chap. 4, pp. 42 ff), especially ischemia and various types of intoxication result in a *cytotoxic/cellular edema* in the adult and child brain. The injury-induced breakdown of the normal metabolic processes of cells and the inability to correct imbalances in the ionic species (Na^+, K^+, Ca^{2+}) initiate further cellular damage and fluid influxes. Ischemia contributes to energy failure leading to depolarization, spreading depression, calcium accumulation, lactate accumulation, and acidosis (Stein and Vannucci 1988). This can lead to further cellular breakdown and damage. Moreover, inflammation, free radicals, excitotoxicity, and calcium influx contribute to the cytotoxic edema (Adelson and Kochanek 1998).

Table 20.4. Syndromes of fatal child abuse. Source: Pearn 1989

Neonaticide
Infanticide
Euthanasia
Syndrome of repetitive physical child abuse
Child neglect
Murder – homicide

20.6.3 Hydrocephalus

As summarized on pp. 54 ff (see also pp. 482 f) hydrocephalus will be a specific type of reaction in infants and children caused by malformation, inflammation, tumors or MBI. Hydrocephalus will be associated with a growing head circumference in infancy

Table 20.5. Examples of published cases of medical malpractice. Source: Oehmichen and Schmidt 1995

Author	Age	Disease	Consequential damages	Medical malpractice	Accused physician
a	Newborn	Scratch infected by staphylococci	Sepis, bilirubin encephalopathy	Fault of organization	Obstetrician
a	Newborn	M. haemolyt. neonat.	Bilirubin encephalopathy	Diagnostic mismanagement	Pediatrician
d	Newborn	M. haemolyt. neonat.	Bilirubin encephalopathy	Diagnostic mismanagement	Pediatrician
a	Newborn	Lues connata	Injection induced necrosis: amputation of the leg	Therapeutic mismanagement	Pediatrician
a	Baby	Enteritis	Mechanical brain injury	Fault of organization	Pediatrician
b	Baby	Congenital hip dislocation	Motor disturbances	Diagnostic mismanagement	Pediatrician
c	3.5 weeks	Pyloric stenosis, electrolyte dissociation	Mechanical brain injury	Therapeutic mismanagement (10% NaCl-solution)	Nurse
b	4 weeks	Enteritis	Intracerebral hemorrhage	Diagnostic mismanagement	General practitioner
b	5 months	Angina tonsillaris, purulent meningitis	Mechanical brain injury	Therapeutic mismanagement	General practitioner

[a] Bappert (1980); [b] Cyran (1992); [c] Mallach et al (1993); [d] BGH, Urt v 14.07.1992

and early childhood because of the intraventricular increase of fluid pressure.

20.7 Forensic Aspects (Expert Witness)

In cases of birth-related lethal or non-lethal cerebral injury, obstetricians are being increasingly subjected to medical malpractice lawsuits (Oehmichen 2000a; Shevell 2001). Public awareness of the phenomenon of physical abuse resulting in injury or death of the child is also growing. In both instances the pediatric neurologist and/or forensic neuropathologist may be called to serve as an expert witness. In cases of acute, unexpected, non-accidental death of a child the forensic neuropathologist is also asked to confirm or establish the cause of death by forensic autopsy and additional investigations (cf. Table 20.4).

20.7.1 Medical Malpractice

Medical malpractice is not rare during the perinatal period. A survey of published selected cases in Germany is given in Table 20.5. Because the placental barrier between mother and fetus is permeable to many types of substances, *medications* taken by the mother *during pregnancy* can injure especially the brain of the unborn child. It follows that pregnant women should restrict their ingestion of medications to a necessary minimum and be discouraged from self-medication (for review see Ashton 1981; Simar 1999). Some other types of medical intervention during pregnancy, such as amniocentesis, entail a risk of brain injury as well as death to the fetus (Keeling 1993b).

Intrapartum monitoring may be accompanied by complications, i.e., injury of the brain (Ashkenazi et al. 1985). The complications arising from breech delivery have long been associated with increased mortality and morbidity among babies delivered vaginally. The consequences of breech delivery in-

clude ischemic encephalopathy, osteodiastasis, displacement tears underlying venous sinuses, and catastrophic hemorrhage. Injury of the craniocervical junction and of the cervical region of the spinal cord may also occur if the neck is hyperextended during delivery. Extracranial lesions of the scalp of soft tissue of the face as well as skull fractures and paralysis of motor and/or sensory facial nerves may be the consequence of *forceps delivery* or – partly – of *vacuum extraction*. If a child is delivered by *cesarean section* and suffers ischemic brain injury, the question arises as to whether the injury could have been avoided if the procedure had been performed sooner or more rapidly.

The forensic expert must distinguish between death of a child that occurs before delivery (fetal death) and death occurring during or shortly after delivery (infant's death). Such a distinction usually cannot be based on neuropathological findings alone, but requires various types of information, including the course of labor and delivery, the external aspect of the newborn corpse, especially the degree of antolysis and/or maceration, and the stage of fetal development et cet. (Wecht and Larkin 1989). Microscopy can sometimes help to establish vitality itself and provides further evidence in determination of the cause of death. As an expert witness, the forensic neuropathologist may be asked to determine whether the death was "avoidable," a question sometimes impossible to answer with certainty.

Laws exist to *protect the newborn and/or unborn child* in virtually every country. They protect the child in a different manner at the different stages before, during, and after birth. Laws also regulate the use of fertility techniques, which can give rise to hitherto unknown problems and are the subject of ongoing debate (Wertz 1995). However, it is not possible to collate the different laws and legal decisions of all the countries. Therefore, this paragraph may refer to the local as well as national laws.

Legal questions often arise in regard to *perinatal brain injury/asphyxia* and/or *cerebral disability* of unknown origin. Both the USA and Germany have seen an increase in the number of civil and criminal proceedings against physicians and nursing personnel involving claims of medical malpractice. Parents who desire a child want only a healthy child. If the child is born with a mental or physical (somatic, motor) disability, the physician is often held responsible. There is an increasing tendency to employ expert witnesses. This applies equally whether the child is injured and survives or dies during or after birth. The most common clinical situation about which expert witnesses are called upon to testify concerns the sequelae of perinatal asphyxia secondary to obstetrical malpractice (Nelson 1999). Here the pediatric neurologist/forensic neuropathologist must answer four central questions (Shevell 2001):

1. What are the child's/plaintiff's disabilities and handicaps?
2. What is the etiology of the disabilities? – Was asphyxia or a mechanical injury the root cause of the observed disabilities?
3. When did the asphyxia or mechanical injury occur? – Was it antenatal, perinatal (i.e., intrapartum) or postnatal?
4. What is the estimated life expectancy of the child/plaintiff?

No single definitive biomarker or gold standard has yet been agreed upon for the diagnosis of perinatal asphyxia (Nelson and Emery 1993). If the *child has died*, the expert witness must – additionally – establish the following (Golding 1993, modified):

5.1 Was the antepartum brain normally formed?
or
5.2 Was there any congenital malformation?

6. Were there any conditions associated with immaturity?
7. Did an asphyxial situation or traumatic event develop during labor (cf. also point 3)?
8. What was the extent/severity and nature of the iatrogenic injury?

8.1 Was the injury foreseeable?
or
8.2 Could it have been avoided, possibly by cesarean section?

In 1998 the Ethics and Practice Committee of the Child Neurology Society in the USA published a survey of the Society's membership. The survey featured a 25% response rate and documented that 42% of the responding members had been the subject of a medical liability lawsuit. Ninety percent had reviewed cases for legal counsel as the expert witness, with 13% reviewing more than 10 cases annually. Seventy percent of those surveyed felt the system was unfair and felt there was a need for peer review of expert witness conduct.

Postnatal MBI can also be caused by a mistaken diagnosis or failure to act, sometimes with fatal consequences. Here are a few examples:

1. When should roentgenography or computer tomography (CT) be performed in blunt head impact (Leonidas et al. 1982; Frush et al. 1998)?
2. Should CT be routine for all closed head injuries (Stein et al. 1991)?
3. Should CT be carried out to prevent the fatal clinical consequences of an epidural hematoma that can be averted by early diagnosis and neurosurgery (Paterniti et al. 1994)?
4. Is hospitalization required for minimal impact to the head (Roddy et al. 1998)?
5. Does an isolated head injury warrant cervical spine evaluation (Laham et al. 1994)?

Perinatal exposure to CNS-active *medications* and errors in dosage or type of medication are especially problematic in pediatric therapy (Folli et al. 1987; Simar 1999; Kaushal et al. 2001; Committee on Drugs and Committee on Hospital Care 2003). Kaushal et al. (2001) detected 616 medication errors among 10,778 prescriptions by physicians (=5.7%), 26 resulting in adverse drug reactions. Because the dosing of most drugs is solely based on body mass, there is the potential for a 300-fold dosing error in children as calculated by Poole and Benitz (2001). In adults a twofold dosing error is usually the maximum encountered (for review, see Committee on Drugs and Committee on Hospital Care 2003).

20.7.2 Physical Abuse

The expert witness may also be asked to give an opinion on whether a child is the victim of physical abuse, especially if the abuse is thought to have resulted in the death of the child. Here the forensic pathologist is responsible for determination of the following:

1. The cause of death (Accident? Disease? Abuse? Homicide?)
2. The manner of external violence (Iatrogenic? Accidental? Non-accidental? Intentional?)
3. What were the circumstances and/or surroundings (the scene) of the death?

The forensic pathologist's findings can have serious consequences at legal, ethical, and economic levels for both the child and its carers (further information see Chap. 25 – pp. 489 ff).

20.7.3 Ethical Aspects

Pregnancy and childbirth are bound up with numerous ethical problems that may be only peripherally connected with neuropathological findings (cf. Wertz 1995). In addition to the question of whether an artificial abortion can be justified for social reasons (see Marshall 2000), questions arise regarding *preimplantation diagnosis* to avoid the birth of a genetically defective child (molecular genetic diagnosis of Huntington's chorea, for example). One question discussed relates to the principle authority to allow such diagnostic intervention (Oehmichen 2000b; Grote and Schwinger 2003) while the other question regards the risk (and frequency) of neurologic defects in cases of in vitro fertilization (IVF), which was recently calculated (*European Journal of Pediatrics* 2003, 162:64) to be1.7 (SD: 1.3–2.2) for all IVF children and 1.4 (SD: 1.0–2.1) for singletons.

A topic of perennial debate is research employing *embryonic stem cells* or fetal tissue that is pluripotent and which may be of use for example in the treatment of organ failure. Here the differences in bioethical principles and legal status differ from country to country and are still subject to change in light of ongoing medical advances and changing social and political climates (Franz and David 2003; Maio 2003). In the USA, the use of fetal tissue is still allowed under special conditions.

A series of medical, legal, and ethical questions are bound up with the topic of *euthanasia* and end-of-life decisions regarding the most severe malformations (Chiswick 2001; McHaffie et al. 2001a, b; Oehmichen and Meissner 2003). The obstetrician or pediatrician is required to make decisions regarding „passive" killing, non-performance of resuscitation, or termination of artificial respiration, especially if a baby has obviously entered the process of dying (Chiswick 1990). In the past, physicians in USA and Germany could allow some newborns with little or no chance of normal life to die after discussion of the infant's prospects with the parents. In a public discussion in the USA, many people agreed that in some cases it was right:

1. Not to resuscitate infants at birth
2. To withdraw life support for infants with poor prognosis
3. To shift resources from care for an infant with a poor prognosis to an infant with a better prognosis
4. To intervene directly to kill a dying infant in order to prevent further suffering (Jonsen et al. 1975)

Since that time, Baby Doe laws have established that handicap alone is not a sufficient reason for refusing treatment, just as a hospital may not refuse to treat a burns patient simply because the patient is deaf. Today, overtreatment rather than undertreatment is usually the villain. Pragmatic strategies are the subject of ongoing discussion and recommendations have been published for helping parents (and staff) with end-of-life decisions (Chiswick 2000, 2001; McHaffie et al. 2001a, b). The laws of most countries concur that artificial respiration should be stopped in the case of brain death. Active euthanasia, by contrast, is banned in most countries (exception: the Netherlands). In April of 2002, the European Court of Human Rights ruled against the right to assisted suicide in the case of a terminally ill English woman whose disease was "so advanced that she cannot kill herself without assistance" (*Times Online*, April 30, 2002, "Diane Pretty loses battle for right to assisted suicide" Frances Gibb).

Wertz (1995) mentions anencephaly as a special case. Although born with only a brain stem, anencephalics do not fit current US and German legal

definitions of brain death and breath spontaneously. They do not have a flat EEG as required for brain death. Their organs may not be taken for transplantation until they die naturally, commonly after several days, by which time the organs have usually deteriorated beyond the point of usefulness.

Obtaining consent for *autopsy of neonates, infants, and children* is another problem. A recent epidemiological study (McHaffie et al. 2001a, b) reported an autopsy rate of neonates in the East of Scotland at 62%. The authors could also confirm that parental perceptions are an important element in determining whether they give or withhold consent to postmortem examination. Because the question of *autopsy* is also an ethical problem (Dahms 1986; Nigro et al. 1990; Stambouli et al. 1993), any request for postmortem examination must have a coherent reason (Chiswick 1995, 2001). Any unexpected death is a reason, as another child's death may be prevented because of a genetic state, an infectious disease, or an injury caused by abuse. The aim of autopsy should be a prevention of another child's death, especially the death of a sibling (see Rimsza et al. 2002).

Autopsy may provide evidence of non-accidental death or of death due to neglect. An autopsy may challenge or verify diagnoses made prior to death. It can serve to monitor possible adverse effects of new treatment to be a quality control of medical treatment, or form the basis for informed genetic counseling. It provides the basis for research and education and can be a source of information in epidemiological surveys (Chiswick 1995). Brodlie et al. (2002) demonstrated that new information was obtained in 26% of 209 neonatal autopsies and in 3% of these autopsies the information was crucial for future counseling.

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Fetal Neuropathology 21

The brains of fetuses should be removed using the same procedure as for newborns. Examination of the fetal brain should be preceded by an estimation of the gestational age based primarily on a comparison of body mass and length at autopsy with normal values (cf. Chap. 20). When examining the brain itself factors other than brain mass should be considered for comparison with a pathological state: the pattern of sulcation, synaptogenesis, as well as the state of myelination and of the neuronal migration process. The development of olfactory bulbs, optic nerves, pituitary stalk, and cranial nerve roots is recorded, and the mass and occipital-frontal length of each hemisphere and its biparietal width are measured. Because of the friability and deformability of the fetal brain, these measurements are best obtained while the brain is floating in either fixative or water.

21.1 Malformations

Fetal malformations may be primarily caused by developmental deficits attributable to genetic or chromosomal abnormalities. Such "constitutional" malformations contrast with secondary malformations related to destructive lesions caused by exogenous influences. *Genetic malformations* of the brain such as microcephaly vera or lissencephaly type II are rare. Mental retardation is often attributable to *chromosomal disorders*. Chromosomal aberations are neither constant nor specific for the CNS abnormalities they cause (Encha-Razavi 1995).

The developing brain is especially susceptible to *injury* over the entire period of gestation and early postnatal life. Numerous noxious *exogenous* mechanisms inflict damage, the sequelae depending largely on the duration of the insult. Among the major exogenous causes of injury are lack of oxygen, toxic and infectious agents, and mechanical loadings.

Brain malformations are not specific: diverse causes can produce similar changes. The malformations have been classified according to Encha-Razavi (1995), Roessmann (1995) and recently Barkovich et al. (2001). Barkovich et al. (2001) have proposed a classification based mainly on differences in pathogenesis, i.e., developmental disturbances. The following types of pathogenetic processes are differentiated.

1. Malformations due to *abnormal neuronal and glial proliferation or apoptosis* (e.g., megalencephaly – Fig. 21.1c, d, microcephaly – Fig. 21.1e, f).
2. Malformations due to *abnormal neuronal migration* (Figs. 21.2, 21.3); for example, lissencephaly, heterotopia (Fig. 21.3b, arrows), and cobblestone complex.
3. Malformations due to *abnormal cortical organization* (e.g., polymicrogyria – Fig. 21.3a, schizencephaly, cortical dysplasia, heterotopia – Fig. 21.3b).
4. Malformations of cortical development, *not otherwise classified* (including malformations secondary to inborn errors of metabolism, i.e., mitochondrial disorders, peroxisomal disorders, etc.).

Syndromes associated with cortical dysplasias (Whiting and Duchowny 1999) can be classified separately according to their morphological features:

- *Neurulation failure* – with an incidence of 1 to 2 per 1,000 live births – is characterized by lack of closure of the posterior neuropore: anen-

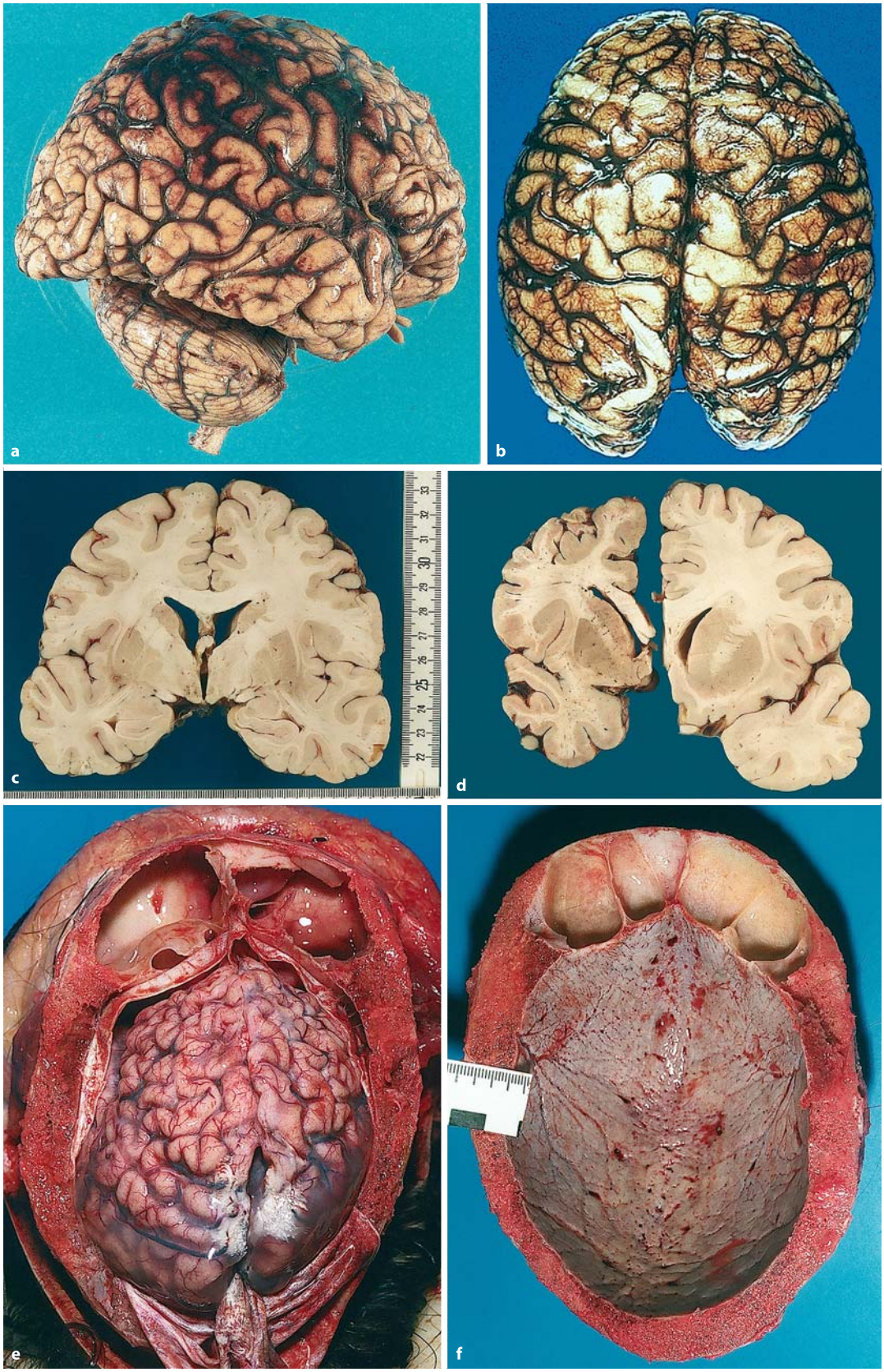

Fig. 21.1a–f. Malformations. **a** Brachiocephaly; **b** dolichocephaly; **c, d** megalencephaly as demonstrated in comparison with a foot-rule (**c**) and in comparison with a normal brain (**d**); the brain mass was 2,170 g at autopsy. **e, f** Microcephaly as demonstrated in situ on occasion of the autopsy with distinct thickening of the skull and extreme enlargement of the paranasal sinus

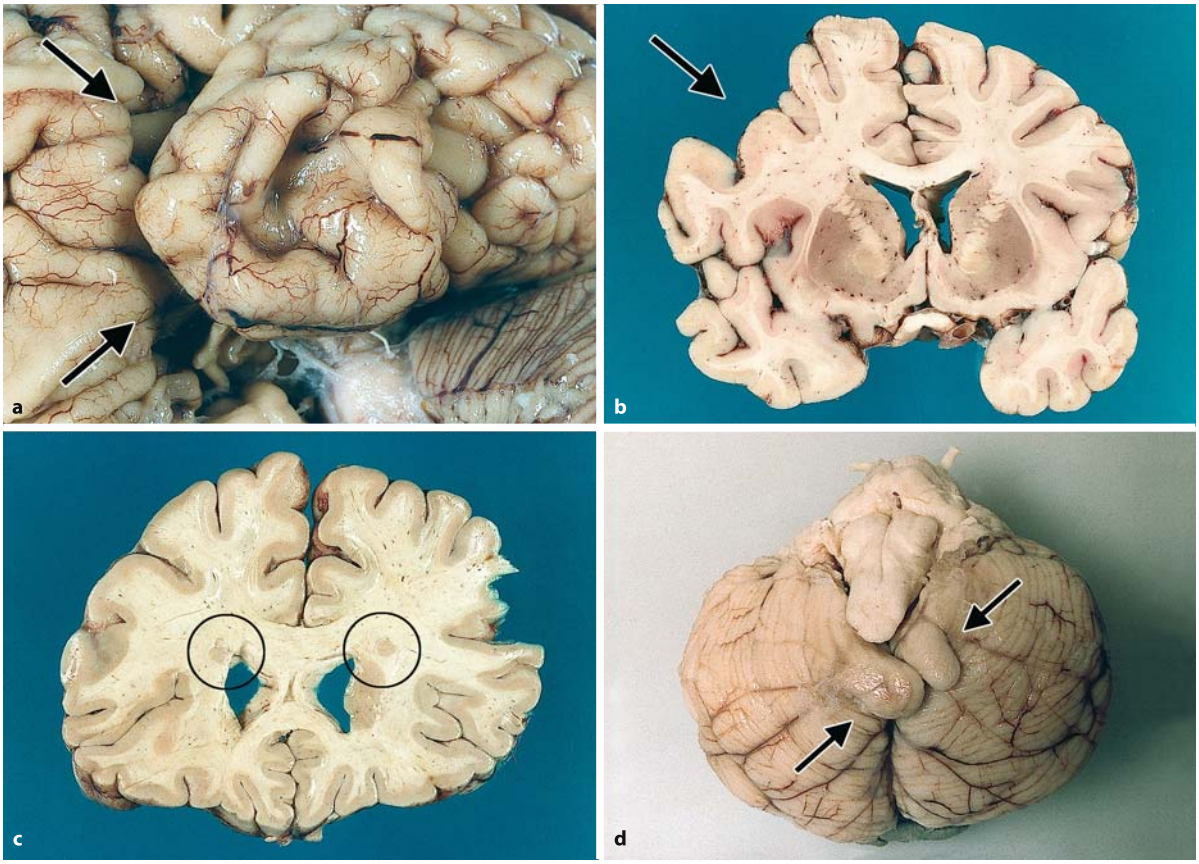

Fig. 21.2a–d. Malformations due to abnormal neuronal (retarded) migration. **a** Opercularization is not finished (*arrows*); **b** alteration of the left cortical surface caused by arachnoidal cyst; **c** bilateral heterotopy at the angles of the ventricles (*circles*); **d** Arnold–Chiari malformation (*arrows*)

cephaly, meningo-encephalocele, meningocele, Arnold–Chiari type II malformation.
- *Prosencephalon growth failure*: arhinencephaly, holoprosencephaly.
- *Abnormalities of midline structure*: agenesis of the corpus callosum, septum pellucidum malformation, Arnold–Chiari malformation (Fig. 21.2d).
- Brain stem growth failure.
- Abnormalities of the aqueduct of Sylvius.
- *Heterotopias*: scattered neurons, nodular heterotopia, polymicrogyria, cortical dysplasia.
- *Faulty neuronogenesis*: microcephaly, microgyria, agyria, lissencephaly.
- *Microdysgenesis* in the sense of cortical cytoarchitectural abnormality as seen in patients with generalized epilepsy (Thom et al. 2000).

21.2 Hypoxic–Ischemic Encephalopathy

Hypoxic–ischemic encephalopathy is a special form of fetal injury whose prevalence is only now being fully appreciated because neuroimaging enables examination of the fetal brain during pregnancy. Injury is attributable to hemodynamic mechanisms in up to 25% of preterm newborns (<1,500 g) at birth and in a much smaller but still meaningful proportion of more mature infants (Del Toro et al. 1991). Injury is caused by a wide spectrum of prenatal pathologic conditions, maternal, fetal, and placental, including ischemia (Callahan et al. 1990), hypertension (leading to peri- and intra-ventricular hemorrhages), and reperfusion after ischemia (leading to peri- and intra-ventricular hemorrhage and hemorrhagic periventricular leukomalacia). Hemorrhagic periventricular leukomalacia can also occur secondary to venous infarction if massive peri- and intra-ventricular hemorrhage has obstructed draining veins (Volpe 2001). The hemorrhaging can also be delayed (cf. Darrow et al. 1988). The factors associated with neuropathological findings in immature newborns are summarized in Table 21.1.

The basic principles of ischemic brain injury may be explained at the molecular level. Oxidative stress is suggested to be involved in normal aging, especially also in the human fetal brain (Yamamoto et

Fig. 21.3a, b. Malformation due to abnormal neuronal migration. **a** Polymicrogyria; **b** glial nodules within the enlarged ventricular system

al. 2002). Advanced glycation end products are generally reported to be negative in neurons of normal young brains.

Hypoxia alone does not appear to inflict brain injury, but a combination of hypotension, reperfusion with ischemia or ischemia alone or hypoxia in combination with hypoglycemia does. The extent of injury also depends on disturbances in oxidative glucose and lactic acid metabolism (Vannucci 1992), as reviewed also by Takashima and Tanaka (1978) and Greisen and Børch (2001). Evidence from human neonates indicates that white matter is selectively exposed to ischemia. Blood flow to the white matter is particularly low in premature infants, amounting to only 17% of the flow to gray matter. Blood flow to the white matter, moreover, appears to be selectively reduced when blood pressure is low, an effect explained by the vascular anatomy: the periventricular white matter (germinal matrix) is a vascular end zone supplied by long penetrating arteries arising from pial arteries on the brain surface. The oligodendrocytes in particular are injured (Liu et al. 2002). Moreover, the subependymal veins appear vulnerable to rupture. The structural immaturity of the veins in premature neonates is causally related to the high incidence of germinal matrix hemorrhage (Figs. 21.4c, d, 21.5a, b) (Anstrom et al. 2004). An additional increase in excitatory amino acids plus additional biochemical alterations are thought to mediate the pathogenesis of this type of encephalopathy.

21.2.1 Neuropathology

As stated above, the nature of morphological changes encountered in the infant brain depends on the time of insult and its duration.

Isolated white matter lesions, so-called leukomalacia or periventricular leukomalacia, are specific to immature brains peaking in incidence at around 34 weeks of gestation. This type of lesion occurs in the periventricular region, centrum semiovale, subcortical region, and in the corpus callosum. Hypoxia and/or ischemia are thought to be principal causes of white matter injury in preterm infants, a hypothesis based on the following two phenomena (Greisen and Børch 2001):

- The nature of the lesion: cystic or gliotic degeneration with little or no evidence of hemorrhage
- The nature of the cerebral vasculature in the immature brain

The acute lesion is usually a coagulation necrosis with axonal disintegration combined with a microglial and astrocytic reaction. The necrotic tissue is increasingly incorporated, digested, and eliminated by macrophages, the resultant cavitation leading to multicystic leukoencephalopathy with calcium deposits and/or hemorrhages.

Isolated gray matter lesions are seen exclusively in full-term infants. A variety of lesions occur depending on the timing of the insult and neuronal maturation: cerebral cortical necrosis, pontosubicular necrosis (Ahdab-Barmada et al. 1980) related to ischemia, Möbius syndrome, and basal ganglia necrosis (Rorke 1992).

Combined gray and white matter necroses lead to various types of lesions, all producing different degrees of cavitation: cystic or multicystic encephalopathy, porencephaly, schizencephaly, basket brain, hydranencephaly, etc. (Larroche 1977).

Ischemic infarction also produces characteristic brain lesions, mainly in the territory of the middle cerebral artery. *Fresh hemorrhage* is the most com-

Table 21.1. Summary of factors associated with neuropathological alterations in immature newborns. Source: Del Toro et al. 1991, with adaptions from Brann 1986, Goddard-Finegold and Michael 1992, Volpe 2001

Predisposing problems
Immature infant with vulnerable cerebral vessels
Abnormal respiratory status, mechanical ventilation
May not be able to autoregulate brain blood flow
Events associated with hypotension/hypoperfusion
Myocardial compromise (e.g., secondary to asphyxia, congenital heart disease, large patent ductus arteriosus)
Significant blood loss
Other causes of shock
Events associated with hypotension/hypoperfusion or reperfusion
Physiologic redistribution of blood flow, especially during hemorrhagic hypotension
Resuscitation
Rapid volume expansion
Motor activity
Tracheal suctioning, other procedures
Seizures and other systemic problems

mon lesion found in the fetal brain (Fig. 21.4), characterized partly by petechial hemorrhages in the subarachnoid and/or subpial space, and partly in the subependymal region and in the germinal zone. Hemorrhage of the choroidal plexus is also common. Intraventricular hemorrhage may occur.

Consequent to the bleeding there are cellular reactions and scarring which have been described by Darrow et al. (1988). The early reactions of macrophages in infants occur at about the same rate as in adults. However, the transfer of iron from macrophages to astrocytes occurs much more rapidly in infants. The same holds true of the absorption of necrotic tissue to form a cyst (see pp. 444 f).

21.3 Intoxication

The age-related particular susceptibility of developing brain tissue to injury from drugs, alcohol, and exposure to environmental toxins has long been known (for review see Larson 1989). The teratogenic effect of individual drugs and alcohol on embryonic growth and the brain‘s general vulnerability are described in Chap. 16–20. It should be pointed out here that mercury can cause cytoarchitectonic abnormalities; alcohol abuse (see p. 383) and the use of drugs such as phenytoin (hydantoin) and warfarin (coumarin) can lead to microcephaly with polymicrogyria and mental retardation. Ionizing radiation (pp. 257 ff) as well as cytostatic treatment of the mother during pregnancy (p. 359) interferes with neuronal proliferation and migration and is also capable of inducing microcephaly with mental retardation.

Growth processes susceptible to chemicals and drugs have been analyzed by Barone et al. (2000). These authors highlight the following temporally and regionally dependent processes contributing to cerebral development: proliferation, migration, differentiation, synaptogenesis, gliogenesis, myelination, apoptosis, and neurotrophic factors.

The morphological changes engendered by these substances closely resemble those described above (Sect. 21.1). Here we deal only with the consequences of illicit drug consumption by mothers during pregnancy, which can have a major impact on the practice of obstetrics and pediatrics in urban areas the world over. The newborn exhibits withdrawal symptoms including staring, sneezing, excessive sweating, depressed respiratory status or mitotic pupils. In such cases, death may result from the deleterious effects

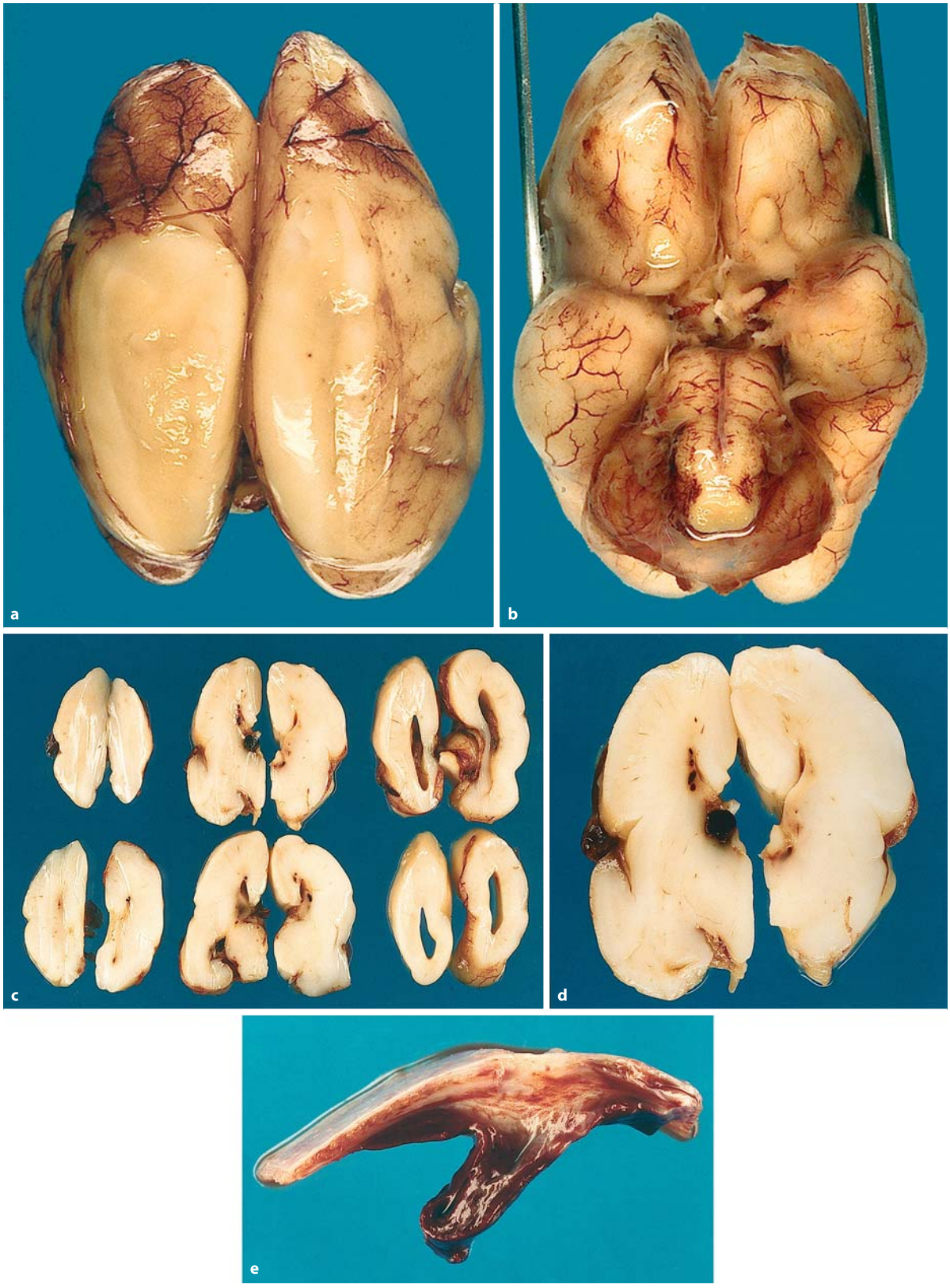

Fig. 21.4a–e. Hypoxic–ischemic encephalopathy. **a**, **b** The brain surface still is smooth without gyri in a child born in the 24th week of gestation, while on the frontal sections a subependymal hemorrhage is seen (**c**, **d**), as well as a bilateral subdural hemorrhage along the falx cerebri (**e**)

of drugs on the placenta or on the fetus. Premature birth, perinatal hypoxia, and meconium aspiration are all known causes of death in the newborn offspring of drug-dependent mothers.

Respiratory distress is an early consequence of the presence of various other drugs in the mother (and fetus) and may lead to death. The incidence of sudden infant death syndrome (SIDS) is estimated to be 5 to 10 times greater in these babies (Chavez et al. 1979). Drug-addicted parents are responsible for an alarming number of deaths attributable to physical abuse or neglect (Mayor's Task Force on Child Abuse and Neglect 1985; for review Larson 1989; Bays and Feldman 2001).

21.3.1 Cocaine

Death can occur from *intracerebral hemorrhage* in infants whose mothers have taken a large dose of cocaine just prior to precipitous and premature delivery (Chasnoff et al. 1986). Cocaine intoxication is known to cause *microinfarcts* in adult brains and it is thought that *fibrosis of the germinal matrix region* of the brain can occur in infants and children born to mothers who have consumed large doses of cocaine periodically during pregnancy. A number of cocaine-related congenital malformations are known, including amniotic band syndrome, cerebro–hepato–renal syndrome (Zellweger) and generalized anasarca (hydrops). Skull defects, including exencephaly, parietal bone defects and ossification center delays and interparietal encephalocele, have been documented in addition to intracerebral hemorrhage and infarction (Bingol et al. 1987).

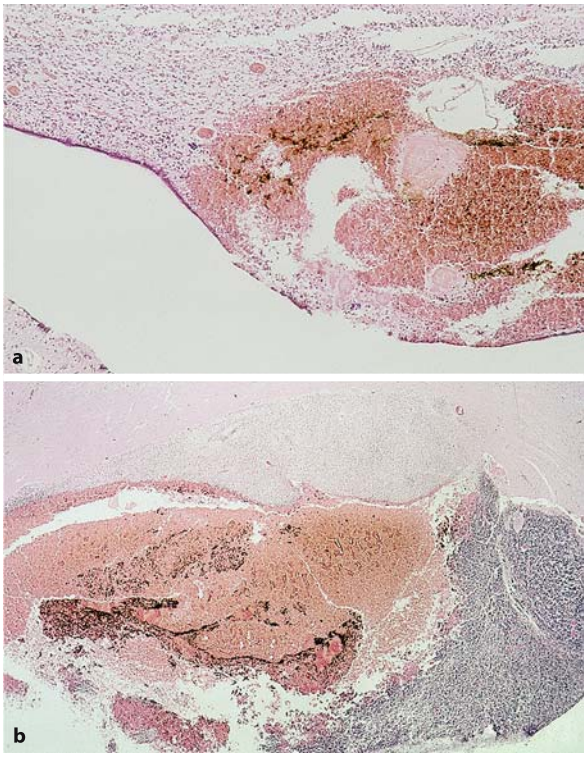

Fig. 21.5a, b. Subependymal hemorrhage as an indication of an asphyxial insult. **a** Supependymal hemorrhage without intraventricular involvement; **b** subependymal hemorrhage within an aggregation of matrix cells associated with intraventricular hemorrhage

21.3.2 Heroin

Fetal death in utero, stillbirths, neonatal death, intrauterine growth retardation, SIDS, meconium aspiration, respiratory depression, and hyperventilation are among the sequelae associated with maternal heroin use during pregnancy. Although uncommon, congenital malformations do occur. Instances of cerebral atrophy, abnormal lamination of the lateral geniculate body, hydrocephalus due to aqueductal stenosis, partial midline fusion of the cerebellum, polymicrogyria, hypertelorism, low-set ears, and wide-spaced nipples have been described (Larson 1989).

Children of heroin-abusing mothers tend to be hyperactive, have temper tantrums, and exhibit a low tolerance to frustration. They have poor fine motor coordination and suffer from speech and language delays, bilateral hearing deficits, attention deficits, and learning disabilities. Impulsivity and the inability to interact socially lead to behavioral problems during adolescence.

21.4 Infection

The neurotropism of infectious agents such as rubella virus, cytomegalovirus, *Listeria monocytogenes*, and *Toxoplasma gondii* is well known and has been described in pathologic reviews. Each can produce meningitis, choroiditis, and multicystic encephalopathy leading to microcephaly and/or hydrocephalus. Some viral infections may even mimic primary malformations such as microcephaly and hydrocephalus.

In *human immunodeficiency virus* (*HIV*) infection, the virus may be transmitted directly from mother to child. While the neurotropism of HIV is well known, only a few neuropathological studies of fetuses born to HIV-infected mothers have been published. A study of a series of 65 fetuses from pregnancies terminated for maternal HIV infection after 16–35 weeks of gestation found neuropathological

changes in only one fetus. The lesion consisted of non-specific necrosis of the hypoxic–ischemic type, apparently caused by prolonged labor. The only pathological findings in the other cases were edema and recent hemorrhages in various sites attributed to prostaglandin medication. The nests of migrating cells found in most of the cases were regarded as common findings in the fetal brain (Encha-Razavi et al. 1992).

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Perinatal CNS Injury 22

In the fetus or newborn infant brain damage can occur in any of numerous forms, many considered to be extraordinary regarding structure and function in comparison with the adult brain (Evrard 2001). An excellent survey has been presented by Laurini (1993). Because of the difficulties of an exact timing and causal assignment, such cases are sometimes summed up under the term «congenital» origin. Basically, five time segments of possible injury may be differentiated during pregnancy, delivery, and the early postnatal period (Bernsau et al. 1994):

1. Prior to conception (chromosomal/genetic)
2. Prenatal, i.e.,
   - Embryonal (<56 days after last menstruation)
   - Fetal (>56 days after last menstruation)
3. Intrapartum
4. Neonatal
5. Postpartum (>5 weeks after delivery)

This chapter deals with damage to the developing infant neocortex acquired late in gestation (prenatally), around the time of birth (perinatally), and/or after birth (postnatally). Such discrimination will be very difficult in the individual case (Naeye et al. 1989). The following questions are to be answered (Freeman and Nelson 1988):

1. Has there been an indication of a distinct and elongated asphyxiant or ischemic or mechanical insult?
2. Are there any symptoms of a hypoxic–ischemic or mechanically caused encephalopathy during the prenatal, natal or postnatal period?
3. Has there been an exclusion of other causes of asphyxia, ischemia or mechanical violence?

A survey on discriminating criteria is given by Bernsau et al. (1994). Using MRI and postmortem examination in 351 full-term infants with neonatal encephalopathy, early seizures, or both, Cowan et al. (2003) distinguished between lesions acquired antenatally and those that developed in the intrapartum and early postpartum periods. Brain images showed evidence of an acute insult without established injury or atrophy in 197 (80%) infants in the group with neonatal encephalopathy, while in only two infants (<1%) was evidence of established injury seen in infants with seizures observed within 3 days after birth; in this group acute focal damage was noted in 62 infants (69%).

The criterion "vascularization" was used by Aktas et al. (2003) in autopsy cases to determine the time (dating) of an ischemic insult. The evaluation was based on the vascular surface density and the number of vessels per stroma, each calculated by stereologic methods. The evaluation concludes that, in particular, the number of vessels per stroma will be a criterion for differentiating whether the insult is pregnancy-related or due to end-stage changes of dying.

Two basic causes of brain injury must be differentiated: asphyxiant–ischemic injury and mechanical brain injury (MBI). Although the causes differ, the results are similar: necrosis and/or hemorrhage. The forensic scientist must often distinguish between prepartum, intrapartum, and postnatal onset of the distress, i.e., the timing of the injuring event.

22.1 Ischemic–Asphyxiant Injury

Definition. Ischemic injury (reperfusion failure) and perinatal asphyxia are applied synonymously as in most cases a retrospective discrimination is not possible. Asphyxia is defined (see pp. 273 ff) as "hypoxia associated with carbon dioxide retention" (Taeusch et al. 1991); regularily it is associated with acidosis and hypotension, occasionally with hypoglycemia and coagulopathy.

Incidence. The incidence of asphyxia in a given population over a defined period is hard to estimate. The sparse available data on the global incidence of neonatal asphyxia show that it ranges from 1.8/1000 to 47/1000 (Stevenson and Sunshine 1989). Low Apgar scores, particularly those recorded at age 5 min, are known to indicate a dramatically increased risk of cerebral palsy in infants weighing <2,500 g (Moster et al. 2001). Babies with 5-min Apgar scores <3 had an 81-fold greater risk of developing cerebral palsy than babies with normal Apgar scores (see also Croen et al. 2001).

In premature infants, hemorrhages of the germinal plate may induce intracerebral or intraventricular bleeding (Chiofalo et al. 1986). The latter is a frequent finding in premature babies weighing <1,500 g. Of 45 neonates in this mass range, 19 (43%) were found to have intraventricular hemorrhage (Papile et al. 1978). It is the most common necropsy finding in neonates and premature babies (Donat et al. 1978). In term infants, intraventricular hemorrhage is always caused by rupture of the choroid plexus, in most premature infants (87%) by rupture of the germinal matrix. The neonatal brain of mature infants also appears to be selectively vulnerable to oxidative stress, which may be associated with subependymal or ventricular hemorrhage.

Clinical. Diagnosis of asphyxia varies depending on the point in time of its incidence (Armstrong 1995):

- Prenatal asphyxia: meconium staining of amniotic fluid, fetal heart rate >170 or <120 bpm (beats per minute), an irregular heart rate.
- Perinatal asphyxia: maternal shock, severe antepartum hemorrhage, infarcted placenta, cord wound tightly around neck, prolapse of cord, 1-min Apgar <3, 5-min Apgar <5.
- Newborn asphyxia: feeding problems, apnea or cyanosis, convulsions, hypothermia, cerebral cry, persistent vomiting.
- Postnatal asphyxia: oliguria, EEG abnormalities, right ventricular dilatation, pulmonary hypertension.

As a direct consequence of asphyxia, the child becomes extremely ill exhibiting coma, seizures, apneic attacks, limb weakness, and a variety of other neurologic signs. One study found that 35% of infants with hypoxic–ischemic encephalopathy had a history of adverse intrapartum events while 5% had experienced additional predisposing antepartum events, and in 20% antepartum events were solely responsible (Volpe 2001).

22.1.1 Causes of Oxygen Depletion

Sequelae of asphyxia are caused by arterial or venous circulatory disturbances.

Arterial circulatory disturbances are usually caused by an acute drop in uterine or umbilical circulation, by cardiac functional impairment in the infant or by arterial occlusion caused by embolus (e.g., by placental fragments) or by thrombus (e.g., vasculitis with bacterial meningitis or MBI). The resulting necroses occur within the area supplied by a single or multiple cerebral vessels. In about one-half of such cases the occlusion occurs in the middle cerebral artery; in the remaining cases multiple smaller vessels are affected (Ahdab-Barmada et al. 1979).

Venous thrombosis rarely involves the superior sagittal sinus, even more rarely the lateral sinus or deep veins of the Galenic system (Baram et al. 1988; Hanigan et al. 1988; Shevell et al. 1989). Characteristics of venous thrombosis include edema and bilateral hemorrhagic infarction of the parasagittal regions (sagittal sinus thrombosis), or of the internal capsule and striatum (deep venous thrombosis). The late sequela of venous thrombosis is *scarring* at varying locations and with varying characteristics.

Conditions leading to asphyxia existing in the mother and/or child must be distinguished from those caused by the placenta and/or cord (Jensen and Berger 1991):

- Maternal conditions: maternal shock (resulting, for example, from placenta previa or abruptio placentae), abnormal uterine contraction, anemia, cardiac arrest, severe pulmonary disease, renal failure, hematological disorders. Larroche (1986) described four cases of multicystic encephalopathy following well-documented episodes of maternal trauma, hypotension or hypoxia (due to

butane intoxication) between 30 weeks of gestation and "a few weeks before term."
- Placental and/or cord conditions: hemorrhages, infarction, infections or meconium staining; abnormal cord length (compression of umbilical vessels).
- Fetal or infant conditions: vena cava occlusion syndrome, hypotension, pulmonary diseases including obstruction of the airways, aspiration syndrome, atelectasis of the lung; cardiac lesions; metabolic acidosis caused by enzyme deficiencies or drugs administered to mother.
- Forensic conditions: indications for cesarean section are sometimes applied too narrowly; delayed delivery or sudden cessation of labor, for example, should have been acted upon earlier. If asystole in utero leads to asphyxia, the obstetrician/midwife must account for any delay in performing a cesarean section.

These events can lead to: (1) circulatory arrest, (2) severe hypotension without hypoxia (oligemia), (3) hypotension with hypoxemia/ischemia, (4) hypoxemia/ischemia with myocardial depression, (5) hypoglycemia, or (6) status epilepticus (Armstrong 1995).

22.1.2 Ischemic Cell Injury

Studies using the rat model of infant hypoxia–ischemia have found a major change in neuronal vulnerability in the CA1 region of the hippocampal area during the first 14 days after delivery (Towfighi et al. 1997). For the first five postnatal days, the vulnerability of the hippocampal region is comparable to that of other areas, but as the animals develop, hippocampal vulnerability increases selectively. By the 13th postnatal day, CA1 and the lateral aspect of CA3 are eminently vulnerable compared with the medial aspect of the CA3 and the dentate gyrus. By the 21st postnatal day, the adult pattern of CA1-selective vulnerability becomes manifest (Tasker 1999).

22.1.2.1 Pathophysiology

In human fetuses and newborns, neurons also exhibit a hierarchic selective vulnerability to ischemic stress as described in Chap. 4 as well as in Chaps. 13–15 (Part III).

Olney et al. (1971) demonstrated that the surfaces of vulnerable neurons have receptors for endogenous excitatory amino acids, the release of which is triggered by ischemia, hypoglycemia, and seizures. These excitatory amino acids (especially glutamate) may cause selective cell death when they bind to the neuron and initiate apoptosis, a multifaceted process recently reviewed by Berger and Garnier (1999) that involves the release and functions of cytokines (especially interleukins – IL-1β, IL-6; tumor necrosis factor-α– TNF-α; and intercellular adhesion molecule-1 - ICAM-1), free radicals, and nitric oxide (NO).

The mechanisms underlying ischemia-induced oligodendroglial death are still unclear (see p. 26). Volpe (2001) indicates important similarities with those implicated in neuronal death. A prominent feature of periventricular leukomalacia, a critical form of neonatal white matter injury, is diffuse injury to oligodendroglia, which are thought to represent early differentiating cells in the oligodendroglial lineage. Kadhim et al. (2001) assert that inflammation plays an important role in the pathogenesis of periventricular leukomalacia. They describe an early macrophage reaction involving the production of specific cytokines, which is temporally linked to coagulation necrosis, the earliest neuropathological finding in periventricular leukomalacia.

Delayed disruption of cerebral energy metabolism is a consequence of transient ischemia (Taylor et al. 1999). Among the prominent biochemical features of perinatal ischemic injury is the loss of cellular ATP, leading to increased (excessive) concentrations of synaptic glutamate and possibly other excitatory neurotransmitters such as glycine as well as to membrane depolarization. The latter phenomenon can facilitate the opening of NMDA-type glutamate receptors, inundating cells with Ca^{2+}. Even if glutamate levels are not high, NMDA receptors open passively if the membrane potential is diminished by hypoxia (Johnston et al. 2001).

There are a number of mechanisms associated with altered metabolism of reactive oxygen species (ROS) that may account for the neonatal brain's susceptibility to ischemic cell injury (Ferriero 2001). Among them are increased accumulations of hydrogen peroxide (H_2O_2) with subsequent neurotoxicity, which may be related to inadequate scavenging abilities attributable to, among other things, lower glutathione peroxidase activity. The ineffectiveness of the scavenging enzymes is aggravated by the developing nervous system's inability to maintain glutathione stores. The immature nervous system has more free iron than the mature nervous system. As H_2O_2 accumulates because of these inadequate defense mechanisms, the infant's nervous system is exposed to this free iron. This exposure stimulates the generation of the OH radical (Fenton reaction), a highly potent free radical capable of inflicting severe damage. The rapid conversion of H_2O_2 to OH within the setting of free iron renders the immature nervous system susceptible to increased cytotoxicity.

Another consequence of hypoxic injury is a rise in intracellular Na^+ and Ca^{2+} and a decline in intracellular K^+. This ionic imbalance combined with a

hypoxia–ischemia-induced breakdown in cellular defense systems exacerbates oxidative stress and produces a net increase in ROS. The ensuing damage to lipids, proteins, and DNA plus inactivation of key cellular enzymes ultimately results in cell death.

Although the exact mechanisms underlying neuronal loss are unclear, it is now known that the major components of cell death during the very early development of the brain are apoptosis (cf. Stadelmann et al. 2001) and necrosis – as in the adult brain (see pp. 56 ff). Various factors determine whether a cell undergoes apoptosis or necrosis, among them developmental stage, cell type, severity of mitochondrial injury, and availability of ATP for apoptotic execution (Taylor et al. 1999).

Ischemia leads to irreversible neuronal damage in a manner strictly dependent on blood flow. As mentioned, in adults normal cerebral blood flow (CBF) to the brain is 50–60 ml/100 g per min. In neonates, especially preterm neonates, it is lower at 10–12 ml/100 g per min (Greisen 1992) due to the incomplete development of synapses and metabolic demand at that age. In children aged 3–11 years, CBF rises to 106 ml/100 g per min (Kennedy and Sokoloff 1957), later eventually falling to adult levels. The blood flow depends on autoregulation, especially on the blood pressure. Infants have a narrower range of autoregulation than adults.

22.1.2.2 Cytopathology

The earliest change seen in neurons is cytoplasmic vacuolation, which occurs 5–30 min after onset of hypoxia and is caused by mitochondrial swelling (Levy et al. 1975). No structural alterations occur in astrocytes, but oligodendrocytes are just as sensitive as neurons. After 24–36 h, neurons exhibit marked eosinophilia of the cytoplasm, loss of Nissl substance (endoplasmic reticulum), and condensation (pyknosis) or fragmentation (karyorrhexis) of the nuclei. Several days later, these signs of cell necrosis appear together with microglia and, 3–5 days after the insult, hypertrophic astrocytes. Cell debris is phagocytosed by foamy macrophages and a glial scar forms over the ensuing weeks. If severe enough, the lesion may induce cavity formation, especially in the cerebral cortex (Rorke 1982, 1992).

Neurons suffer functional damage 8 min after onset of hypoxia under conditions of normothermia with normal blood pressure and blood flow (Schneider et al. 1975); although, as a rule, hypoxia is accompanied by a decline in blood flow and functional damage to neurons occurs within 4–5 min.

In the fetal brain, eosinophilic cells or neurons (indicative of ischemic cell damage) are only rarely demonstrable, except in the well-developed neurons of the thalamus. The more common response includes cytoplasmic swelling, chromatolysis, and nuclear pyknosis or karyorrhexis (Ahdab-Barmada and Moossy 1980). The age of an injury can be estimated based on the reactive changes (Squier 1993): the anoxic cell response, the microglia/macrophage reaction, and finally the astrocytic reaction, which is not recognized earlier than in the second half of gestation (Table 22.1).

22.1.3 Neuropathology

The earliest recognizable macroscopic sign of acute ischemic injury is edema. In the newborn brain as well as in the immature brain edema rarely leads to the flattening of the gyri or changes in the cerebellar tonsils seen in brains of older children and adults. Coronal slices of the fixed brain reveal compression of the lateral ventricles. The cortex, often nearly indistinguishable from white matter before myelination, is evident as a conspicuous white band that contrasts with the translucent gray color of the white matter, which appears to sink back from the cortex. A pink flush attributable to congestion of the vessels may be evident in the white matter.

Six basic types of ischemic brain injury have been distinguished (Berger and Garnier 1999; Volpe 2001):

- *Selective neuronal cell damage*, especially in the cerebral cortex partly associated with white matter lesions (Fig. 22.1a), hippocampus, cerebellar cortex (Fig. 22.1b) and anterior horn cells of the spinal cord occurring within 10 min of systemic ischemic insult (Williams et al. 1992).
- *Status marmoratus* (Fig. 22.1c), occurring mainly in the basal ganglia and thalamus. This is characterized by gliosis, loss of neurons, and (atypical) hypermyelination.
- *Parasagittal brain damage*, especially prevalent in the occipital and parietal regions of mature newborns; sulci are more susceptible than gyri.
- *Periventricular leukomalacia* (Fig. 22.1a – arrows), chiefly encountered in white matter dorsal and lateral to the lateral ventricle in immature fetuses. It arises 6–12 h after ischemic insult (Banker and Larroche 1962) in the form of swelling and rupture of axons, necrosis of oligodendrocytes and activation of microglia (within 24–48 h). In 25% of cases, leukomalacia is accompanied by parenchymatous hemorrhage.
- *Intra- or periventricular hemorrhages* are particularly common in the vascular bed of the germinal matrix where blood vessels are easily ruptured by sub- and postpartum fluctuations in cerebral blood flow. If secondary *bleeding* in the necrotic periventricular and pontine areas enters the ventricular system, it can lead to *ventricular*

Table 22.1. Sites of predilection for selective neuronal injury in premature versus full-term neonates. (+ More common, Ø no difference). Source: Volpe 2001

Brain region	Premature	Term newborn
Neocortex		+
Hippocampus		
Sommer's sector		+
Subiculum	+	
Deep nuclear structures		
Caudate-putamen		+
Globus pallidus	+	
Thalamus	Ø	Ø
Brain stem		
Cranial nerve nuclei	Ø	Ø
Pons (basis)	+	
Inferior olivary nuclei	+	
Cerebellum		
Purkinje cells		+
Internal granule cells	+	
Spinal cord		
Anterior horn cells (alone)		+
Infarction (including anterior horn cells)	+	

bleeding or even *massive intracerebral hemorrhage*. Rupture of the veins in the choroid plexus can also induce bleeding into the ventricle. Subpial hemorrhages may mimic primary *subarachnoid bleeding* (see below).

- Small *subarachnoid hemorrhages* are a common finding in the brains of newborns, especially if they have been born prematurely. Between 5% and 14% of preterm or sick infants suffer parenchymal *cerebellar hemorrhages* (Rorke 1982) caused by mechanical violence, ischemia and/or prematurity (Volpe 2001). In preterm infants *periventricular* and *intraventricular hemorrhages* are chiefly caused by asphyxia-induced rupture of vessels of the germinal matrix or choroid plexus (Donat et al. 1978; Armstrong et al. 1987).
- *Focal or multifocal brain damage*, especially in regions supplied by one or more of the main cerebral arteries. It results from arterial embolism or venous thrombosis after the 28th week of pregnancy, which does not produce scars but one or more cysts.
- Selective neuronal death in the ventral gray matter of the pons and in the subiculum of the hippocampal formation classically termed "*pontosubicular neuronal necrosis*" (Friede 1989; Rossiter et al. 2002) is now known to be related to hyperoxemia (Ahdab-Barmada et al. 1979) and prolonged high levels of oxygen administration to these infants.

22.1.3.1 Qualitative Differences

Detailed autopsy findings on ischemic brain injury in infants were recently presented by Marín-Padilla (1996, 1997, 1999). He distinguished the following age-related morphological changes:

1. Leukomalacia, infarction, cavitation
   In premature infants born after 30 weeks or less of gestation leukomalacia is found in the peri-

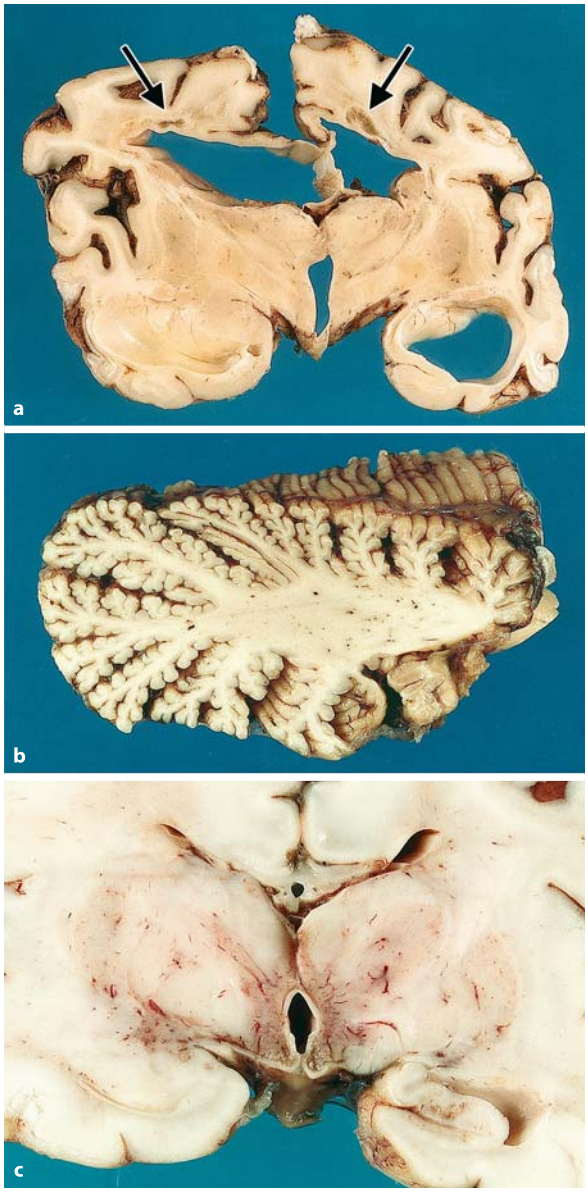

Fig. 22.1a–c. Asphyxial lesions with primary cortical involvement and secondary white matter damage. **a** Enlargement of the ventricles and reduction of the cortical structures as well as demyelination (*arrows*) within the parietal lobe of a 14-year-old girl; **b** atrophy of the cortical structures of the cerebellum of a 13-year-old boy; **c** status marmoratus in the basal ganglia of a two weeks old girl

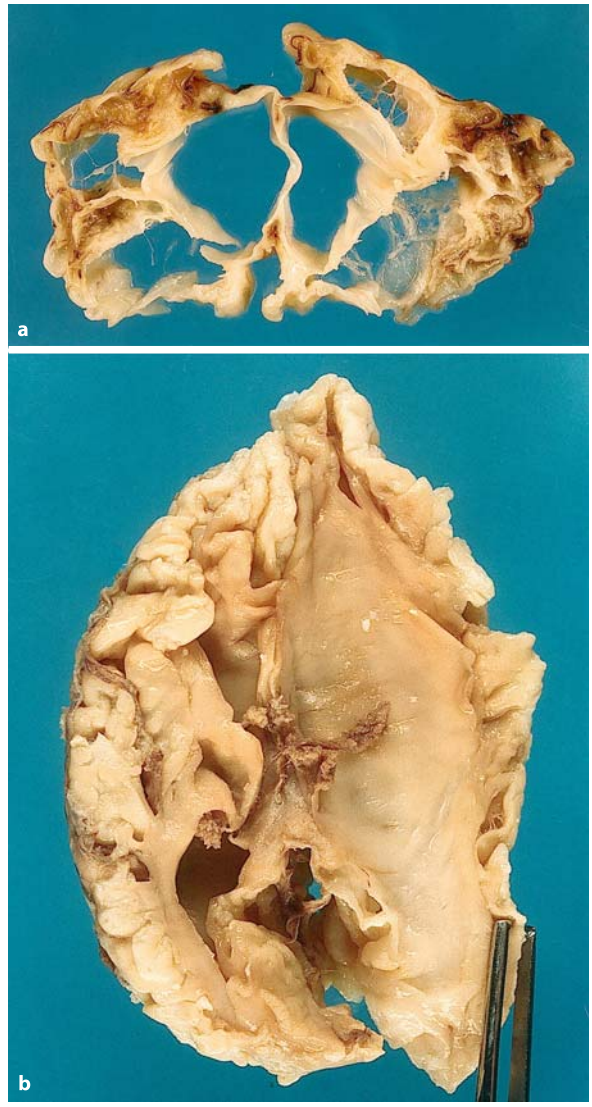

Fig. 22.2a, b. Asphyxial brain alteration. **a** Multicystic encephalopathy in a 6-year-old boy; **b** porencephalopathy in a 3-year-old girl

ventricular zone, i.e., in the ependymal germinal matrix, and the perforating vessels of the external glial-limiting membrane are particularly vulnerable to perinatal asphyxia. Between 28 and 32 weeks, the matrix is most prominent in the thalamostriate groove at the level of the head of the caudate nucleus at or slightly posterior to the foramen of Monro (Yakovlev and Rosales 1970; Larroche 1979; Rorke 1982). This is the most common site of germinal matrix hemorrhage. Focal hemorrhagic lesions often result from injury of vessels of the periventricular zone (Rorke 1982; Larroche 1991; Larroche and De Vrier 1997; Sarnat 1992; Encha-Razavi 1995).

The morphological sequelae of hypoxic–ischemic brain injury in infants include (Volpe 2001):

- Periventricular hemorrhagic infarction: a relatively large area of hemorrhagic necrosis in the periventricular white matter, just dorsal and lateral to the lateral angle of the lateral ventricle.
- Destruction of the germinal matrix (Fig. 21.5): the hematoma is often replaced by a cyst, the walls of which include reactive astrocytes and hemosiderin-laden macrophages.
- Hydrocephalus.

Ischemic white matter injury, in the form of widespread diffuse gliosis (Greisen and Børch 2001) or extensive multicystic destruction of the hemispheres, typically occurs in the immature brain of the preterm infant. The white matter is liable to injury because the vessels supplying it derive from two sources – the surface of the brain and the periventricular zone – separated by a relatively poorly perfused watershed area.

The gliotic scars and cystic alterations attributable to white matter injury include the following:

- Multicystic encephalopathy (Fig. 22.2a): the white matter has been mostly replaced by multiple large cysts with smooth clean walls. The cysts are located chiefly in the subcortical white matter or extend as far as to the lateral ventricles, which are dilated due to tissue loss.
- Porencephaly: large cystic defects of the cerebral hemispheres resulting from injury of both the cortex and the underlying white matter (Fig. 22.2b).
- Hydranencephaly/hydroencephaly: obliteration and replacement by thin-walled, fluid-filled cysts of most of both cerebral hemispheres.

2. Hemorrhagic lesions (Fig. 22.3)
   Premature infants suffering from perinatal asphyxia, circulatory disturbances, and/or mechanical violence are liable to a variety of acquired hemorrhagic lesions, including extradural, subdural, subarachnoid, subpial, periventricular, and infracortical hemorrhages (Friede 1989; Larroche 1991; Encha-Razavi 1995).
3. Gray Matter Injury
   Preterm newborns are also susceptible to gray matter injury but only to a limited extent and with specific topography. Neuronal necrosis most commonly occurs in the pontosubicular region (cf. Stadelmann et al. 2001), i.e., at the base of the pons and the subiculum of the hippocampus (Hashimoto et al. 1991; Mito et al. 1993). In 60% of cases, neuronal death was observed in the fascia dentata of hippocampus (Torvik et al. 1992). Both periventricular leukomalacia (Armstrong et al. 1987) and pontine neuronal necrosis (Skullerud and Westre 1986; Armstrong et al. 1987) can give rise to intraventricular bleeding.
   Histologically a pattern of karyorrhexis is followed by glial and macrophage infiltration with marked endothelial proliferation. Protracted cases are characterized by mineralization of cells, diffuse proliferation of glial cells with an extensive fibrillary network and, sometimes, herniation of cysts. In rare cases, the thalamic nuclei exhibit status marmoratus, a reactive hypermyelination as a tissue reaction.

Parasagittal injury is a bilateral injury that tends to occur at the "watershed" zone, the sulcus between the first and second frontal and parietal gyri. Injury, usually non-hemorrhagic, but sometimes hemorrhagic, is severest to the neuronal elements. Parasagittal injury is typical of full-term infants suffering perinatal asphyxia. The most common sites of the diffuse form of hypoxic–ischemic-selective neuronal injury in premature and term newborns are shown in Table 22.1.

However, in spite of this classification we must state that in most cases it is not possible to reconstruct the causal event by morphological criteria as, for example, in the case demonstrated in Fig. 22.3.

22.1.3.2 Topographical Differences

The age-dependent topographical differences can be explained as follows (cf. Marín-Padilla 1996, 1997).

The *periventricular zone* in younger preterm infants is vascularized by numerous arterioles and venules and has a variable venous drainage system (Marín-Padilla 1996). *Early periventricular hemorrhages* are small, multifocal, and caused by direct injury of the vascular endothelium, i.e., by endothelial cell necrosis, rupture of the vessel wall, or focal thrombosis. The hemorrhagic site fills with microglia/macrophages in the first hours after insult. There is a local proliferation of fibrous astrocytes, giving rise to a periventricular scar (Cherian et al. 2004). Throughout the injured site, residual periventricular gliotic scarring may develop and consists of closely packed fibrous astrocytes with interwoven fibers running parallel to the ependymal surface, possessing a few blood vessels. Glial nodules alternating with scattered foci of ependymal epithelium line the ependymal surface. Mineralized and/or calcified cellular elements and hemosiderin-laden macrophages may persist indefinitely in the scar (Gould et al. 1987). The sequelae include post-hemorrhagic hydrocephalus (i.e., hydrocephalus ex vacuo), periventricular gliosis, and distinct changes in the superimposed developing gray matter. Associated with the residual lesion are thinning of the neocortex, periventricular leukomalacia plus significant secondary structural and functional alterations of the overlying gray matter.

The *external glial limiting membrane* (subpial) is a second highly vulnerable area in younger premature infants. It consists of closely apposed glial endfeet covered by basal lamina. During vascularization of the developing neocortex, meningeal capillaries progressively perforate this membrane, penetrating the nervous tissue. The glial endfeet and their perforating capillaries are vulnerable to perinatal

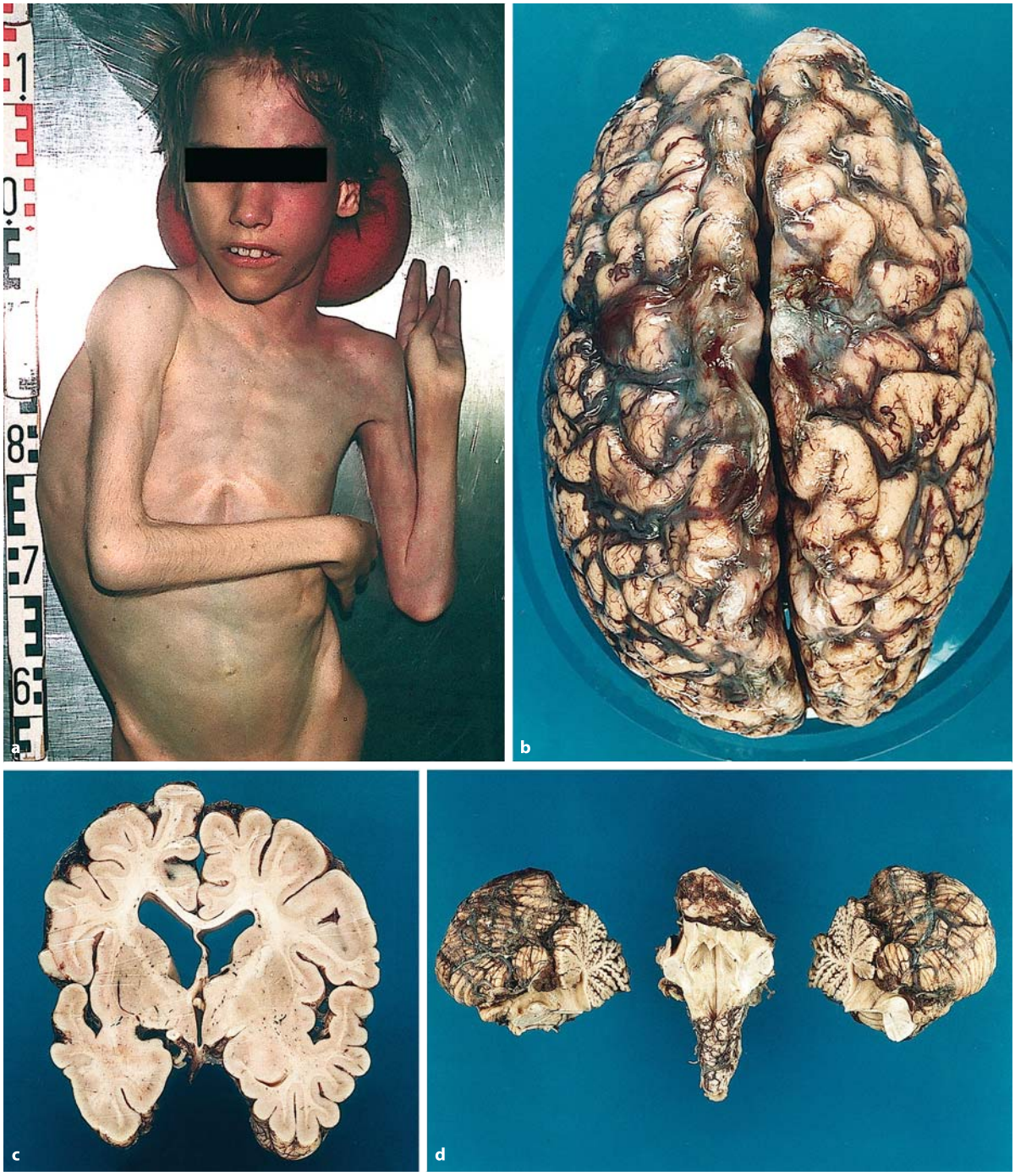

Fig. 22.3a–d. Perinatal brain injury without knowledge of the cause: **a** severe type of motor (spastic) paralysis with joint contraction and deformity; **b** slight to distinct external and **c** internal atrophy of the cerebrum and **d** cerebellum obviously caused by brain hypoxia/ischemia with the clinical features of spasticity, seizures and severe mental retardation

asphyxia, which often induces layer I (subpial) hemorrhages. The earliest morphological change in cases of asphyxia is swelling of the glial endfeet (edema). If the edema persists, the glial endfeet disintegrate, the subpial membrane undergoes focal disruption, and the perforating vessels rupture and cause a layer I hemorrhage. The necrotic debris and blood are scavenged by macrophages. Regeneration of the glial cells and proliferation of fibrous astrocytes create permanent marginal heterotopias at a level slightly above the neocortex.

White matter lesions are also seen in older premature infants. The white matter is rendered vulnerable by its vigorous metabolic rate, rapid growth, and increasing distance from new perforating vessels caused by the expansion of the intervening gray matter. Perinatal white matter injury can result from a combination of edema, hypoxia, ischemia (vascular compression), impaired perfusion (border zones), and vascular injury with or without hemorrhages.

Acute white matter lesions are hard to recognize. They can vary from small subcortical lesions to large lesions extending from periventricular to subcortical regions. Their salient feature is local axonal destruction, which is followed by tissue necrosis (infarction), edema, liquefaction, disintegration, reabsorption by macrophages, and early cavitation. The cystic cavities are lined by minimal reactive gliosis. The principal pathologic feature of healing white matter lesions is the capacity of the overlying gray matter to continue its development.

Gray matter lesions acquired perinatally are associated with respiratory difficulties, premature birth, etc. They often result from hemorrhagic and/or hypoxic–ischemic injuries, or a combination of both. The pathological picture is characterized by acquired cortical dysplasias, such as reactive gliosis (acquired microgyrias, leptomeningeal heterotopias, multicystic encephalopathies, ulegyrias, porencephalopathies, and hydranencephalopathies). All cases exhibit scarring as characterized by a subpial gliosis and a gliosis of the subcortical white matter.

Microgyria are characterized by astrocytosis of the gray matter in association with islands of gray matter tissue. *Ulegyria* result from severe damage to the gray matter in the depth of a sulcus while the corresponding gyral crest is spared. The surviving gyral crests are isolated by the almost total destruction of their corresponding sulci.

22.1.4 Dating of Asphyxiant Injury

For the forensic neuropathologist (see above), the important questions are: When did the asphyxia occur? What caused it? Did medical malpractice play a role?

The questions can be answered postmortem if the asphyxia can be differentiated from mechanical trauma or other types of injury. The important morphological criteria are summed up in Table 22.2, published by Squier (1993) (see also: pp. 414, 429, 433, 435, 436, 439).

If the child survives, it can be difficult for the clinician as an expert witness to make this distinction. Shevell (2001) has proposed the following operational definition that provides criteria for identifying whether an asphyxia occurred during the antepartum, intrapartum, or post partum period.

Antepartum criteria include the mother's report of diminished fetal movement, parameters of impaired fetal growth, and a non-reactive non-stress test (Shevell et al. 1999).

Intrapartum criteria include meconium staining, abnormalities in the fetal heart rate (e.g., late decelerations, bradycardia, etc.), significant metabolic acidosis in a cord or early infant blood sample (pH<7.0, base excess >12), and persistently low Apgar score (<6 beyond 5 min) (Shevell et al. 1999).

The major clinical *postpartum criterion* is neonatal encephalopathy (see above) marked by alterations in consciousness and tone, brain stem function, seizures, etc.

The American College of Obstetrics and Gynecology and the American Academy of Pediatrics (1992) highlight four diagnostic criteria for perinatal asphyxia:

1. Profound metabolic acidosis
2. Apgar score less than or equal to 5 beyond 5 min
3. Observation of a neonatal encephalopathy
4. Observation of multi-organ dysfunction

These criteria have been largely endorsed by MacLennan and Force (1999).

22.2 Mechanical Injury (Birth Injury)

The incidence of perinatal mechanical injury has declined dramatically in recent years due to improvements in obstetrical management and better indications for cesarean section. A distinction must be made between injuries of the head (extracranial hemorrhages and skull fractures), the coverings (dural hematomas, subarachnoid hemorrhages), the brain itself (intracerebral hemorrhages), and to the spinal cord and peripheral nerves.

22.2.1 Extracranial Hemorrhages

The following types of extracranial hemorrhages are distinguished (pp. 111 ff, 408 f):

- *Caput succedaneum*: blood collects in the loose subcutaneous tissues after birth injury. Bleeding may extend beyond the margins of the bony sutures and spread over large areas of the skull. Subcutaneous hemorrhage of the scalp secondary to massive congestion is very common following vaginal delivery.
- *Subgaleal hemorrhage*: blood aggregates beneath the (subaponeurotic) aponeurosis covering the

Table 22.2. Time-dependent reaction of cells and tissue in response to ischemic injury during development of the central nervous system. Source: Squier 1993

Site and reaction	Time after injury
Macrophages	
Microglial proliferation	3 h to 3 days
Macrophages	4–5 days
Macrophages showing evidence of phagocytosis	4–6 days
Astrocytes	
Astrocyte proliferation	12 h to 4 days
Astrocytes with cytoplasmic processes	3–11 days
Astrocytic fibrillary gliosis	6 days
Capillaries	
Endothelial swelling	1–3 days
Endothelial reduplication	5 days
Coagulation necrosis	3 h
Retraction balls	3 h
Neuronal karyorrhexis	12–48 h
Mineralization	8–14 h
Cysts	14–42 days

scalp and connecting the head muscles. It may extend diffusely over the entire roof of the skull. This type of hematoma is most common in newborns and small children. A common cause of subgaleal hematoma in newborns is vacuum extraction, which places great mechanical strain on the head and may cause injuries of the scalp and skull in addition to the hematoma. If the mother's pelvis is narrow, subgaleal hematomas may also result from displacement of parietal bones in relation to one another, widening of the occipital synchondrosis, and rupture of the sagittal suture between the parietal bones. Subgaleal blood tends to coagulate rapidly and may be mistaken for local edema on palpation.

- *Cephalic hemorrhage*: subperiostal hemorrhage is almost always caused by mechanical violence. This type of hematoma happens when dragging forces applied to the scalp cause the pericranium to detach from localized areas of the skull, with the result that blood accumulates beneath the periosteum of the skull. Because the bleeding does not extend across suture lines, this type of injury differs from the less harmful caput succedaneum and subgaleal hematomas. In most cases of cephalhematoma, the bleeding overlies the parietal bones, with only occasional involvement of the occipital and frontal bones. Twenty-five percent of cases involve linear fracture of the parietal bone beneath the cephalhematoma. The main causes of this type of injury appear to be repeated traumatic contact of the infant's skull with the maternal pelvis and the application of forceps. Its incidence is greatly increased if the infant is in the occiput posterior or occiput lateral position and by the use of midforceps.

Although the volume of blood is usually small, it may be enough to cause anemia and elevated bilirubin levels. In most cases, the infant does not manifest CNS symptoms or abnormal behavior. In cephalhematomas, absorption of the blood is often followed by calcification. A calcified ridge may disappear entirely or it can ossify and persist into adulthood in the form of a flat hyperostosis of the outer table.

22.2.2 Skull Fracture

Linear fractures must be distinguished from depressed fractures.

Linear fracture, a non-depressed fracture usually located parietally, is the most common bony lesion of the skull. It may be associated with cephalhematoma or epidural hematoma and is most often caused by direct compressive forces.

Depressed fracture is also preferentially located in the parietal bone. It is characterized by localized impression without loss of bony continuity. Its most common cause during delivery is local compression by the use of forceps.

Occipital osteodiastasis involves separation of the squamous and lateral parts of the occipital bone. It is often associated with posterior fossa subdural hemorrhage, cerebellar contusion injuries, etc.

22.2.3 Intracranial Hemorrhages

Intracranial hemorrhages can be primary and spontaneous or they can occur secondary to asphyxia. Other possible causes are mechanical violence, hemorrhagic infarction, coagulation disorders (thrombocytopenia, coagulation factors deficiency, particularly of vitamin K), vascular lesions (aneurysms, vascular malformations), and cerebral tumors.

The following six types of perinatal mechanically induced hemorrhage are distinguished, the localization depending in large part on the maturational stage of the infant:

1. Epidural hemorrhage (EDH)
2. Subdural hemorrhage (SDH): encountered mainly in full-term infants
3. Mechanically caused subarachnoid hemorrhage (SAH): encountered mainly in premature infants
4. Intraparenchymal hemorrhage
   - Intracerebral, intraventricular (IVH) and intracerebellar (ICH) hemorrhage
   - Cortical hemorrhage

22.2.3.1 Epidural Hemorrhage (EDH)

EDH occurs between the bone and the periosteum on the inner surface of the skull (see above). In newborns and very young infants, it is a very rare lesion. It is the result of a rupture of the middle meningeal artery or of major veins or venous sinuses. The majority of cases exhibit a linear fracture commonly attributable to an unintentional fall – it is rarely the result of proven child abuse (Shugerman et al. 1996). In rare cases, it is caused by birth (Lebkowitz 1936). The main clinical symptom is increased intracranial pressure (bulging anterior fontanel).

22.2.3.2 Subdural Hemorrhage (SDH)

Neonatal SDH is almost always attributable to birth, mostly in full-term infants. SDH results from head deformation during delivery. Factors of risk are the duration and manner of delivery, the relationship between fetal head diameter and maternal pelvic structure (cephalopelvic proportions), and whether delivery required extraction by forceps, vacuum or rotational maneuver. Fortunately, improved obstetrical techniques have rendered SDH the rarest type of intracranial hemorrhage (Luerssen 1991).

Depending on its severity, survival time and localization, SDH can lead to ventricular compression or enlargement. If a delayed SDH is situated over one of the cerebral hemispheres, a ventricular enlargement is almost always delayed. If the hemorrhage occurs in the region of the tentorium or posterior fossa, acute hydrocephalus is the likely consequence because of aqueductal, fourth ventricular, or incisural obstruction. The neurologic symptoms associated with SDH are usually attributable to direct compression of the neural structures of the posterior fossa and not to ventricular dilation. Therapy should therefore center on ventricular decompression and prompt elimination of the mass in the posterior fossa.

The following types of SDH are associated with mechanical violence to specific anatomic structures:

- *Tentorial laceration*: tentorial SDH is limited to the free edge of the tentorium, usually close to the junction of the tentorium and falx. Two types can be distinguished:
  - Infratentorial (posterior fossa) type, which is associated with inferior extension of the tentorium or with tearing of the cerebellar bridging veins.
  - Supratentorial type, which is caused by superior extension of the tentorium.
- *Occipital osteodiastasis*: occipital diastasis can arise after breech delivery, with SDH in the posterior fossa and laceration of the cerebellum.
- *Falx laceration*: an uncommon type of lesion associated with SDH. The source of bleeding is usually the inferior sagittal sinus.
- *Superficial cerebral (bridging) vein rupture* (see also pp. 126 ff)*:* this type of injury leads to subdural hematoma over the convexity, which is usually centered over the lateral part of the convexity. The *clinical picture* of SDH over the convexity is characterized by minimal or no clinical deficits, chronic effusions, and focal signs such as hemiparesis, focal seizures, deviation of eyes, and homolateral pupillary abnormalities (Volpe 2001).

Table 22.3. Time-dependent stages of reactivity to intracerebral hemorrhages in immature infants. Source: Darrow et al. 1988

Stages	Cytological reaction	Cases (n)	Duration of hemorrhages (days)
1	Intact red blood cells, no macrophage reaction	10	1–5 (19)
2	Few isolated foci of macrophages containing hemosiderin	4	2–12 (21)
3	Red blood cell ghosts in the center of the hemorrhage; iron staining in astrocytes	3	5–21
4	Macrophages containing hemosiderin predominate	1	50–60
5	Hematoidin predominates	1	113–117
6	Cyst with a few iron-positive macrophages present within cyst wall	1	114–120
7	Iron-positive macrophages are not in the cyst wall but in the cyst cavity	1	>120

22.2.3.3 Subarachnoid Hemorrhage (SAH)

Isolated mechanically caused SAH is a common event in newborn and premature infants but rarely causes complications. Primary SAH is caused by mechanical violence or circulatory disturbances. In full-term infants, mechanically caused wounding to the head and brain during delivery is the most common cause of SAH, the predisposing factors being the same as for SDH. In premature infants, hypoxia is thought to be the main etiological factor (Volpe 1981). SAH may also occur secondary to subdural or intracerebral hemorrhage.

SAH is localized over the cerebral convexity, especially in the posterior fossa. The source of hemorrhage may be small subarachnoid arteries, bridging veins or subpial arteries. Clinically there may be no or minimal neurological deficits. Mature infants sometimes suffer seizures, sometimes catastrophic deterioration. Hydrocephalus secondary to SAH is delayed in most cases if it does occur.

22.2.3.4 Intraparenchymal Hemorrhage

Intracerebral hemorrhages are described in part above, but will be discussed here again due to their importance.

- Intracerebral (ICH), intraventricular (IVH) and intracerebellar hemorrhages

  As mentioned above, hemorrhages of the germinal plate in premature infants and newborns can induce IVH (Chiofalo et al. 1986). IVH is the predominant form of intracranial hemorrhage in neonates. It is the most common autopsy finding in premature babies and newborns (Donat et al. 1978).

  ICH has a variety of causes, among them venous infarction, mechanical laceration, occipital compression of the skull (compliant skull), extension of intraventricular (fourth ventricle) or subarachnoid hemorrhage secondary to venous infarction, and primary cerebellar hemorrhage. The possible etiologic factors include hypoxic events, difficult breech, or forceps extraction. ICH may also be caused by thrombosis of the internal veins or the great vein of Galen, producing an associated bilateral hemorrhagic infarction of the striatum and/or the thalamus. If the basal veins of Rosenthal are obliterated as well, the infarct will include total bilateral involvement of these grisea, i.e., central cerebral nuclei.

- Cortical hemorrhage

  Focal hemorrhages involving the cerebral cortex and subcortical white matter are rare in the perinatal period for two reasons. First, focal blunt traumatic violence is unusual at this age, and, second, the fetal/neonatal skull is relatively elastic due to its open sutures and incomplete ossification. The biomechanical conditions of the skulls and brains of young infants differ therefore from those of adults.

  Young infants are, however, liable to tears of the white matter in the orbital and temporal lobes and in the first frontal convolutions. These tears may extend into the cerebral cortex or even to the walls of the lateral ventricles (Lindenberg and Freytag 1969). The reason why tears and not cortical hemorrhages occur is believed to be the

soft consistency of the still unmyelinated brain, the pliancy of the skull, the smoothness of the intracranial fossae, and the shallowness of the subarachnoid space.

22.2.3.5 Dating of Intracerebral Hemorrhages in Immature Infants

Darrow et al. (1988) created a schedule of cytological timing for intracerebral hemorrhages in preterm infants using Prussian blue reaction and the Gomori trichrome stain. They compared the cytological reactivity with the age of hemorrhages that occurred postnatally in infants born after 24 to 36 weeks of gestation (see also p. 408). The hemorrhagic event was timed by intravital ultrasound and the cytological reaction was determined by analysis of histological specimens after autopsy. The timing of 20 of these cases observed over a period of 120 days is presented in Table 22.3 following the seven time-dependent stages differentiated by the authors. The authors found no gestational age-related differences in apparent duration of the hemorrhages. The first three stages appeared to follow a time pattern identical to that of adults (see pp. 190 ff). In preterm infants, stages 4 through 7 showed distinctly more rapid absorption of the hemorrhage to form a large cyst, making the intermediate and later stages increasingly different from those in adults.

22.2.4 Spinal Cord Injury

The relative elasticity of the vertebral column combined with the inelasticity of the spinal cord make the latter especially vulnerable to mechanical violence. Towbin (1969) thought that spinal cord injury is a causal factor in approximately 10% of neonatal deaths.

The preferential sites of injury of the fetal spinal cord depend on fetal positioning in the uterus (Friede 1989). Breech delivery mainly puts at risk the lower cervical and upper thoracic regions; cephalic delivery, the upper and middle cervical regions (Menticoglou et al. 1995). Allen (1976) made a compilation of the factors predisposing to birth injuries of the spinal cord (Table 22.4) and discussed the relevant biomechanics and pathophysiology in detail.

The acute spinal cord lesion is characterized by epidural and intraspinal hemorrhages and by edema. The hemorrhages are associated with stretching, laceration, disruption or transection of the cord.

Chronic changes involve formation of scars, i.e., of fibrotic adhesions between the dura, leptomeninges, and spinal cord. Focal areas of necrosis give rise to cystic cavities of the cord, e.g., syringomyelia.

Table 22.4. Factors predisposing to birth injuries of the spinal cord. Source: Allen 1976

Direct causes
Excessive longitudinal traction at the time of delivery "stretch injury"
Extreme flexion of spinal column
Torsion of spinal column
Contributing influences
General
Dystocia
Primiparity
Prematurity
Abnormal presentation
Occiput posterior presentation
Brow presentation
Face presentation
Breech presentation
Opisthotonic posture
Ischemic or vasculo-occlusive disease
Vertebral artery
Anterior spinal artery
Arteria radiculomedullaris magna
Fetal
Vertebral malformations
Foramen magnum malformations
Hydrocephalus

The biomechanical basis of this type of injury is an excessive longitudinal or lateral traction of the spine or an excessive torsion. The clinical sequelae are stillbirth or early neonatal death, or neonatal respiratory failure or neonatal weakness and hypotonia.

22.2.5 Peripheral Nerve Injury

Because peripheral nerve injury seldom leads to death, the forensic neuropathologist is rarely asked for his expert opinion regarding such injuries. At most, the neuropathologist may be asked to testify in cases of maltreatment during delivery. The following types of peripheral nerve injury can be distinguished:

Table 22.5. Age-related risk factors for venous sinus thrombosis in infants. Source: De Veber et al. 2001

Risk factor		Neonates (<1 month) (*n*=69)	Non-neonates (>1 month, <18 years) (*n*=91)
Acute systemic illness		84%	31%
Perinatal complications (*n*=36)		51%	-
Hypoxia	43%		
Premature rupture of membranes	6%		
Maternal infection	6%		
Placental abruption	3%		
Gestational diabetes	3%		
Dehydration (electrolyte imbalance)		30%	21%
Head and neck disorders		16%	38%
Infection		10%	23%
Chronic systemic disease		4%	60%
Prothrombotic state		20%	54%

- *Brachial plexus injury*: this type of injury is thought to result from stretching of the brachial plexus, the roots of which are anchored to the cervical cord, due to extreme lateral traction secondary to obstetrical factors. The traction is exerted via the shoulder during delivery of the head in breech deliveries, and via the head during delivery of the shoulders in cephalic deliveries.
  The clinical picture of damage to the brachial plexus depends on the extent of the injury. Total plexus palsy for example is associated with paralysis of the intrinsic muscles of the hand, Erb's palsy, with weakness of abduction and external rotation at the shoulder, of flexion and supination at the elbow, and of extension at the wrist and fingers.
- *Diaphragmatic paralysis* (phrenic nerve injury): this type of injury may occur as an isolated symptom secondary to mechanically caused injury of cervical nerve roots supplying the phrenic nerve or in association with brachial plexus injury. Clinically it is characterized by respiratory difficulties in the hours immediately following delivery. Cyanosis occurs, as does tachypnea, but the blood gas values are suggestive of hypoventilation.
- *Facial paralysis* is characterized by weakness of the facial muscles of both the upper and lower parts of the face. A recent study of 357 vertex deliveries by forceps extraction shows a close relationship between the incidence of facial palsy and delivery by forceps (Hagadorn-Freathy et al. 1991). There are direct correlations between the part of face affected and the position of the head in utero. The common dominator is thought to be the position of the face on the sacral promontory.

Other types of peripheral nerve palsies are rather rare and will be only enumerated here: laryngeal nerve palsy, radial nerve injury, median nerve injury, sciatic nerve injury, lumbosacral plexus injury, and peroneal nerve injury.

22.3 Venous Sinus Thrombosis

In infants cerebral venous sinus thrombosis is a very rare disorder occurring during the perinatal and postnatal periods. Whereas clinical diagnosis was once extraordinarily difficult, today's neuroimaging techniques allow early and definitive diagnosis. De Veber et al. (2001) made an excellent survey of the disease based on a review of 160 cases gathered from the recent literature.

The risk factors have been related to age and are summarized in Table 22.5. In neonates, the most frequent cause is acute systemic illness, especially hypoxia. In non-neonates, venous sinus thrombosis is usually associated with chronic systemic diseases or prothrombotic states.

Affected infants are usually aged <3 months (about 50% of cases), 43% of victims being neonates, 54% less than 1 year old. The clinical feature is marked by seizures while neurological symptoms, both focal and diffuse, are less common in neonates than in non-neonates.

In both neonates and non-neonates the superior sagittal sinus (in 55%) and the lateral sinuses (in 51%) are most commonly affected, followed by the straight sinus (24%), the internal cerebral vein (10%), the vein of Galen (9%), the jugular vein (9%), and the cortical veins (6%).

The outcome of venous sinus thrombosis depends on the timeliness of diagnosis and initiation of antithrombotic therapy. About half of children return to normal by the end of therapy, 40% retain neurologic deficits, and about 10% will have succumbed to the disease.

The hallmarks of the morphological picture (Vinters 1995) are thrombosis of a venous sinus and hemorrhagic necrosis in the adjacent cortex. Diagnosis is generally made macroscopically.

In children, thromboses associated with dehydration (see Chap. 25) or infections are of particular forensic interest if there is suspicion that they had not been treated according to generally accepted medical standards. A high hemoglobin, if present, is helpful in making the diagnosis.

22.4 Late Sequelae of Perinatal Brain Injury

Perinatal brain injury can lead to motor and intellectual disabilities and handicaps. In "compromised baby" cases, the typical child/plaintiff has a variant of cerebral palsy, which is by definition a non-progressive motor deficit. Population-based epidemiological studies have shown that in the majority of cases the cause of cerebral palsy is unknown, fewer than 20% of cases being attributed to perinatal asphyxia (Nelson and Ellenberg 1986; Pharoah et al. 1996). Children suffering perinatal brain injury can experience repeated episodes of aspiration of gastric contents or of pneumonia secondary to dysphagia. They can also suffer seizures of variable frequency. Intelligence is not necessarily affected; children with normal intelligence can have most severe forms of motor (spastic) paralysis. If a child suffers repeated episodes of pneumonia or seizure or is in a vegetative state, it is always at risk of acute death resulting from infection, status epilepticus, and/or vegetative or metabolic decompensation.

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Postnatal Natural CNS Death 23

At least 20% of infant deaths during the first year of life are attributed to sudden infant death syndrome (SIDS) (Table 23.1). Differential diagnosis is complex and requires the exclusion of numerous known diseases. Bentele (1993) comprehensively surveyed the diagnostic alternatives to SIDS, while Oehmichen (1990) reviewed CNS disorders in infants, with particular reference to the data of Brazy et al. (1987) (Table 23.2). In 1987, a maximum of 4% of all infant deaths in the former Federal Republic of Germany (Oehmichen 1989) were caused by diseases of the nervous system. A survey of sudden unexpected death in hospitalized children was recently carried out by Buchino et al. (2002). The authors summarized the natural causes, as well as therapeutic misadventures, failure to monitor, homicide, and unexplained cases. After striking changes in rates of SIDS around 1990, case control studies (Carpenter et al. 2004) gave evidence of highly significant risks associated with prone sleeping (see Saternus and Adam 1985) and with turning from the side to the prone position; if the mother smoked, significant risks were associated with bed sharing, especially during the first weeks of life.

In the present chapter, we will discuss only a few of the CNS diseases likely to challenge the forensic neuropathologist. More detailed accounts are found in the relevant textbooks and reference books of clinical neuropathology (e.g., Larroche et al. 1997; Graham and Lantos 2002; Peiffer and Schröder 2002). A major part of this chapter will deal with the phenomenon of SIDS.

23.1 Metabolic Diseases

Metabolic disease with primary CNS involvement can be a direct cause of sudden death in infants, or primary systemic metabolic disturbances occurring outside the CNS can lead to secondary brain injury resulting in death. A number of metabolic diseases induce alterations included in the differential diagnosis of non-natural diseases, e.g., spongy changes of white matter, astrocytosis, and loss of myelin (Martin and Schlote 1972). Metabolic diseases may be present at birth or may arise during the neonatal period, e.g., fatty acid oxidation disorders (Wilcken et al. 1994) which can cause a sudden unexpected death in infancy (Brackett et al. 1994; Roe and Ding 2001). The hallmarks of *Leigh's disease* (subacute necrotizing encephalomyelopathy) are capillary proliferation and tissue rarefaction combined with a diffuse

Table 23.1. Types of death in infants aged >7 days to <1 year in Germany in 1985 (*Statistical Almanac* 1987). The number of SIDS cases is based on an incidence of 1 case per 1,000 newborns. Source: Oehmichen 1989

Children born in 1985	586,155			100.0%
Infant deaths in 1985	2,976	=	100.0%	0.5%
Unnatural deaths	440	=	14.8%	0.08%
Diseases and malformations (natural deaths)	118	=	4.0%	0.02%
SIDS	600	=	20.2%	0.01%

Table 23.2. Sudden death due to CNS diseases. Source: Brazy et al. 1987, Oehmichen 1990

Maldevelopment	**Asphyxia**
Arnold–Chiari syndrome	Antepartum or intrapartum asphyxia
Dandy–Walker syndrome	**Idiopathic degenerative disorder**
Jubert's syndrome	**Genetic diseases**
Möbius' syndrome	**Neoplasm**
Sturge–Weber syndrome	
Isolated spinal cord lesions	**Inflammation**
Trauma during delivery	Meningitis
Skeletal disorders	Encephalitis
Achondroplasia	
Osteogenesis imperfecta	
Expanding mass lesions	**Unnatural death**
Infratentorial subdural hematoma	Mechanical violence
Cerebellar hematoma	Asphyxia
Tumor	Intoxication
Vascular deformity	
Arteriovenous malformations	

but pronounced proliferation of astrocytes throughout the white matter (Fig. 23.1). Four major systemic metabolic diseases with secondary CNS involvement will be discussed here: bilirubin and hypoglycemic encephalopathies as well as hemorrhagic shock associated with encephalopathy syndrome and iron deficiency. Metabolic diseases or events are also seen in adults and are described elsewhere (pp. 606 ff).

23.1.1 Bilirubin Encephalopathy

Improvements in the testing for rhesus incompatibility during pregnancy and the introduction of exchange transfusions in 1950 have led to a dramatic decline in the incidence of this condition. Bilirubin

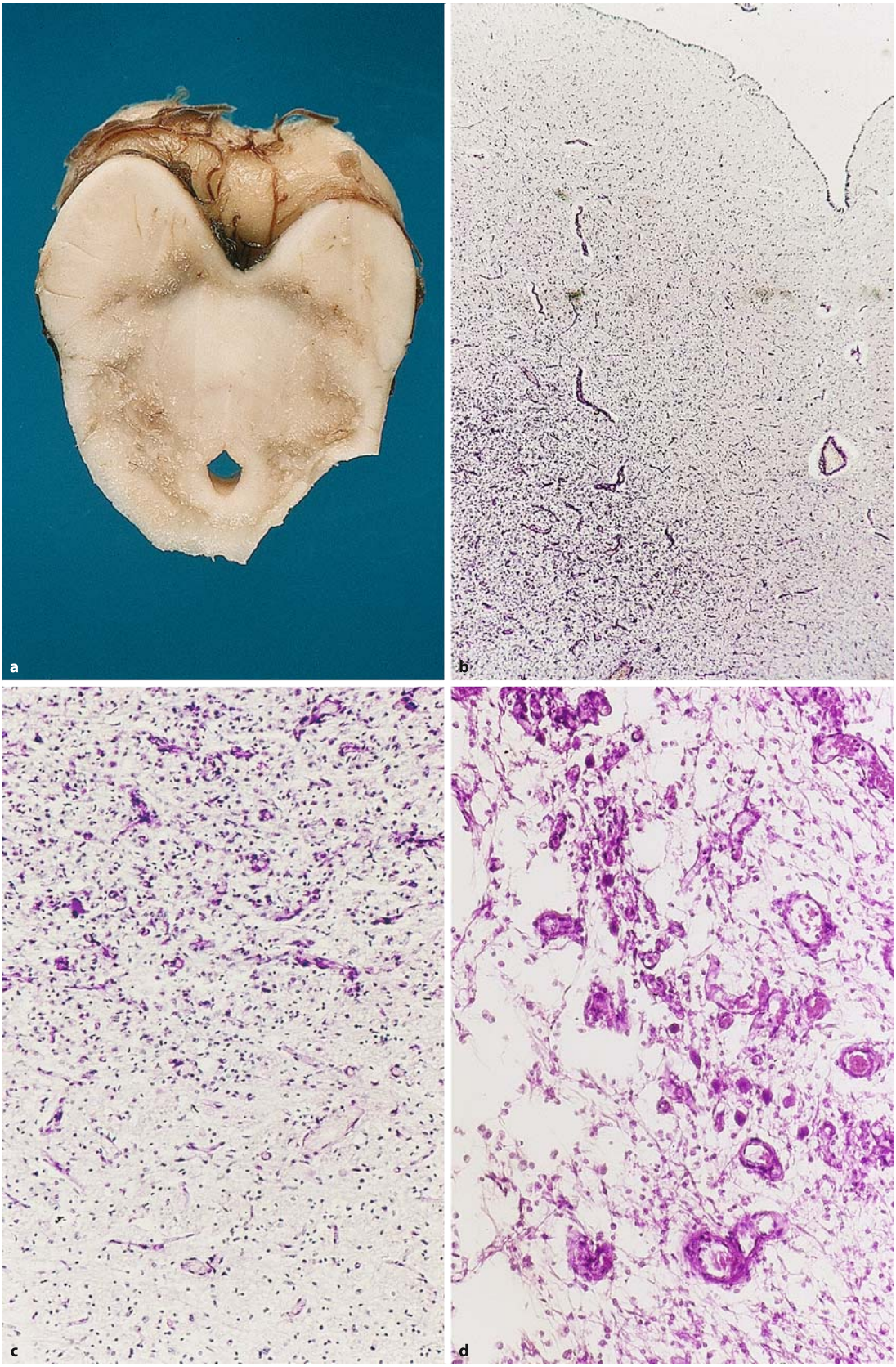

Fig. 23.1a–d. Subacute necrotizing encephalomyelopathy (Leigh's disease). **a** Gliosis of the midbrain, **b** perivascular proliferation of endothelial cells and activation of astrocytes, as seen in (**c**) and (**d**) (**b–d** PAS; magnification **b** ×50, **c** ×200, **d** ×500)

is a breakdown product of blood and is conjugated in the liver with water-soluble glucuronic acid. In the plasma, unconjugated (indirect) bilirubin is usually bound to serum albumin. The absence of the requisite metabolic capacity for the enzymatic conjugation process in the neonatal liver is widely believed to cause neonatal hyperbilirubinemia.

23.1.1.1 Pathophysiology

The occurrence of erythroblastosis in bilirubin encephalopathy is dependent upon the severity of the hemolytic anemia. It is common with serum bilirubin levels >30 mg% and rare at levels <20 mg%. Bilirubin encephalopathy is also seen in infants with relatively low bilirubin levels but with one or more additional predisposing factors, including hypoxia, prematurity, low birth mass, and acidosis or septicemia (Gartner et al. 1970; Friede 1989). Thus, the pathogenesis of bilirubin encephalopathy is multifactorial. Two questions must be answered:

1. How does bilirubin manage to penetrate the blood–brain barrier (BBB)? In newborns, the BBB can be disrupted by numerous causes (Volpe 2001), including asphyxia, severe acidosis, hypercarbia, intracranial infection, or an abrupt increase in blood pressure, especially if combined with impaired autoregulation, or an abrupt increase in venous pressure, all of which are associated with an increased passage of bilirubin into the brain. But the molecular mechanisms in the case of non-disrupted BBB are not understood completely (Wennberg 2000). It is probable that bilirubin is capable of crossing an intact BBB because the bilirubin anion binds to phospholipids which are highly lipophilic and thus readily capable of moving bilirubin across the barrier (Brodersen 1981; Brodersen and Stern 1987; Hayward et al. 1986; Bratlid 1990). Experimental studies have suggested that bilirubin/albumin can pass across a disrupted BBB (Rapoport 1983; Hansen 1995). Disease or hypoxic–ischemic-induced injury may disrupt the BBB and facilitate the transport of bilirubin/albumin into the brain of adults as well (see pp. 46 f).
2. What mechanism underlies bilirubin's toxic effect? The toxicity of a bilirubin load in brain tissue depends on the relative affinities of albumin and the target neurons (Wennberg 2000). Injury occurs mainly to the neuronal membrane with secondary impairment of mitochondrial function. In the CNS, it is the "free" – i.e., no longer bound to albumin – form of bilirubin that causes neuronal injury (Brodersen and Stern 1987).

23.1.1.2 Neuropathology

The hallmark of bilirubin encephalopathy is selective, symmetrical icteric discoloration of nuclear groups of neurons, with no staining of other tissue. The distinctive regional distribution is determined by the topography of bilirubin transport across the BBB. The locus ceruleus, subthalamic nucleus, pallidum, and Ammon's horn are the sites most often affected. Staining of the thalamus and striatum is less common. The nuclei of the cranial nerves in the tegmentum exhibit marked icteric staining, as do the oculomotor and dentate nuclei and the cerebellar flocculi (Ahdab-Barmada and Moossy 1983, 1984).

At the cellular level, the *acute phase* of bilirubin encephalopathy is marked by early neuronal changes manifesting as swollen granular cytoplasm, with frequent disruption of neuronal and nuclear membranes plus microvacuolation. These alterations are followed by more characteristic changes such as eosinophilic degeneration, shrinkage and pyknosis of neurons, vacuolation of cytoplasm, chromatolysis, and sponginess of the neuropil (Friede 1989). Yellow pigment is a common feature. By the end of the first week, nuclear and cytoplasmic membranes become poorly defined and there is evident cytoclasis and dissolution of affected neurons, i.e., fading. The topography of the neuronal lesions in bilirubin encephalopathy differs from that of hypoxic–ischemic cell injury.

Subacute lesions are associated with longer survival. They involve neuronal loss, a scattering of macrophages, and a reactive astrocytosis. The most common pattern associated with survived bilirubin encephalopathy (*posticteric encephalopathy*) is neuronal loss in the pallidum, subthalamic nucleus, and the vulnerable sector of the Ammon's horn (end plate and Sommer's sector). The tissue lacks bilirubin pigment.

23.1.2 Hypoglycemic Encephalopathy

Postnatal hypoglycemia has been implicated in neurologic deficits and retarded development (Cornblath et al. 1964; Haworth and McRae 1965). Mean plasma glucose levels reach a nadir of 55–60 mg/dl at 1–2 h after delivery in healthy full-term infants and begin to rise even before first feedings at 3–4 h (Srinivasan et al. 1986). Hypoglycemia is characterized by blood glucose levels <30 mg/dl (<25 mg/dl in plasma) in term infants and <20 mg/dl (<15 mg/dl in plasma) in preterm infants (Cornblath and Schwarz 1976; Heck and Erenberg 1987; Cowett 1992). (For details of hypoglycemic encephalopathy in adults, see pp. 286 ff, 607 f.)

23.1.2.1 Pathophysiology

As in the mature brain, glucose is the primary fuel for the production of metabolic energy and maintenance of normal function in the immature brain (Vannucci 1992; Vannucci and Yager 1998). It is best to regard the encephalopathy caused by hypoglycemia in terms of its early biochemical effects on brain metabolism and the sequelae of hypoglycemia combined with hypoxemia, ischemia, and/or seizures. In combination, these effects are of major clinical and neuropathological importance because hypoglycemia in neonates is rarely an isolated event and alone is usually not severe enough to induce brain injury, but may well be able to in combination with other insults to brain metabolism.

Hypoglycemia is known to potentiate the harmful effects of hypoxemia or asphyxia on the newborn brain even when acting in the postasphyxial period. Brain ischemia thus inflicts more severe damage when it is in combination with hypoglycemia than with normoglycemia. More importantly perhaps, ischemia is especially likely during even moderate hypotension due to developmental reasons of impaired cerebrovascular autoregulation.

23.1.2.2 Neuropathology

The entity of a perinatal hypoglycemic encephalopathy is still under discussion. The hypoglycemia in an infant is often attributable to the diabetic status of the mother. The brain may be malformed due to fetal hyperinsulinemia. Insulin is the growth hormone of the fetus before human growth hormone (hGH) takes over after birth, accounting for the hyperinsulinemia and hypoglycemia of the infant of the diabetic mother. The fetal brain has too low a metabolic rate and is too metabolically versatile, burning many substrates, for hypoglycemic encephalopathy can cause necrosis as it does in the adult.

The brain associated with hypoglycemia is macroscopically characterized by microcephaly (hypoplastic brain), i.e., widened sulci, atrophic gyri and diminution of myelinated white matter, with obliteration of the lateral ventricles. At the microscopic level, neuronal injury predominates, glial injury also being evident (Anderson et al. 1967). The neuronal lesions are situated in the upper cortical layers, a topography that differs from that produced by ischemia, i.e., selective involvement of deep and intermediate cortical layers (Rorke 1982; Friede 1989). Periventricular leukomalacia may be a marker of glial injury (Glauser et al. 1990). Unlike the picture in hypoxic–ischemic injury, the border zones and Purkinje cells are not selectively affected.

23.1.3 Hemorrhagic Shock and Encephalopathy Syndrome (HSES)

HSES is a devastating disease that affects previously healthy infants less than 1 year old and is associated with significant mortality and neurologic morbidity. It is characterized by sudden onset of hyperpyrexia, shock, cerebral symptoms (coma, seizures), and bleeding due to severe coagulopathy as well as diarrhea and hepatorenal failure. Laboratory investigation reveals falling hemoglobin and platelet counts, renal impairment, evidence of disseminated intravascular coagulation, metabolic acidosis, and raised serum transaminases. Microbiological cultures are uniformly negative. The condition has a high mortality and morbidity (Little and Wilkins 1997). The etiology is unknown and no specific treatment is known (Thebaud et al. 1999). Because of the sudden onset, SIDS is to be excluded (cf. Blau 1991; Trounce et al. 1991; Little and Wilkins 1997); because of the hyperpyrexia, heat stroke is to be excluded (Conway and Singer 1991), and the toxic impression of the disease requires toxic shock syndrome (Larkin et al. 1982) to be excluded; finally, the brain edema associated with liver involvement means that Reye's syndrome must be also excluded.

Clinical Features. The primary symptoms are fever, diarrhea, and metabolic acidosis. The specific symptoms are shock, consumption coagulopathy, hepatorenal dysfunction as well as somnolence, coma, and seizures.

Neuropathology. The common finding is marked brain edema (Jardine et al. 1997) and white matter involvement (Shida et al. 1996), including petechial hemorrhages as a result of intravascular microthrombi (Levin et al. 1989). At autopsy, gastrointestinal hemorrhages and fatty liver disease and/or centrilobular liver necrosis are found (Chaves-Carballo et al. 1990).

In a recent investigation (Thebaud et al. 1999) of 14 patients, computed tomography (CT) displayed diffuse areas of low density, mainly in the cerebral cortex, as well as intraventricularly, and parenchymal hemorrhages. Magnetic resonance imaging (MRI) showed hemorrhagic cortical lesions. Postmortem examination of the brain conducted in three patients showed necrotic and hemorrhagic lesions, mainly in cortical areas. Cerebral infarcts were described by two teams in single cases (Zureikat et al. 1990; Bratton and Jardine 1992).

23.1.4 Iron Deficiency

Iron deficiency is the most common nutritional deficiency in the world. Iron is an essential component of hemoglobin (55% of the total body Fe), myoglobin (15% of the total body Fe), and cytochromes. Iron deficiency leads to anemia, i.e., a reduction of the oxygen transport capacity in the blood. Moreover, iron is normally present in every griseum of the CNS as a component of certain enzymes and intracellular pigments (hemosiderin pigments). Some of it is unmasked and thus gives a positive reaction with Prussian Blue stain.

Definition and Clinical Features. Iron deficiency is defined as an abnormal value for at least two of the following three indicators: serum ferritin, transferrin saturation, and free erythrocyte protoporphyrin. Persons with iron deficiency and a low hemoglobin value are considered to have iron deficiency anemia. Although iron deficiency is more common in developing countries, a significant prevalence was observed in the United States during the early 1990s among certain populations, such as toddlers and females of childbearing age (Looker 2002). Iron deficiency can be caused by:

- Starvation
- Poor diet
- Poor absorption
- Damage to the digestive system
- Infection
- Alcoholism
- Acute or chronic loss of blood (hemorrhages)

In adults, iron deficiency may be caused by acute hemorrhages, chronic blood loss, and disturbances of iron resorption. Biochemically, iron deficiency results in decreased heme proteins, iron-containing enzymes, and reactions in which iron is involved as a cofactor. Consequently, there are changes in nucleic acid biosynthesis, oxidative respiration and mitochondrial function, detoxification of metabolic byproducts and catecholamine metabolism (Prasad and Prasad 1991).

Pathophysiology and Neuroanatomy. Iron, transported by transferrin, enters brain endothelial cells via receptor-mediated endocytosis (Connor and Fine 1987). Iron is most commonly located in oligodendrocytes of rat and human brains (Dwork et al. 1990). Iron-rich areas in the brain include the globus pallidus, ventral pallidum, substantia nigra reticulata, interpeduncular nucleus, cerebellar nuclei, facial nucleus, and the superior olive (Hill and Switzer 1984). Free iron has been implicated in the pathophysiology of several brain diseases, including Parkinson's and Alzheimer's disease, superficial siderosis, and multiple sclerosis; excessive iron deposition in the already iron-rich basal ganglia has been demonstrated with Hallervorden-Spatz syndrome (Beard et al. 1993; Swaiman 2001).

Neurology and Neuropathology. Iron will be essential during the time of rapid development of the human fetal brain, i.e., from the 10th to 18th weeks of pregnancy. Malnutrition during these periods of rapid brain growth may have devastating effects on the nervous system and can affect not only neurons, but also glial cell development and growth. Effects on glial cells may change myelin development especially because myelin continues to form around axons for several years after birth (Back and Volpe 1997).

Babies born to mothers who had poor diets may have some form of mental retardation or behavioral problems. Also, children who do not receive adequate nutrition in their first few years of life may show delayed development. The following symptoms are seen in children: developmental delay, pediatric stroke, breath holding spells, pseudotumor cerebri, and cranial nerve palsies (Yager and Hartfield 2002). Often the effects of malnutrition and environmental problems, such as emotional and physical abuse, can combine to create behavioral problems. Therefore, the exact causes of behavioral disorders are difficult to determine (Brick and Erickson 1998). In adults, the most common sequelae are disturbances of attentiveness, concentration, and fatigue. Special neuropathological findings are not described.

23.2 Stroke

Incidence and Pathogenesis. Stroke in children is estimated at about 2.6 and 3.1 per 100,000 per year, in white and black children, respectively (Schoenberg et al. 1978; Broderick et al. 1993). The following essential risk factors should be mentioned (Nicolaides and Appleton 1996; Kirkham et al. 2000; Roach 2000; – for review: Sträter et al. 2002) in addition to so-called idiopathic ischemic strokes (Abram et al. 1996; Schievink et al. 1996; Kirkham 1999):

- Congenital heart malformations
- Hemoglobinopathies (sickle cell disease)
- Hematological and coagulation disorders (venous thrombosis or embolus from the heart)
- Infectious diseases (varicella zoster, HIV)
- Collagen diseases
- (Rare) inborn metabolic disorders
- Inborn abnormal respiratory control (Takashima and Becker 1989)
- Hereditary factors
- Drugs
- Dehydration

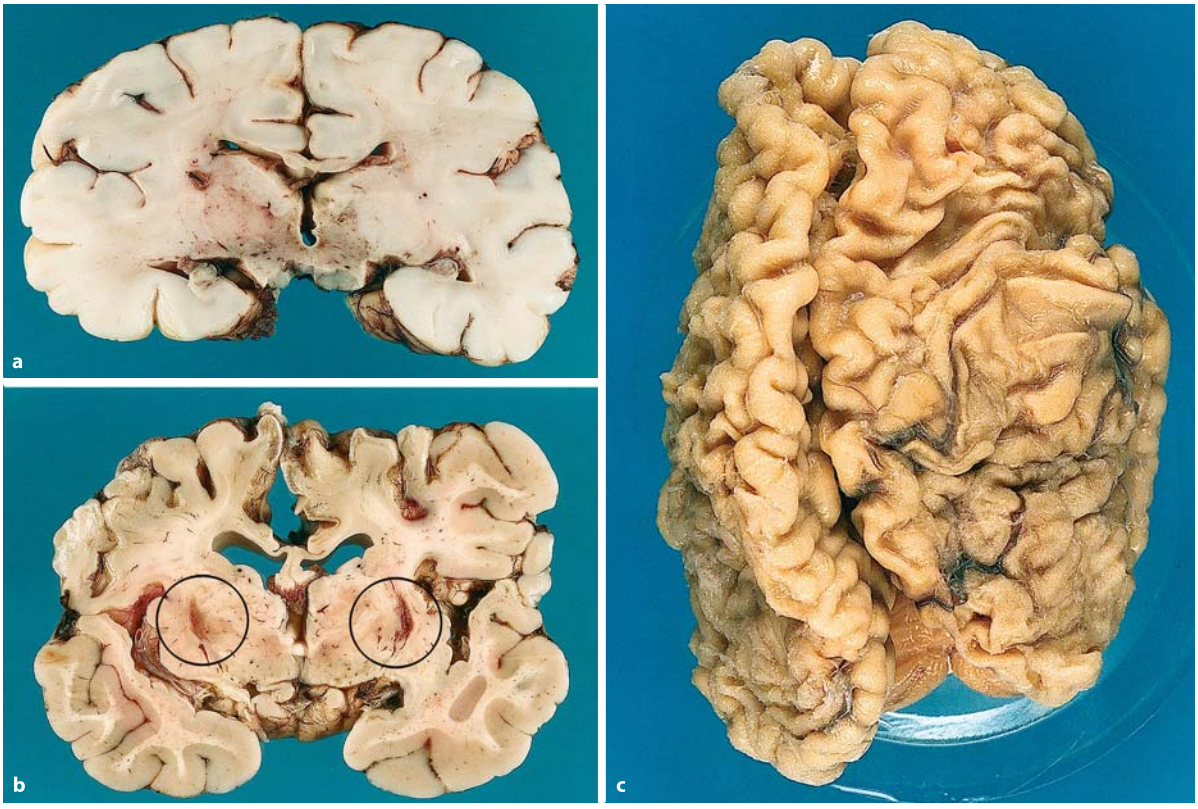

Fig. 23.2a–c. Generalized ischemic stroke. **a** Cardiac arrest in an 11 day old boy who survived for 10 days; **b** near SIDS with apnea and resuscitation in a 5-year-old girl who survived for about 5 years with bilateral cortical atrophy of the frontal lobes and cystic alterations of the putamen (*circles*); **c** schizogyric alteration of the brain surface in a 3-year-old boy who survived the stroke for about 3 years

Neuropathology. The brain morphology commonly is characterized by the features of a pale, ischemic infarct (Fig. 23.2; see also Fig. 23.4a, b), while a hemorrhagic infarct occurs rarely (Humphreys 1991). The morphology and neurological features are comparable with stroke in adult brains which are described elsewhere (pp. 564 ff). The outcome is obviously dependent on the cause of stroke and the extent of brain damage. Idiopathic strokes in childhood were reviewed by Abram et al. (1996). Nearly half of their patients (n=42) had a poor outcome (43%) with moderate to severe hemiparesis (n=14), recurrent stroke (n=7), and death (n=1).

23.3 Infectious Diseases

Although primary infectious diseases of the CNS are rare in newborns, a large number of infectious diseases may be transmitted from mother to fetus in utero. Only acute bacterial meningitis and acute abacterial meningoencephalitis will be described here (for further information, see pp. 582 ff).

23.3.1 Bacterial Meningitis

Incidence. Prompt diagnosis and appropriate therapy are major challenges in the care of newborn patients (Volpe 2001). Of major clinical importance in newborns are bacterial infections of the CNS, which are often associated with bacteremia, i.e., sepsis. Bacterial meningitis has an incidence of 0.3 per 1,000 live births, sepsis of 1.5 per 1,000 live births (Klein and Marcy 1995; Saez-Llorens and McCracken 1998). Meningitis is most commonly associated with group B streptococcus and *Escherichia coli*. The pathogenetic sequence runs almost invariably from bacteremia to meningitis. The bacteria are usually acquired during labor or delivery and are associated with infection of the maternal urinary tract and/or genitals.

Neuropathology. Acute changes associated with bacterial meningitis include arachnoiditis, cerebral edema, vasculitis, infarction, ventriculitis, and encephalopathy (Larroche 1975; Friede 1989). Among the chronic changes (Larroche 1975; Friede 1989) are hydrocephalus, multicystic encephalomalacia and

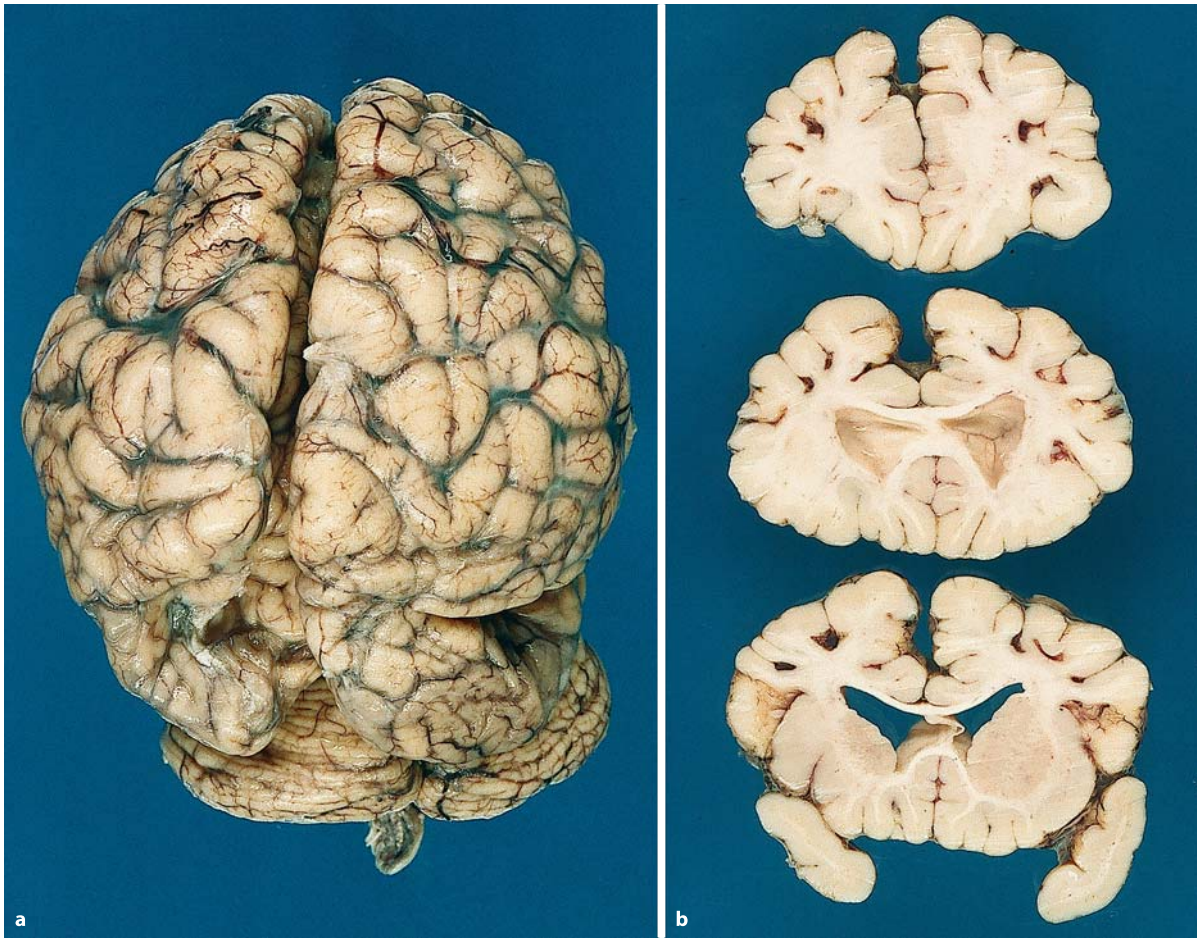

Fig. 23.3a, b. Chronic changes after survival of a bacterial meningitis. **a** Microcephaly with bilateral infarct of the occipital lobe and an arachnoid cyst in the right frontal lobe; **b** hydrocephalus

porencephaly or microcephaly, atrophy of the cortex and white matter as well as defects of cortical development (Fig. 23.3).

Clinical Features. The first stage of disease is marked by symptoms of sepsis and respiratory disturbances. Neurological signs include seizures, stupor/irritability, focal cerebral signs, bulging of the anterior fontanel, extensor rigidity – opisthotonus. In cases of late onset, the picture is dominated by the neurological signs. Meningitis must be suspected in all cases involving sepsis and confirmed or excluded by laboratory evaluation. A bacteriogram can determine which antibiotic will be most effective. Moreover, sepsis caused by meningococci may lead to death without expression of a purulent meningitis. In those cases, the above-mentioned clinical symptoms may exist but the diagnosis will be performed exclusively by microbiological examination of the blood.

23.3.2 Abacterial Meningoencephalitis

Although very rare in the industrialized world, in developing countries, especially Africa, other types of infection are common in newborns and young infants. This is especially true of *acquired immunodeficiency syndrome* (AIDS). The ability of the human immunodeficiency virus (HIV) to be transmitted during pregnancy and its neurotropism are well established (Price et al. 1988). CNS involvement in AIDS is characterized by progressive encephalopathy with cerebral atrophy, inflammatory infiltrates, multinuclear giant cells, and in some cases vascular mineralization (Sharen et al. 1986). Opportunistic infections are uncommon in this age group.

Children infected transplacentally may exhibit developmental abnormalities consisting of delayed acquisition and varying degrees of cognitive dysfunction (Epstein and Sharer 1988). Some may develop a progressive encephalopathy with neuro-

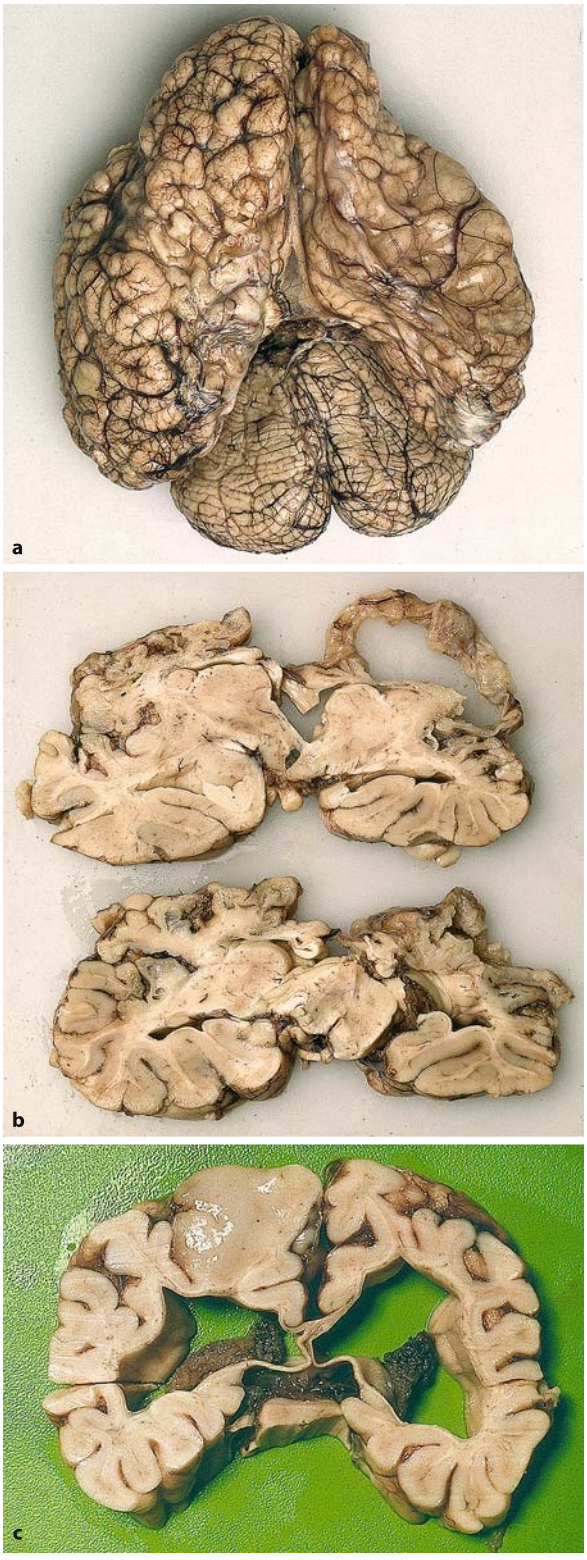

Fig. 23.4a–c. Glial tumor associated with perinatal hypoxic damage. Four-year-old boy with multiple neurologic deficits suddenly died, demonstrating a massive hydrocephalus, porencephaly (**b, c**) and an expansive brain tumor

pathological features (Price et al. 1988) that are concordant with adult subacute encephalitis except for the pronounced vascular impairment with calcification of the basal ganglia.

Half of all cases of abacterial meningoencephalitis exhibit prostaglandin medication-induced fresh cerebral hemorrhages at various localizations, and cerebellar heterotopias, which are regarded as a common finding in fetuses. One case was described with hypoxic–ischemic-type brain damage associated with recent periventricular hemorrhage, and comprised pronounced diffuse necrosis of both gray and white matter with diffuse gliosis, neuronal loss, macrophagic reaction, and rare calcifications (Encha-Razavi et al. 1991).

23.4 Tumor

There are two main types of brain tumor of early childhood: those presenting at birth or in the first 2 months of life (about 1–3% of childhood brain tumors) and those presenting during the first and second years of life. Congenital tumors of the brain and spinal cord comprise only 5% of all congenital tumors. As many as a quarter of brain tumors diagnosed by the end of the first year of life were evident at birth (Berry 1993). Rickert et al. (1997a; Rickert 1998) have reviewed the frequency of various types of brain tumor in the early postnatal period. According to these authors, teratomas constitute the most common type of congenital brain tumor (Rickert et al. 1997b), whereas tumors of neuroepithelial origin predominate in the first 2 months after birth (Buetow et al. 1990). The latter appear either in the pineal region or in continuity with a pharyngeal teratoma. Although often large, they are almost always histologically benign.

Wakai et al. (1984) and Rickert (1998) surveyed the major types of non-teratomatous, i.e., neuroepithelial and mesenchymal, tumors: ependymoma, astrocytoma (Fig. 23.4c), medulloblastoma, including so-called primitive neuroectodermal tumors, and choroid plexus papilloma (and carcinoma) are encountered with comparable frequency. The prognosis in each of these entities depends on the stage at diagnosis and the histological type and localization of the tumor.

Regardless of tumor type, the most common clinical presentation is enlargement of the head due to hydrocephalus or tumor mass. The neonatal skull's ability to expand sometimes allows these tumors to become quite large. A quarter of such infants are stillborn, and vaginal delivery may require decompression of the skull.

23.5 Sudden Infant Death Syndrome (SIDS)

23.5.1 Definition and Incidence

Despite extensive discussion in 1994 regarding the need for a redefinition (Rognum and Willinger 1995), SIDS is still described according to the original definition put forth by Beckwith in 1969 (Beckwith 1970), but still modified: Sudden Infant Death Syndrome (SIDS) is the sudden and unexpected death of a child under the age of 1 year which remains unexplained after complete autopsy, including scene investigation, review of the medical records and toxcology (Froede 2003).

Differential diagnosis of SIDS requires exclusion not only of the diseases listed in Table 23.2 (see p. 452), but of the effects of external violence as well (Byard and Krous 1999), which do not always leave macroscopic signs of injury detectable upon external examination (Bergman 1997). It is especially difficult to discriminate SIDS victims from victims of accidental or inflicted asphyxia, including smothering, compression of the chest (Oehmichen et al. 2000), intoxication, drowning or shaking mechanisms (pp. 493 ff). A number of influences can be lethal although they do not leave any external injuries or visible changes (cf. Table 23.3).

SIDS cannot be diagnosed with certainty unless a complete autopsy has been performed, augmented by review of the clinical history and examination of the scene of death. The autopsy itself must fulfill the criteria summarized in Table 23.4. Exclusion of blunt violence, especially to the CNS, is one of the principal indications for routine autopsy in victims of SIDS.

Although autopsy fails to explain the death, the finding of non-lethal injury is still significant. In such cases, the cause of death is more suitably termed "undetermined" or "unascertained" than SIDS.

The following criteria are typical of SIDS:

1. SIDS predominantly strikes infants aged between 2 and 5 months
2. SIDS is more common in colder seasons and in colder climates
3. SIDS strikes boys more often than girls
4. SIDS mortality varies from country to country: Golding (1989) found the incidence to range from 1 to 4 victims per 1,000 live births, however since then is has reduced distinctly to about 0.5 per 1,000 live births

The number of SIDS deaths has declined dramatically as parents meanwhile have learned to avoid the prone position and have begun instead to lie their babies on the back (supine) or side (see above). 1985 Saternus and Adams for the first time gave evidence of this essential pathogenetic factor, which meanwhile is worldwide accepted. Mitchell et al. (2000)

Table 23.3. Various causes of sudden death associated with discrete or no external injuries. Source: Kirschner and Wilson 2001

1. Sudden infant death syndrome (appropriate age group)
2. Cardiac arrhythmia
3. Viremia or culture-negative bacteremia; Gram-negative shock
4. Seizure disorder
5. Endogenous or exogenous hyperthermia or hypothermia
6. Asphyxiation of various types including birth asphyxia, suffocation, drowning
7. Electrocution
8. Undetected drug or poison
9. Metabolic insults including inborn insults as well as acquired diseases such as hypoglycemia, etc.

Table 23.4. Demonstration of SIDS death at autopsy by exclusion of other causes, a task routinely performed using a series of supplementary investigations. Source: Kirschner and Wilson 2001

1. Complete autopsy without significant gross or microscopic findings
a. Absence of significant fatty change in heart, liver, and skeletal muscle
b. Absence of significant inflammation in heart, lungs, and brain
c. Usual skeletal muscle and lymphoid tissue architecture
2. Normal vitreous electrolytes
3. Negative toxicologic and microbiologic studies
4. Negative metabolic and genetic testing, as required
5. Negative scene and circumstance investigation
6. Negative medical and family history, including history of previous infant and child deaths

point out, moreover, that the decline in SIDS diagnoses has seen a concomitant rise in diagnoses of accidental asphyxia due to unsafe sleeping conditions and in cases where family background and autopsy findings suggest more complex mechanisms. This shift in diagnostic profile is probably the result of more careful interpretation of the extensive investigations now routinely performed (exhaustive autopsy testing, rigorous review of clinical history, and examination of the scene of death) rather than of arbitrary reclassification.

23.5.2 Neuropathology and Pathophysiology

Though the precise cause of the SIDS phenomenon is still unknown, a series of systematic morphological studies suggests that CNS involvement plays a central role in SIDS. A disturbance of the CNS function is also in discussion by trying to reconstruct the agonal process (see p. 506).

In accordance with the prevailing definition, SIDS victims exhibit no specific neuropathological findings that can account for the sudden, unexpected death. If no plausible cause of death can be found, two additional questions arise:

1. Does the brain exhibit primary pathologic changes that could explain the fatal event?
2. Does the brain show secondary changes that may be associated with the fatal event?

Each question has been the subject of investigations based on the following hypothesis, first proposed by Steinschneider in 1970 and since supported by many studies (particularly that of Naeye and coworkers, 1973, 1976; for a survey, see Valdes-Dapena 1988): the fatal process underlying SIDS involves a disturbance of respiratory regulation that results in clinically observable apnea attacks (Schulte et al. 1982) and functional impairment of ischemic-injured neurons.

Close examination of the respiratory control centers in the brain stem of SIDS victims produced the following two opposing theories (van Beek et al. 1984):

1. The function of the respiratory center is impaired secondary to developmental retardation
2. Primary hypoxia of extracerebral origin induces ischemic injury of the CNS, which is then functionally impaired, and normally induces disturbances

These two theories form the basis for the two main hypotheses currently under discussion.

23.5.2.1 Primary CNS Changes

Clinical evidence suggests that prenatal stress may alter the course of neurologic maturation (Gould et al. 1977; Amiel-Tison 1980; Henderson-Smart et al. 1983). Moreover, recently reported morphometric evidence of the retardation of neuronal development in the brain stem of SIDS victims is supported by enzyme-biochemical and immunohistochemical findings (for references, see below). The high dendritic spine density and low activity of one catecholamine-synthesizing enzyme plus a disturbed endorphin system in the brain stem have all been interpreted as signs of neuronal retardation.

High Dendritic Spine Density. The chrome-silver method as modified by Golgi is capable of precisely delineating the post-synaptic terminals of the fiber system, i.e., the dendritic spines. All types of spines progressively increase during the early postnatal period and decrease thereafter (Marín-Padilla 1972). Scheibel and coworkers (1973; see also Takashima et al. 1980) showed that during the perinatal period in cats the reticular neurons of the brain stem possess spine-like pleomorphic protrusions, referred to by the authors as shaggy excrescences. These spines begin to develop in utero and attain their density peak between the 34th and 36th weeks of gestation. Between the 20th and 30th day after birth the dendrites lose these spines and display thereafter a smooth, spineless profile (Takashima and Becker 1986). This finding in the brain stem is countered by findings of the same authors that, in cats (and in humans), the spines of cortical neurons usually persist on mature dendrites. The authors theorized that the reticular dendrite-spine system serves as the basic control of respiratory rhythm and the rest–activity cycle. It may be postulated therefore that once they have lost their spines, dendrites are unable to regulate complex functional processes such as the sleep–wake pattern of respiration and repetitive output sequences.

Dendritic spines in the brain stem of SIDS victims were first investigated systematically by Quattrochi and coworkers (1980). They evaluated the number of dendritic spines on magnocellular and parvocellular reticular neurons in the paramedian and lateral reticular areas of the medulla and the dorsolateral areas of the pons. They found that reticular dendritic spines, though absent in control brains, persisted in the brains of SIDS victims: 17 of 19 SIDS victims had spines, only 2 of 9 controls. The authors attributed this persistence to maturational retardation.

Quattrochi and coworkers (1985) later corroborated this finding in a double-blind study involving 61 SIDS and 34 control cases. Concurrent quantitative analysis of spine density in the seven brain nu-

clei examined found it to be significantly higher in SIDS cases than in controls ($p<0.0001$). The authors thought retardation of brain stem development in SIDS victims may have caused a disturbance of respiratory regulation.

Takashima and coworkers (1985) reported a decreased number of spines in their study of ventilator-dependent, premature-born infants using the Golgi technique. Neuronal development, especially in the cortex however, is usually unrelated to the maturity of the fetus at birth (Purpura 1975). These authors, therefore, suggested that neuronal development in the brain stem could differ from that of the cortex and that reticular spine development may also be influenced by external factors, e.g., use of ventilator, artificial environment.

These findings do not fit into a system in which the persistence of spines is regarded as an index of immaturity. The premature loss under these other conditions is instead interpreted as reactive. Spine loss due to external impact is also reported by other authors who, however, investigated only cortical dendritic spines. A lesion experimentally inflicted along the afferent projections to the visual cortex, for example, led to a reduction in the number of apical dendritic spines 30 days later (Globus and Scheibel 1966).

In their review of the Golgi impregnation technique, Braak and Braak (1985) pointed out that optimal impregnation results cannot be achieved on autopsy specimens, since the latency period between death and fixation has a deleterious effect on impregnation. Long agony or delayed fixation produce such changes as a reduction in the number, length, and caliber of dendrites as well as in the density of dendritic spines. Unfortunately, most of these changes cannot be distinguished from those artifacts found in poorly fixed material.

Reduced Catecholamine-Synthesizing Enzyme Activity. Denoroy and coworkers (1980, 1987) also postulated a primary respiratory control disturbance in SIDS victims. They examined nine areas of the brain stem for the activity of enzymes involved in catecholamine synthesis, based on the assumption that most brain stem regions associated with respiratory control possess catecholaminergic cell bodies or terminal fibers. Levels of the adrenaline-synthesizing enzymes were found to be significantly lower in a few medullary areas including the medulla oblongata centralis, the areas of the hypoglossal and dorsal nuclei of the vagus and of the n. tractus solitarius in brains of SIDS victims than in those of controls. In the n. ambiguus the same enzyme exhibited significantly diminished activity in SIDS victims, but not in the partial SIDS children, i.e., infants with minor pathological alterations which do not explain the death. The authors attributed these biochemical findings to abnormal control of central respiration and arousal.

The same authors suggested that postmortem degradation influences enzyme activity, although they could find no correlation between enzyme activity and the postmortem interval. However, studies showing a time-dependent reduction in enzyme activity have also been published (for review, see Oehmichen 1980, 1990). Clarification of the regulatory function of the adrenergic neurons remains for future studies. However, a more recent Japanese study (Ozawa and Takashima 2002) found an increase in substance P in the medulla and pons, a decrease in tyrosine hydroxylase-positive catecholaminergic neurons in the ventrolateral medulla, and vagal nuclei in the medulla oblongata and basal ganglia, a decrease in tryptophan hydroxylase-positive serotonergic neurons in the periaqueductal gray matter, and a decrease in 5-hydroxytryptamine 1A and 5-hydroxytryptamine 2A receptor immunoreactivities in the ventrolateral medulla and vagal nuclei in the medulla oblongata. The authors suppose a delayed neuronal maturation or developmental abnormality of the nociceptive reaction of cardiorespiratory and arousal control in SIDS.

Disturbance of Endorphin Immunoreactivity. The respiratory nuclei of the brain stem contain a high concentration of opiate receptors that react with endorphins. Endorphins are known to contribute to the suppression of respiration in the fetus and in newborns (Moss 1986) as well as in adults (Tabona et al. 1982). Moreover, infants exposed to narcotics in utero (Pierson et al. 1972; Rajegowda et al. 1978; Bauchner et al. 1988) are at greater risk of SIDS than infants not exposed in utero. These findings and certain characteristics unique to SIDS, in particular the sudden, silent death during sleep, led some authors to hypothesize that SIDS is caused by hyperactivity of the endogenous opioid system (Kuich and Zimmerman 1981a, b).

Met-encephalin immunoreactivity was measured by Kuich and Franciosi (1983) and levels of substance P in the medulla oblongata by Bergström et al. (1984). Their findings suggested that met-encephalin was not conspicuously overproduced in the brain or brain stem of SIDS victims while substance P levels in the medulla oblongata were significantly higher than in controls. Levels of met-encephalin in the medulla declined with age in controls, but not in SIDS victims, while the ratio of substance P to met-encephalin was higher in SIDS victims than in controls.

These findings are difficult to interpret. The elevated substance P levels may be due to hypoxia (Arregui et al. 1981), but substance P is known to have a stimulating effect on respiration. The authors speculate that diminished release of substance P may cause

its accumulation in neurons. There is some evidence that morphine inhibits release of substance P (Yaksh et al. 1980).

Taken together these findings offer scant concrete support for the hypothesis that the endorphin system is involved in SIDS. Despite the persuasive theoretical arguments for such a relationship, more compelling and reproducible qualitative and quantitative findings are needed.

Arcuate Nucleus Hypoplasia. Kinney and Filiano (1995) determined that at least some SIDS victims may be rendered vulnerable by a defect in cell populations within the ventral medullary surface. They thought this to be particularly true of the arcuate nucleus, whose cells play a role in central chemoreception. The same authors (Filiano and Kinney 1992) had previously identified two SIDS cases almost completely lacking an arcuate nucleus, suggesting that at least a subset of SIDS victims (2/41 cases) are characterized by arcuate nucleus hypoplasia. Meanwhile Matturri et al. (2002) declared that on the basis of morphometric results of the neuronal population in the different portions of the ventrolateral medulla in SIDS victims, infants without the full complement of neurons and neuropil (arcuate nucleus hypoplasia) are at risk for SIDS because they are unable to develop appropriate cardioventilatory control during this crucial developmental period. These authors could demonstrate severe bilateral hypoplasia in 16 cases (=26%), a partial bilateral hypoplasia in 11 cases (=18%) and a unilateral hypoplasia in 8 cases (=13%) while well-developed arcuate nuclei were demonstrated in 27 cases (=43%) of a total group of 62 cases of SIDS victims (compared with 25 controls).

Increased Spine Density and Brain Stem Hyperplasia. Another series of studies has found changes in the opposite direction. O'Kusky and co-workers (O'Kusky and Norman 1994, 1995; O'Kusky et al. 1995) found increased numbers of dendritic spines in the hypoglossal nucleus and increased density of synapses in the medullary reticular formation, with a generalized hypertrophy of the brain stem in SIDS victims.

Genetic Aspects. Mutations or polymorphisms with unclear biological significance are accepted as possible cause of death in some of the SIDS victims (Hunt 2004). According to Opdal and Rognum (2004) the genetic components of sudden infant death can be divided into two categories:

1. Mutations that give rise to genetic disorders that constitute the cause of death by themselves. These cases in which a mutation causes a lethal disorder should be diagnosed not as SIDS but as explained death. Mutations leading to death include long QT syndrome and severe acute hypoglycemia. The most well-investigated mutation is the A985G mutation in the medium-chain acyl-CoA dehydrogenase (MCAD) gene, which is a prevalent mutation causing deficiencies in fatty acid metabolism and also CNS – edema – and muscle alterations.
2. Polymorphisms that may predispose infants to death in critical situations. One polymorphism that may induce sudden death in infancy may be in the interleukin-10 (IL-10) gene promoter and the ATA/ATA genotype (Opdal et al. 2003). Other polymorphisms associated with sudden death in infancy may be the L-allele of the serotonin transporter gene and the L/L genotype (Weese-Mayer et al. 2003) as well as dysgenesis of the testes syndrome whose gene is localized on chromosome 6q22,1-q22.31 (Puffenberger et al. 2004).

23.5.2.2 Perfusion Disturbance or Ischemia

Ischemic injury of the brain stem of SIDS victims was studied earlier than both dendritic spine density and the number of catecholamine-synthesizing enzymes in the brain stem. All subsequent investigations have been based on the preliminary studies of Naeye (1976), who described numerous morphological alterations in SIDS victims. All of these changes have been explained by hypoxia, hypoventilation (Becker and Takashima 1985), hypoperfusion (Takashima et al. 1978a), or hypotension (Gilles 1969; Taylor and Roessmann 1984). Moreover, the following alterations may be explained by these factors, which are described in SIDS victims as well: delayed myelination of the brain stem (Naeye and Drage 1975), carotid body atrophy (Naeye et al. 1976), delayed myelination of the vagus (Sachis et al. 1981), white matter lesions in the form of subcortical leukomalacia in watershed zones of the hemispheres and periventricular leukomalacia (Takashima et al. 1978b), a macrophage reaction (Gadson and Emery 1976; Missliwetz et al. 1986), neuronal hypoxic damage (Leech and Alvord 1977), cerebral edema (Wünscher et al. 1971; G Molz, personal communication, 1988), and finally neuronal apoptosis (Waters et al. 1999).

Brain Stem Gliosis. Here, too, Naeye (1976) was the first to observe the presence of gliosis in the reticular formation of SIDS victims. Because similar changes are seen in patients with congenital heart disease, this gliosis was attributed to cerebral hypoperfusion (Saternus and Adam 1985) or chronic hypoxia. A reactive gliosis was observed by a number of investigators in the brain stem of SIDS victims, but not in control brains, despite substantial overlaps in the number of such cells. Other authors however could detect no reactive gliosis in SIDS victims (cf. Table 23.5). Neither the quantitative nor the qualita-

Table 23.5. Survey of the literature on gliosis in the brain stem of SIDS victims. Source: Oehmichen 1995

Author	Number of cases		Staining technique	Topography	Results
	SIDS	Controls			
Naeye (1976)	28	18	Holzer	Reticular formation	**Gliosis**
Takashima et al. (1978a)	46	19	Holzer, PTAH, H&E	14 areas of brain stem	
Kinney et al. (1983)	45	20	Luxol fast blue	Reticular formation	
Becker (1983)	46	10	GFAP, PTAH	4 areas of brain stem	
Ozawa and Takashima (2002)	32	23	GFAP	Medulla, pons	
Ambler et al. (1981)	32	26	H&E	Areas of brain stem and cerebellum	**No gliosis**
Summers et al. (1978)	34	15	PTAH, Cajal	Reticular formation	
Pearson and Brandeis (1983)	18	13	H&E	8 areas of brain stem	
Oehmichen et al. (1990)	11	11	Albumin, GFAP	6 areas of brain stem	
Stoltenberg-Didinger and Kordes (1990)	68	12	H&E, GFAP, vimentin, PAS, Luxol fast blue	10 brain regions	
Sawaguchi et al. (2002a, b)	27	11	H&E, GFAP, vimentin	Midbrain	

tive investigations provided findings that *definitely* confirmed the hypothesis of astrogliosis in the brain stem of SIDS victims.

Purkinje Cell Density. If there is hypoperfusion or ischemia, the brain stem is affected by the reduced supply of oxygen, but also, and especially, the cerebellar cortex is similarly affected. Certain anatomic structures render Purkinje cells especially liable to hypoxia-induced injury, which reduces their numbers and therefore density.

Oehmichen et al. (1989) compared the Purkinje cell density in parasagittal sections from the left and right cerebellar hemispheres of 12 SIDS cases with that in age- and sex-matched controls (Fig. 23.5). The Purkinje cell density was found to be slightly higher in the cortex of SIDS victims aged 5 months and younger than in the controls.

Studies of the cerebellum confirmed the findings of the same team in the brain stem: SIDS cases exhibited no sequelae of hypoperfusion or chronic hypoxia. However, Emery (1979) found brain stem gliosis, leukomalacia, and calcifications, all purported to be caused in large part by a hypoxic insult, in about half of all SIDS cases. Since the aforementioned systematic observations, which were made in a small number of cases, could not confirm these findings, it would be necessary to perform an extensive prospective study to clarify this point.

Alz-50 Antibody Reactivity. Alz-50 antibody is immunoreactive with brain tissue of Alzheimer's patients. It can also be demonstrated immunocytochemically in neurons of vibratome-prepared brain tissue of SIDS victims (Sparks and Hunsaker 1991; Sparks et al. 1996). Using paraffin-embedded material, Oehmichen et al. (1998) compared the number of Alz-50-immunoreactive neurons in the hippocampus region and in nuclei of the medulla oblongata at the level of the inferior olivary protuberance in SIDS victims (n=10) with that in two control groups (infants who died of subacute hypoxia/ischemia with subsequent reperfusion, n=9; and infants who died of acute ischemia without reperfusion, n=7). The hippocampal cortex and inferior olivary nucleus of SIDS victims possessed a significantly (p<0.05) higher percentage of Alz-50-reactive neurons than those of the control groups (median in SIDS victims: 100%; in victims of subacute hypoxia/ischemia: 33.6–81%; in victims of acute ischemia: 89.2–99%).

This higher expression of Alz-50 in SIDS victims may be caused by ongoing hypoxia/ischemia during agony and are supported by more recent investigations: Lavezzi et al. (2003) demonstrated the expression of the c-fos proto-oncogene – a marker of activated neurons, particularly by hypoxia – in the medulla oblongata nuclei involved in breathing after birth. In 60% of the analyzed cases (n=22) the authors observed numerous positive c-fos neurons in the dorsal motor nucleus of the vagal nerve.

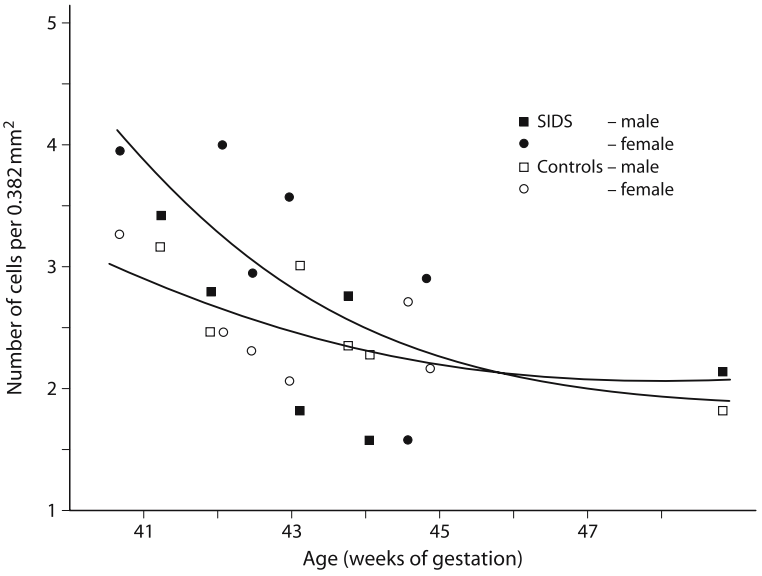

Fig. 23.5. Number of Purkinje cells in relation to postconceptional age in parasagittal sections of SIDS victims and age- and sex-matched controls (source: Oehmichen et al. 1989)

But the present paucity of data prohibits definitive explanation. The above findings concur with observations of prolonged agony in SIDS victims (Meny et al. 1994, 1996; see also Poets et al. 1999). Butterworth and Tennant (1990) demonstrated significantly lower pH and higher lactate levels in about half of the brains of 66 SIDS victims than in those of 18 non-hypoxic controls, implying that the SIDS infants suffered prolonged agony with hypoxia or incomplete ischemia prior to death. Although the molecular mechanism underlying the increase in Alz-50 immunoreactivity has yet to be clarified, Alz-50 antibody reactivity appears to represent an accurate method for distinguishing between SIDS cases and cases of sudden infant death due to other causes, i.e., it offers a positive criterion for the diagnosis of SIDS.

23.5.3 Conclusion

The tentative conclusions offered here apply to both the pathogenesis and postmortem diagnosis of SIDS. Studies are still lacking regarding the true significance of Alz-50 antibody in the differential diagnosis of SIDS. Thus after more than 20 years of continued research and discussion we can only repeat what Emery said in his short review of 1979:

- Not all of the brain changes observed in SIDS victims are specific to SIDS.
- Nor are they specific to hypoxia and/or hypoperfusion. They can also occur, for example, secondary to hypoglycemia or hyponatremia.
- A certain percentage of SIDS cases do exhibit identical changes, but not *all cases*.
- It is still not certain which changes are the cause and which are the effect.

Thus, neither the causes of the brain abnormalities observed in SIDS victims nor their underlying mechanisms are known, nor are their relationships to one another or to SIDS itself (cf. Oehmichen 1990; Kinney et al. 1992).

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Postnatal Mechanical Brain Injury (MBI) 24

24.1 Incidence

The majority of mechanical brain injury (MBI) victims are younger than 18 years (Gopinath and Narayan 1994). Mechanical trauma is the leading cause of death and disability in children, accounting for over 50% of all childhood fatalities. The majority of such cases involve MBI, which is the major factor affecting mortality and outcome (Luerssen et al. 1988; Aldrich et al. 1992). Various reports show that 5.5–25% of children under 2 years old are admitted to hospital because of head injury (Di Rocco and Velardi 1986). Of 8,363 children up to 3 years of age hospitalized over a 5-year period, 3% had suffered head injury (Canestri and Monzali 1970). Of all children hospitalized with MBI, 15–19% have suffered severe mechanical violence to the head (Tullous et al. 1992). The mortality rate among these children ranges from 33% to 50%; the survivors, however, often experience permanent disability of some type (Gopinath and Narayan 1994).

Most MBI in children older than 4 years is caused by motor vehicle accidents (Craft 1989; Herrmann 1991; Levin et al. 1992). The percentage of motor vehicle accident-related MBI increases with age, constituting 20% in children up to 4 years of age, and as much as 60% in adolescents. Younger children are most liable to suffer pedestrian- or bicycle-related injuries (Craft 1989; Sosin et al. 1996), whereas adolescents are usually injured in motor vehicle accidents as passengers (Levin et al. 1992).

The major causes of MBI among infants, toddlers, and young children are assaults/child abuse and falls, which together account for 50–75% (Herrmann 1991) of injuries. Child abuse involving MBI comprises about 4.4% of all cases of clinically treated MBI (Herrmann 1991; for details see Chap. 25). In older children, fewer than 20% of MBI are the result of falls and assaults/abuse, while sports- and recreation-related injuries are among the most common causes (Kraus et al. 1987; Luerssen et al. 1988; Levin et al. 1992).

Table 24.1. Children's Coma Score (*CCS*) and subscores. Source: Raimondi and Hirschauer 1986, modified

Score	Response
	Ocular response: maximum score = 4
4	Pursuit
3	Extraocular muscles (EOM) intact, reactive pupils
2	Fixed pupils or EOM impaired
1	Fixed pupils and EOM paralyzed
	Verbal response: maximum score = 3
3	Cries
2	Spontaneous respirations
1	Apneic
	Motor response: maximum score = 4
4	Flexion and extension
3	Withdraws from painful stimuli
2	Hypertonic
1	Flaccid
Total maximum score = 11 **Total minimum score = 3**	

24.2 Clinical Features

In total, severe brain injury occurs less frequently in children than in adults (Luerssen et al. 1988; Dias 2004). Mortality is lower for children than for adults. The frequency with which children deteriorate rapidly after an initial lucid interval (the so-called talk and die syndrome) is also lower than in adults (3% versus 10% – see Snoek et al. 1984). Surgical mass lesions such as subdural and epidural hemorrhages occur less frequently in children than in adults and, when present, are associated with a lower mortality (Luerssen et al. 1988).

Infants under 1 year of age are less likely to fully recover from blunt head injury than older children: a poor outcome is seen in 13.4% of children under 1 year old versus 4.9% of children between 1 and 3 years old (Jennett 1972; Raimondi and Hirschauer 1984). Infants and toddlers with moderate brain injury often experience rapid recovery, apparently without residual signs of sensory, cognitive, motor, or behavioral impairment. But about 20% of brain-injured children subsequently exhibit hyperkinesis, difficulty in anger control, lowered attention span and headache, the so-called posttraumatic syndrome (Dillon and Leopold 1961). Unremarkable neurological or IQ findings in such children, therefore, provide no guarantee that permanent and significant brain damage has not occurred.

As in adults, assessment of the severity of MBI in children is based on a Coma Score developed especially for this age group [Children's Coma Score (CCS), Raimondi and Hirschauer 1984, 1986]. This instrument is based in large part on a Children's Outcome Scale (COS) with five categories:

I Excellent recovery
II Moderate, but non-disabling deficit
III Severe motor or cognitive deficit
IV Vegetative
V Dead

The CCS is shown in Table 24.1. The maximum total score on the CCS is 11, the minimum 3. Of importance for outcome in children are the symptoms of brain swelling (open sutures and fontanels), ocular deviation, hemiparesis, unilateral/bilateral retinal hemorrhages, seizures, etc. It must be pointed out, however, that the use of a coma score to grade comas in children is controversial and the subject of continued debate (Levin et al. 1992; Lieh-Lai et al. 1992; Gotschall et al. 1995). Another "practical outcome scale" was recently proposed (see Crouchman et al. 2001) and remains to be proven in practice.

A special type of head injury in children is characterized by the term "*head-injured child who talks and dies*" (Adams 1976; Marshall et al. 1983). The definition may be made by the negative development of the CCS, which in these cases starts at a value of 8 or better, and all of the children are "talking" *after* the traumatic event, but they then deteriorate, and eventually perish from their brain injury (Humphreys et al. 1990). Children involved in traffic accidents (Fig. 24.1) or falls, who show neurological deterioration after a lucid interval, have an expanding intracranial hematoma in only 35% of cases (Humphreys et al. 1983; Bruce 1984). Thus, a number of other causes of deterioration are cited. These include acute cerebral edema, early convulsions (Humphreys 1983), a migrainous event, functional disturbances of the rostral brain stem, bacterial meningitis, or a concomitant viral meningoencephalitis (Bruce 1984; Snoek et al. 1984).

24.3 Biomechanical Aspects and Causal Events

The prevalence of head injuries over trunk and limb injuries in infants is attributed to the disproportionately large size of the infant's head compared to the

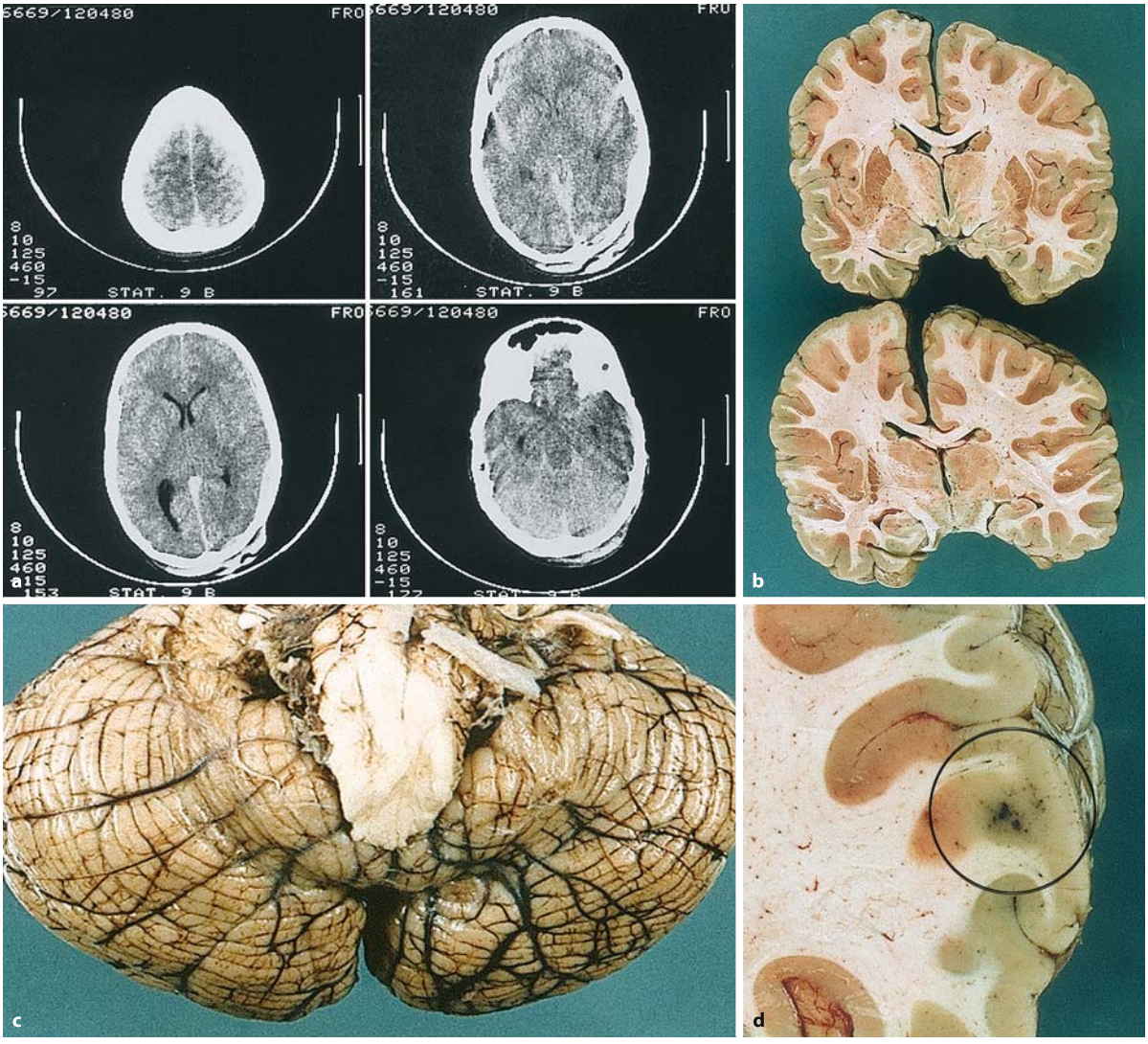

Fig. 24.1a–d. Head-injured child who "talks and dies." A 10-year-old boy, who was injured by a car, was transported to a hospital. Three hours later symptoms of increasing intracranial pressure lead to a hospitalization, where the boy died within 48 h. Morphologically an extensive brain edema was seen (**a–c**); only extremely discrete cortical hemorrhages could be observed (**d** – *circle*)

rest of the body (Smith et al. 1975; Chamberlain and Simpson 1979). It is widely accepted that the brains of younger children are more vulnerable to mechanical violence than the brains of older children or adults, especially to deceleration–impact caused by falls, or acceleration–burst resulting from blows to the head. For example, we note that approximately 50% of children whose fontanels are not closed suffer skull fractures from either acceleration or deceleration, whereas only 29% of children with closed fontanels and sutures suffer fractures (Bruce et al. 1978). Good outcomes are separated from poor outcomes in the morbidity and mortality of childhood head injuries at about the age of 1 year, when fontanel closure is complete (Raimondi and Hirschauer 1984). The reactions induced by impact injuries of the head and brain during the first year of life are shown in Table 24.2.

Moreover, the impact response of the infant head also depends on the age-dependent mechanical properties of the skull and sutures. Human tissue samples containing bone and sutures were mechanically tested for their response to bending and tension by Thibault et al. (1999). The constitutive behavior was implemented in three-dimensional finite element models of the pediatric head to examine the sensitivity of skull and brain strains to variations in the impact direction. The head impact simulations demonstrated the directional dependence of skull fracture and MBI risk.

Death from *mechanical violence inflicted to the head* usually results from diffuse axonal injury (DAI)

Table 24.2. Characteristic differences in the types of reactions induced by mechanical brain injury in infants (<1 year) versus those in adults. Source: Kirschner and Wilson 2001

1. In infants younger than 1 year there may be a significant mechanical violence to the head *without visible evidence of impact* to the scalp. But in any case there will be a subgaleal hematoma seen at autopsy
2. The thin pliable skull prevents a cavitation mechanism of the contralateral cortex, which is seen in the more rigid skull of the older children and adults. *Thus cortical hemorrhages at the contralateral site are extremely rare.*
3. The subdural space is narrower and less tolerant of space-occupying lesions
4. The unmyelinated infant brain with its higher water content more rapidly produces life-threatening *cerebral edema*

with associated contusional tears or lacerations of the cortex, and global hypoxemia/ischemia, which is sometimes secondary to apnea induced by brain injury. The common result of these injuries is cerebral edema. In infants, contusional injuries in the sense of cortical hemorrhages usually extend along lines of force through the brain rather than being confined to the point of impact on the cortical surface. Such injuries may manifest as small, hemorrhagic tears at the junction of the gray matter and white matter, less often as areas of hemorrhages deeper within the white matter (Lindenberg and Freytag 1969).

In children under two years of age, the three major causes of brain injuries are falls from heights, physical abuse, and traffic accidents. It is noteworthy that injury resulting from each of these causes, with the exception of falls from cots or baby carriages, becomes more common once the child begins sitting up and, especially, when it begins to walk. The poor balance and muscle coordination typical of this age group are the principal causes of MBI. But in most instances, infants fall from furniture without incurring discernible injuries (Levin 1972; Helfer et al. 1977; for further references – see pp. 507 ff).

Among the major causes of head injury in children, *falls* are grouped in two main categories:

- Falls from a height of about 90 cm or less, i.e., from cots, cribs, baby carriages, high chairs, etc. Falls of this type usually induce only slight if any injury.
- Falls from furniture or down steps; this type of fall is often related to independent ambulation with inadequate supervision.

Among the injuries suffered by 47 infants using *walkers*, head injuries and skull fractures comprised 10.6% (Kavanagh and Banco 1982). The accidents were usually caused by the walker toppling over or being pushed over by a sibling or falling down stairs.

Vertical falls from a height are a major cause of death in children in urban areas, usually involving children under 5 years of age (Spiegel and Lindaman 1977), the peak incidence occurring near 2 years. The most common pathology appears to involve head injuries without fractures, sometimes associated with intracranial hematomas (Smith et al. 1975).

Almost a quarter of all children involved in *road accidents* suffer mild to severe head injuries with or without skull fractures (Illingworth 1979). The high death rate of *car occupants* in the first year of life (Baker 1979) is attributed to two factors:

1. The characteristics of the skull and brain in the early months of life predispose them to mechanically induced cerebral tears (Lindenberg and Freytag 1969).
2. The tendency of infants to occupy the front seat and/or be carried in someone‘s arms (Baker 1979).

The principal cause of non-accidental head injury in children under 2 years old is *child abuse*. Infants at this age are more likely to suffer from whiplash shaking than older children. If there is no actual head impact, whiplash and rotational displacements account for findings such as those demonstrated experimentally by Ommaya et al. (1968) (for further information see Chap. 25).

24.4 Skull Fracture

In children, mechanical loading to the skull can cause disruption of the bones and localized disjunction or disruption of the sutures. Skull lesions are a relatively common sequela to violence to the head in infants.

Fracture of the skull may constitute the only proof of head traumatic loading since bony lesions often beget no clinical symptoms (Roshkow et al. 1990), especially in younger children. In any case children with mechanical loading to the head who do not suf-

fer skull fracture should be hospitalized. In about 10% of these infants, the mechanical head loading leads to complications, i.e., delayed intracranial hemorrhages or brain damage (Choux 1986). Serious sequelae are observed in 8% of children following incidence of MBI regardless of whether they have incurred a simple fracture (except for depressed fractures) or no fracture (Harwood-Nash et al. 1971).

Though it was commonly supposed that infants up to 8 months are more likely to suffer skull fracture than older children, Choux (1986) pointed out that in a number of series reported by various authors, older infants had a similar percentage of skull lesions, namely about 40%.

Diagnosis of skull fractures is based on X-ray imaging of the skull or CT scans. In infants, a fracture may be confused with sutures, intrasutural bones, accessory sutures or synchrondosis. False fractures are sometimes seen in the occipital region at the level of the parietotemporal suture.

There are five basic types of skull lesion:

- Linear fracture
- Depressed fracture
- Open fracture
- Growing fracture
- Disjunction/disruption of sutures

The most common type of skull lesion is *linear fracture*, observed in 70–80% of all cases (Harwood-Nash et al. 1971; Di Rocco et al. 1980; Choux 1986). In more than 80% of cases, such fractures are due to a fall; in 5%, a traffic accident. Choux (1986) differentiates four types of linear skull fracture:

Type 1: fracture line from one suture to another
Type 2: right angle fracture extending from the coronal suture to the sagittal suture
Type 3: small fractures extending only a few centimeters from a suture to a bone of the vault
Type 4: diastatic suture separation

The following biomechanical inferences are possible:

- In infants, linear fractures stop at the level of a suture (types 1 and 2)
- If the impact is moderate, a linear fracture beginning at the center of the parietal bone will extend to one suture only (type 3)
- Most linear fractures are transverse except at the level of the occipital bone; sagittal (longitudinal) fractures usually induce more severe clinical manifestations
- The occipital bone is involved comparatively often in children because of the relative bulging of the occiput, scant musculature, and the frequency of backward falls in infancy
- Linear fractures are bilateral in a small percentage of cases (13%); multiple fractures are not rare, especially in battered children

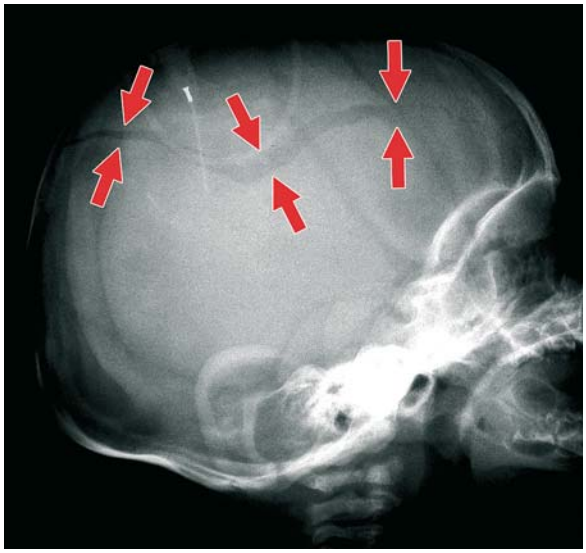

Fig. 24.2. Bursting fracture in a surviving child, 5 years old

Linear fracture is usually recognizable as a thin linear defect, with the same spacing along the entire course of the trajectory (Fig. 24.2). Healing is rapid, typically taking only 1–2 months. In some instances, the fracture may grow considerably in the first days after the incidence; if skull X-ray is repeated 2 or 3 weeks later, it is possible to recognize the evolution of a growing fracture.

Parietal linear fractures (Hobbs 1984; Brown and Minns 1993) and extradural hemorrhages (Livingston et al. 1991; Nee et al. 1993) can be caused by short falls, which do not induce initial unconsciousness. A fall of just 1 m is sometimes sufficient to cause skull fracture in adults and children, even if it is onto a padded surface (Weber 1985). Bursting fractures may be caused by vehicular accidents (Fig. 24.3a).

Growing fracture may result from progressive enlargement of linear fractures (see above) and leave a permanent skull defect (spurious meningocele) (for details see p. 478).

A *dural tear* and the presence of *pulsating cerebrospinal fluid* (CSF) at the level of the fracture are the principal pathological characteristics (Rosenthal et al. 1970). The secondary enlargement is explained by the accumulation of pulsating CSF at the level of the fracture, but it is not known why this enlargement ceases after only a few months. The clinical picture is marked by local symptoms (soft and pulsating palpable skull defect) and neurological deficits, especially seizures.

Depressed fracture (Fig. 24.4) comprises only 25% of all skull fractures (Choux 1986). This form of skull lesion is much less common in young infants (<6 months old) than in older children. A depressed fracture is likely to have been caused by high force

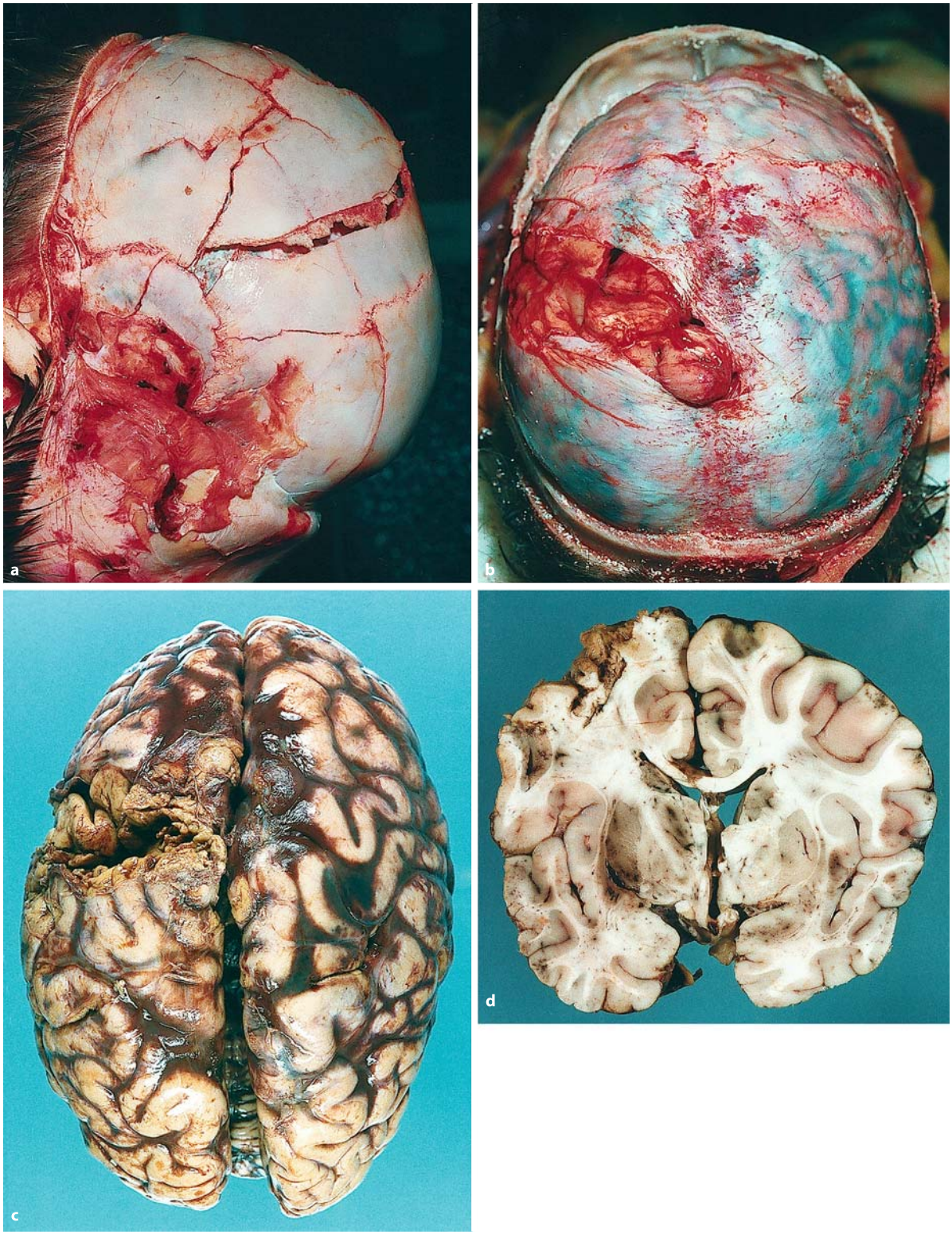

Fig. 24.3a–d. Bursting fracture caused by vehicular accident. **a** Calvarian fracture lines; **b** tears of the dura; **c** laceration of the brain tissue; **d** multiple hemorrhages within the brain parenchyma as well as cortical hemorrhages

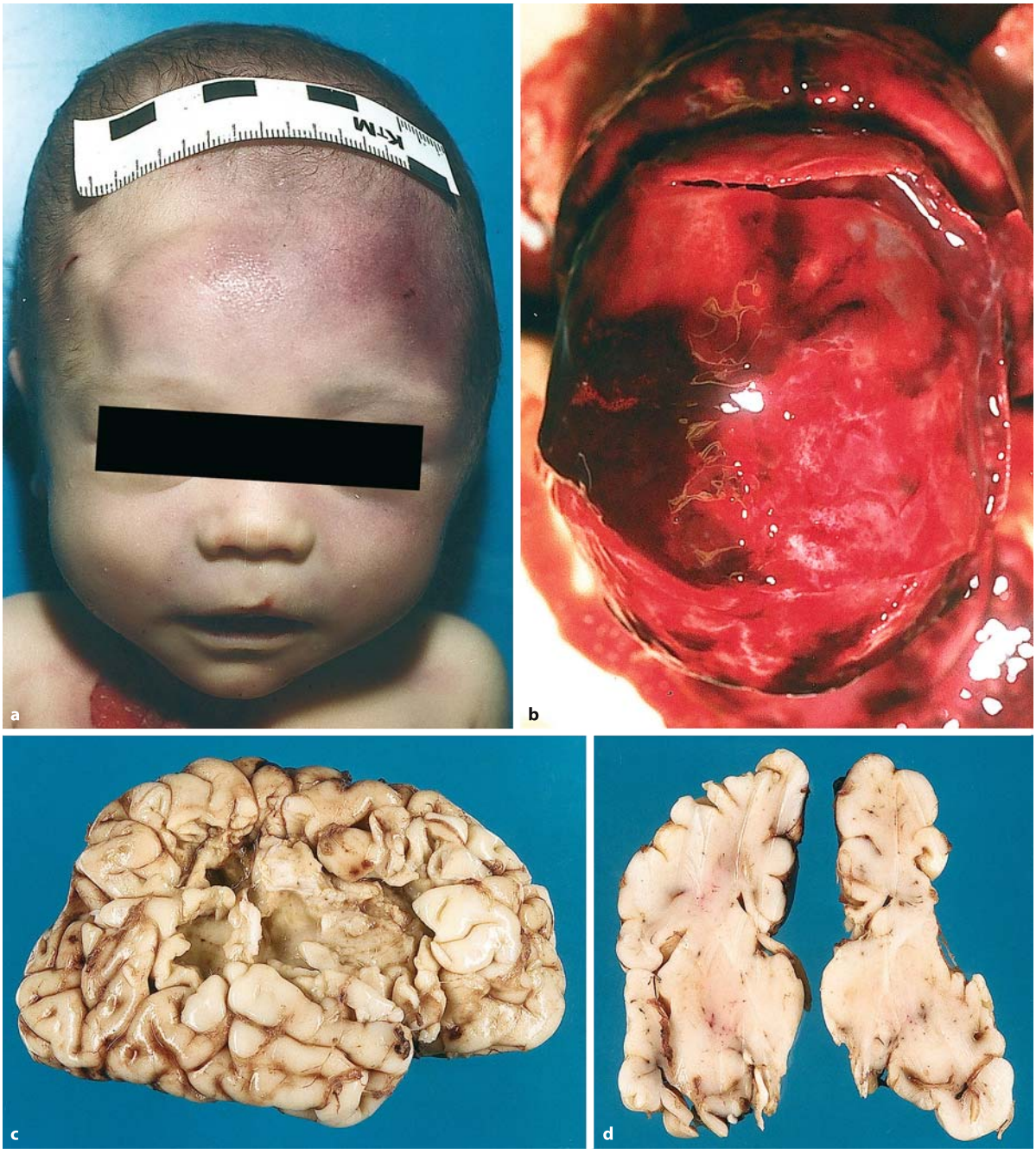

Fig. 24.4a–d. Depressed fracture after multiple blows against the head in a case of physical abuse. **a** Deformed head with multiple subgaleal hematomas; **b** depressed fracture in the frontal skull; **c** damage of the lateral right cortical tissue of the frontal and parietal lobes associated with the depressed fracture which is associated with mechanically induced destruction of the brain parenchyma (**d**) in frontal sections of the brain

impact, including physical abuse, if it is depressed, wider than 3 mm, multiple, stellate, and crosses a suture line or is located at the base of the skull (Hobbs 1984; Brown and Minns 1993). Depressed fractures may be caused by falls (40%), followed by traffic accidents (22%), birth (16%), and "other" causes (22%). The frequency of such fractures in conjunction with birth is particularly striking, generally caused by application of forceps or the pressure of the obstetrician's hand. Depression also occurs in deliveries that are easy and non-traumatic.

In general, depressed fractures in infants may be free of symptoms: there may be no neurological deficits, no loss of consciousness, no seizures. Subgaleal

hematomas are common at the level of the depressed fracture. The following types of depressed fractures have been distinguished (Melvin and Evans 1971; Choux 1986; Ersahin et al. 1996):

1. *True depressed fracture*: the depressed bone remains connected to the cranial vault.
2. *Ping-pong "fracture"* (most common in neonates): localized depression of the vault without breakage of the cranial bone (resembles a "green stick fracture").
3. *Perforating depressed fracture* (Fig. 24.4): local impact causes a perforating hole fracture with a depressed bone fragment that is disconnected from the vault.
4. *Open fractures* can result from penetration of the skull by a sharp instrument, or in association with linear or depressed fractures, complicated by scalp laceration and/or dural tear. In cases involving open fractures with underlying dural and brain damage, the fracture is usually extensive and conspicuous.

In a study of 530 cases of depressed skull fracture, Ersahin et al. (1996) found the prognosis to be generally good. The outcome, however, depended in large part on whether the fracture was associated with intracranial lesions. Moreover, the deeper the bone was depressed, the greater the risk of both dural tear and cortical laceration, and the worse the prognosis (see also Levi et al. 1991).

24.4.1 Growing Fracture

A peculiarity of *childhood* – less common in open, more common in closed brain injuries – are so-called growing fractures of cortical bones caused by a mechanically induced increase in intracranial pressure. Fractures of the skull convexity with laceration of the dura can lead to *cephalohydrocele* secondary to drainage of CSF into the galea.

Growing fractures are characterized by the following four features (Lende and Erickson 1961):

- Occurrence in infancy or early childhood
- Fracture accompanied by dural tearing
- Brain injury beneath the fracture
- Continued growth of the fracture to form a cranial defect

Pathophysiologically the growing fracture is explained by a mechanically induced brain edema that pushes and holds apart the fragments of the still soft cortical bone. At the site of injury, the dura retracts from the bone. As a consequence, the bone is vascularized only by the fascia and muscles, but not from the side of the dura, resulting in inadequate synthesis of osteoblasts (Jennett et al. 1981). The pliability of the child's skull due to its incomplete ossification plays a decisive role. The development of a *failure of CSF absorption* after subarachnoid hemorrhage (SAH) favors the formation of a growing fracture by drainage of CSF through the fracture line and forcing the injured tissue – already disaggregated by the edema – into the fracture. Fifty percent of such cases are diagnosed within the first year of life, 90% until the end of the third year (Lende and Erickson 1961; Döpper et al. 1972). The lesion may resorb the calvarial bone to the extent that a lytic skull lesion is simulated (Numerow et al. 1991).

Microscopically the scarred areas within the galea and between the fractured bones contain typical central nervous system tissue. The tissue generally exhibits gliosis and is closely connected with collagenous connective tissue fibers. Ependyma-coated lacerations corresponding to mechanically induced porencephalic cysts are also found occasionally.

24.5 Dural Hemorrhages

24.5.1 Epidural Hemorrhage (EDH)

In infants, EDHs are rare due to the tight adherence of the dura to the skull, especially at the sutures (in particular the coronal sutures) and because of the elasticity of the infant skull. They are generally produced by contact forces commonly associated with accidental falls. EDH is also rare in older children (for review see Choux et al. 1986).

EDH is extremely uncommon in newborns. In contrast to subdural hemorrhage (SDH), EDH rarely results from physical abuse (Shugerman et al. 1996). It is mainly associated with a parietal linear fracture, but may also be caused by injury of the meningeal arteries or venous sinuses during a complicated breech presentation or forceps delivery; a fracture is not always present (Takagi et al. 1978; Gama and Fenichel 1985). Lebkowitz (1936) suspected that the EDH may be caused by a marked degree of overlapping of the parietal bone and squamous portion of the temporal bone, while Campbell and Cohen (1951) supposed a detachment of the dura from the inner table. These suppositions accord with those of Takagi et al. (1978), who, on the basis of the fibrovascular connections between the bone and the dura mater, proposed that a bleeding point could be present in the bone (see also Choux et al. 1986). Compared to adults, children rarely suffer mechanically induced rupture of the meningeal artery.

The *localization* of EDH in infants under 2 years old is comparable with that in older children. The

volume of EDH in infants is sometimes sufficient to induce anemia. The excessive volume may be explained by the elasticity of the skull and disjunction of the suture.

The *clinical picture* is determined by loss of consciousness, usually after a lucid interval. Neurological deficits (hemiplegia, hemiparesis), pyramidal signs, and seizures are also observed. Early computed tomography scanning enables correct diagnosis and is associated with an excellent prognosis (Stein et al. 1991; Paterniti et al. 1994).

24.5.2 Subdural Hemorrhage (SDH)

SDH almost always results from mechanical violence. Especially in infants under 2 years old SDH is generally of mechanical origin. This is true if simultaneous subcutaneous hematoma or skull fracture is present in an otherwise normal child. SDH in this age group may result from unobserved falls or repeated shaking (for text and figures – see below), the latter being especially likely if there are no signs of head impact or skull fracture. SDH occurs mostly in infants under 6 months of age, in whom the incidence is particularly high: 59.2% from head injuries in children present in hospital reported by Hendrick et al. (1964) and 46% by Choux et al. (1986). This contrasts with the incidence of SDH in children of all ages, which ranges from 4.3% (Choux et al. 1986) to 12% (Ingraham and Matson 1954; cf. also Hendrick et al. 1964) in a large series of pediatric head injuries. SDH is also seen in newborns, especially in premature infants (18% in full-term infants, 11% in preterm infants, Larroche 1977). SDH in neonates has many possible causes, breech delivery being the most significant.

Acute SDH (hemorrhage during the first 2 days after a traumatic event) is to be distinguished from subacute SDH (hemorrhage occurring between the third day and 3 weeks) and chronic SDH (hemorrhage lasting longer than 3 weeks; see Choux et al. 1986; see also pp. 130 ff).

The *pathophysiology* of SDH depends on the type of vessel that ruptures. If the bleeding is arterial, SDH is commonly associated with cerebral contusional injuries. However, SDHs are usually associated with venous lesions. Under these circumstances the following three mechanisms underlie SDH:

- Tearing of bridging veins
- Laceration of the dura
- Lesion of the sinus secondary to skull fractures or suture diastasis

The most frequent cause of SDH is tearing of the bridging veins at the level of the sagittal sinus, which accounts for the high incidence of interhemispheric or parasagittal SDHs.

SDH is characterized *clinically* partly by a lucid interval lasting from 16 to 72 h, convulsions, respiratory distress, bulging of the fontanels, anemia, and retinal hemorrhages (Gutierriez and Raimondi 1975).

Treatment of EDH and SDH can include:

1. External drainage
2. Trephination to evacuate the clot
3. Osteoplastic bone flap for removal of a solid clot

24.5.3 Chronic Subdural Hemorrhage (SDH)

The pathology of chronic SDH in infants and children closely resembles that in adults (see pp. 132 ff). A hallmark of SDH in infants may be the phenomenon *neomembrane*, which in the absence of an acute hemorrhage often comprises the only lesion. Neomembranes form a thin layer of richly vascularized tissue of dull appearance that adheres to the inner surface of the dura mater and contains small tortuous blood vessels forming spiders or irregular patches. Neomembranes frequently exhibit multicentric fresh hemorrhages plus evidence of old hemorrhages in the form of rust-colored pigmentation. They can also completely envelop the site of *chronic SDH*, one membrane in contact with the dura, the other with the arachnoid. Histologically, neomembranes are characterized by loose connective tissue with a mesh of actively proliferating fibroblasts, neutrophils, eosinophils and macrophages, few collagen fibers, and numerous distended, thin-walled sinusoid capillary vessels. The multicentric recent and old hemorrhages are accompanied by clusters of hemosiderin-bearing macrophages.

Neomembranes should not be dated by their thickness or by the appearance of the hematoma. Evidence of repetitive bleeding is a common finding, and the hematoma is not necessarily the same age as the neomembrane. Estimation of the age is based on the density of collagen fibers (Friede 1971), which increases over a period of weeks and months. After years, old membranes become solid and replace the hematoma or form the rigid wall of a hygroma (see below). Ultimately, they transform into dense collagen tissue resembling dura mater.

24.5.4 Subdural Hygroma

Encapsulated subdural lesions filled with clear or xanthochromic fluid are called “hygroma” or “hydroma” (Fig. 24.5b) (see also p. 135). Hygroma is thought to be the residue of an incompletely orga-

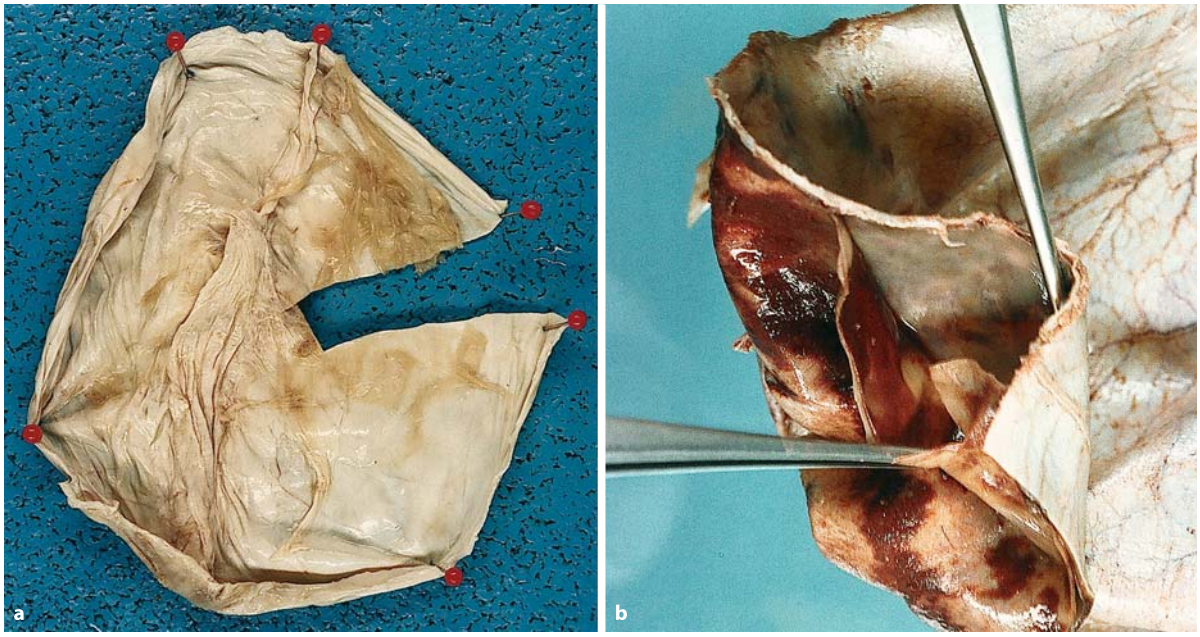

Fig. 24.5a, b. Subdural neomembrane and hygroma. **a** The neomembrane was observed in a child, who died as a SIDS victim; no iron was demonstrable. **b** The cause of this hygroma was not explained by the caregivers of this child

nized chronic SDH. The hematoma liquefies into a low viscosity fluid, which turns from a turbid dark brown to xanthochromic, finally becoming clear. A capsule of dense collagen tissue maintains the cavity. Hygromas generally occur under conditions conducive to hematomas; they have similar shapes and occupy the same sites. The corresponding neuroradiologic evolution involves transformation from hyperdensity to hypodensity, SDH being isodense with brain (and hence easily missed) on computed tomography around the fourth day.

24.6 Subarachnoid Hemorrhage (SAH)

Focal SAH is the common finding in both inflicted and accidental MBI. Rupture of saccular aneurysms however is extremely rare in infants and children and they usually bleed after impact (Prahlow et al. 1998). But SAH, however, is also a common birth trauma.

Mechanical loading causes extravasation of blood from small vessels of the arachnoid meshwork, from whence it may spread over the convolutions or collect in the sulci. Moreover, SAH is common at autopsy of premature infants and is regarded as a hypoxic lesion; if slight, it is of no clinical importance. In rare cases, however, the blood collected at the base of the brain and the posterior fossa can occlude the cisternae and the foramina of Magendie and Luschka. This leads to impaired CSF circulation, with consequent hydrocephalus (Larroche 1972). The histology is characterized by iron-laden macrophages within the thickened meninges.

Blood accumulation within the arachnoid meshwork throughout all or part of a lobe may lead to compression of the underlying brain with subsequent necrosis. The lesion then closely resembles an arterial infarct causing secondary hemorrhage. Subarachnoid hematomas also occur in infants who have been given exchange transfusions to treat hyperbilirubinemia with blood group incompatibility, septicemia or coagulation disorders (Larroche and De Vries 1997).

24.7 Cerebral Contusion and Laceration Injury

Cerebral contusional injuries appear to be very rare in newborns. The precise incidence is unknown due to past difficulty in establishing the diagnosis in vivo. They are seen as a focal region of necrosis and hemorrhage, usually involving the cerebral cortex and subcortical white matter (Pape and Wigglesworth 1979). The low incidence is attributed to the rarity of blunt mechanical violence in the perinatal period and the relative resiliency of the neonatal cranium (no ossification of suture lines, thin cranial bones with incomplete calcification, rendering the skull more plastic) and cerebral mantle. These properties make acceleration loading to the brain – which pro-

duces cerebral contusional injuries in older children and adults – less likely in newborns.

24.7.1 Neuropathology

The cerebral cortex and subcortical white matter in particular exhibit focal necrosis and hemorrhage in homolateral and contralateral sites as well as in inferior orbital, frontal, and temporal positions. Contusional injuries involve the gyral crests, but can extend as a wedged-shaped lesion into the white matter. The contusional hemorrhages will be reabsorbed with resultant amber-colored areas of gliosis. Contusional injuries associated with skull fractures are more severe and relatively uncommon. In infants under 3 years, cortical hemorrhages are rare in the contralateral region, even in fatal cases. Only 2 of 11 possible cases were found to have such lesions (Courville 1965).

In newborns and young infants, slit-like tears in the hemispheric white matter are more common. These tears may extend to the cerebral cortex or even to the walls of the lateral ventricle. A few cases also exhibit isolated intraventricular hemorrhages (Kobayashi et al. 1985) or basal ganglia hemorrhages (Kang et al. 1989).

Children suffering such injuries almost always exhibit varying degrees of soft tissue injury of the face and scalp. Moreover, depending on the direction of the compressive forces (González-Tortosa and Poza 1996), they exhibit multiple and often extensive comminuted calvarial and basilar cranial fractures together with subarachnoid and parenchymal hemorrhages.

24.7.2 Biomechanics

In the newborn, focal areas of cortical necrosis and hemorrhage are produced by direct compression. White matter tears result from shearing forces within the subcortical cerebral substance created by extreme and rapid deformation of the brain (Lindenberg and Freytag 1969), which is possible due to the pliability of the newborn skull. An additional factor predisposing to tears may be the comparative paucity of myelin in the developing white matter.

Biomechanically, these types of pathologic alterations are produced by dynamic loading conditions. In contrast, *crushing head injuries* are the result of static mechanical loading over a large area of the head by forces applied for longer than 200 ms, which causes relatively slow deformation of the cranium (Gennarelli 1993; Duhaime et al. 1995).

24.7.3 Clinical Features

Prominent among the characteristic symptoms resulting from cerebral contusional injuries are seizures, focal motor deficits, especially hemiparesis or monoparesis, and deviation of eyes to the side of the lesion. If the child survives, cognitive recovery is generally good, although some children have relatively mild fixed focal deficits (Duhaime et al. 1995; Prasad et al. 1999).

24.8 Mechanical Vessel Injury

Isolated mechanical injury of the large vessels supplying the brain with blood (*carotid arteries* and *vertebral arteries*) are rare. The literature up to 1993 (Garg et al. 1993) includes only 16 cases in which the injury led to stroke. A mechanical lesion of the vertebral artery at the C1–2 level was the most common cause of stroke. Manipulations of the cervical spine by chiropractors may also induce mechanical injury resulting in vertebrobasilar occlusion (Zimmerman et al. 1978). Moreover, it is important to know that obviously mechanically induced intracranial *aneurysms* (for review see Ventureyra and Higgins 1994) comprise about one-third of all intracranial aneurysms. In rare instances, they result from birth-caused MBI (Piatt and Clunie 1992). *Thrombosis* may be a result of MBI during the postnatal period as well. Whereas intracranial bleeding-induced occlusion of small vessels is relatively common, thrombosis of the superior sagittal or transverse sinus is rare (Kapp 1985), and of the sigmoid sinus almost unknown (Taha et al. 1993).

24.9 Secondary Alterations

24.9.1 Edema and Hypoxia

As mentioned above, injuries of the immature brains of children can lead via hyperemia to a breakdown of the blood–brain barrier, inducing *vasogenic edema*. An accompanying ischemic–hypoxic process can lead to *cytotoxic edema* due to the intracellular flux of water and electrolytes (see above, p. 47).

The secondary brain injury is aggravated by additional biochemical factors. *Excitatory amino acids* (glutamate and aspartate) can themselves cause or

augment secondary brain injury (Katayama et al. 1990). A positive correlation between extracellular levels of these neurotoxic substances and the severity of brain damage has been shown (Choi et al. 1994). Glutamate was found to be significantly elevated in the CSF immediately after the incidence of trauma and persisted at elevated levels for 168 h (Baker et al. 1993; see also Palmer et al. 1993).

In animal experiments, up to 70% of rats subjected to impact plus hypoxia had motor weakness contralateral to the impact side 24 h after impact, while only 29% of rats subjected to impact alone had demonstrable weakness (Ishige et al. 1987). This phenomenon may explain the extreme effect of hypoxia on MBI by the development of a cytotoxic edema. Regional and global ischemia and associated hypoxic–ischemic episodes (Robertson et al. 1992) result in an energy failure that leads to depolarization, spreading depression, calcium and lactate accumulation, and acidosis (Stein and Vannucci 1988). The morphological sequelae can include hippocampal injury, often limited to focal neuronal necrosis in the CA1 subfield (Kotapka et al. 1993). In other cases, ischemic lesions may arise in the basal ganglia, even after incidence of minor MBI (Dharker et al. 1993).

Regarding the development of edema after impact a special feature must be described: clinically it is not uncommon for the head-injured child to "*talk and die*" (for review see Humphreys et al. 1990), i.e., there is an interval after the traumatic event during which the child is able to verbalize. This is followed approximately 30–50 h after the event by a rapid neurological decline and the child dies. The initial Glasgow Coma Scale rating was nine or better and the children demonstrated irritability and restlessness just prior to their deterioration. At autopsy, the brain usually revealed multiple cortical hemorrhages, brain edema with herniation and ischemic encephalopathy. In such cases, the question of medical malpractice must be addressed, whether the death was avoidable. If the intracranial bleeding was only slight but the brain swelling excessive, the cause of the delayed symptoms and death must be sought, the possibilities including acute delayed edema or acute congestion (cf. also p. 42).

24.9.2 Inflammation

MBI can also trigger a *local (sterile) inflammatory response* in the brain. Cytokine levels, especially interleukin (IL) levels (IL-1, IL-6, and IL-10), in the CSF are elevated (Bell et al. 1997); there is complement activation (Kaczorowski et al. 1995), leukocyte infiltration (Clark et al. 1994), and activation of microglia (DeKosky et al. 1996). Among the systemic effects of MBI in both adults and children is the suppression of cell-mediated immunity that may account for the high incidence of secondary infection during the subacute phase of recovery. Combined with the cerebrovascular response and edema, the biochemical "cascade" induces in addition diffuse cerebral swelling and uncontrolled intracranial hypertension (Adelson and Kochanek 1998).

24.10 Late Sequelae

The morphological and functional sequelae of MBI, i.e., cerebral contusional injuries and lacerations as well as mechanical vascular diseases, are of paramount importance for the surviving child. In rare instances death can occur in causal association with it, months or even years after the incidence of primary injury. The sequelae remain basically the same whether the injury is incurred prenatally, perinatally or postnatally.

Only two of the possible sequelae will be discussed here: hydrocephalus and seizures. The overall incidence is low. Both phenomena can be the result of congenital malformation, but may also arise from prenatal or postnatal injury. Hydrocephalus which requires shunting is usually not caused by postnatal head injury. Death from hydrocephalus can be caused by a shunt complication, infection or – in connection with other cerebral injury – by aspiration, pneumonia or vegetative circulatory failure, the cause of which usually cannot be determined with certainty. Convulsive disorders are relatively often associated with sudden, unexpected death (cf. Sect. 24.10.2) of indeterminate cause.

24.10.1 Hydrocephalus

General information on hydrocephalus is provided elsewhere. In this section, the phenomenon of hydrocephalus in infants and children is described, which may be acquired, for example by mechanically caused brain injury, and/or which may be congenital (see pp. 54 ff).

Based primarily on CT-MRI demonstration, the following *types of hydrocephalus* have been distinguished (Shaw and Alvord 1995):

- Hydrocephalus as one of the major distinct types of developmental anomaly (Dandy–Walker malformation, Chiari malformation, etc.).
- Hydrocephalus as a phenomenon commonly associated with but not constituting a major symptom of developmental anomaly (holoprosencephaly, schizencephaly, porencephaly).

- Other types of hydrocephalus:
  - Caused by obvious obstruction
  - Caused by overproduction of CSF
  - Of unknown cause

In childhood, *hydrocephalus* (Friede 1989) features a rapid rate of cranial enlargement because of the open fontanels and the suture diastasis. Additionally, hair is sparse on the distended skull and subcutaneous veins are congested. Pressure on the orbital roof displaces the eyeballs downward and outward. Among the neurologic signs are spasticity of the lower and, to a lesser extent, upper limbs, tremor, ataxia, imbalance, and clumsiness of fine finger movements. Intellectual impairment correlates closely with the severity of physical disability (Laurence 1969). The cerebral hemispheres are distended and fluctuate, and they collapse when the CSF is drained. The cranial bones are thin and eroded. The ventricles are enlarged and the ventricular surfaces often possess transverse, rib-like arches that run perpendicular to the sagittal sinus. The distended hydrocephalic hemispheres may have abnormally thin walls, which may dwindle a few millimeters in thickness. If CSF pressure is relieved by shunting, a hemispheric thickness of 2 cm allows normal intellectual development in some cases (Scarff 1952).

If *hydrocephalus* is *not treated*, tissue damage and hemispheric atrophy are the inevitable results of the chronic distension of the cerebral hemispheres. A number of mechanisms may underlie the atrophic changes seen in the white matter:

1. Stretching and tearing of nerve fibers
2. Increased diffusion of CSF into the periventricular white matter
3. Shearing forces created by the rounding, stretching, and flattening of the ventricular corners

Children who are *born prematurely* may not exhibit any clinical symptom of hydrocephalus except for ventricular enlargement (Luerssen et al. 1986). It takes much less force to compress the cortical mantle in preterm infants than to overcome restrictions of the dura or the skull.

Children with *acquired hydrocephalus* are characterized as described above. It is imperative therefore that physicians attending young children with head injury make frequent measurements of head circumference. In older infants, whose fontanels have closed, the only early clinical symptom of mechanically induced hydrocephalus may be a leveling off or reversal of an otherwise gratifying neurologic recovery. Diagnosis of hydrocephalus will be confirmed by CT.

Hydrocephalus that *occurs shortly after incidence of MBI* is due to blockage of ventricular outflow pathways by intraventricular or extraventricular hematomas or mass effects. In newborns, all types of perinatal injuries may be associated with hydrocephalus as well as with subarachnoid, subdural, intracerebellar, and periventricular–intraventricular hemorrhages. Any type of lesion inducing acute ventricular enlargement can also lead to *delayed hydrocephalus* by preventing the absorption of CSF. In a group of infants with intracranial hemorrhages resulting from birth injury, the vast majority exhibited symptoms of hydrocephalus within the first 6 months of life (Lorber and Bhat 1974). All of these infants with post-hemorrhagic hydrocephalus exhibited abnormal cranial enlargement, some suffered seizures, etc. Outcome depended in large part on the extent of the primary injury. Older children usually experienced delayed onset of drowsiness, behavioral changes, hypertonic extremities, or visual disturbances. Delayed hydrocephalus can also develop in adults and children as one of the sequelae of mechanically induced cortical atrophy (Levin et al. 1981) associated with enlargement of the ventricular system. Both cerebral infarctions and intracerebral hematomas are often accompanied by general or localized enlargement of the ventricles.

24.10.2 Seizures

The *incidence* of postnatal seizures is reported to range from 1.5 to 12.2 per 1,000 live births (Keen and Lee 1973). Seizures are more likely to have resulted from obstetrically induced MBI if accompanied by intracerebral hemorrhages (in 20–40% – Chiofalo et al. 1980). The rate of seizures is higher in infants born prematurely, especially if they suffer intraventricular and/or subependymal hemorrhage (Chiofalo et al. 1986; seizures in children and adults – see also pp. 529 ff).

One of the purported *pathophysiological* causes of seizures in infants is impaired energy supply secondary to hypoglycemia, hypoxemia, or ischemia, which may induce failure of the sodium–potassium pump. Hypocalcemia is regarded as the major cause of neonatal seizures, as a result of intracranial birth injury.

Seizures in neonates differ considerably in their *clinical manifestations* from those in older children, due primarily to the neuroanatomic development characteristic of the perinatal organizing period (Volpe 1977). In premature infants, intraventricular hemorrhage is caused by an increase in venous and capillary pressure with secondary failure of the left heart, giving rise to acidosis, hypoxia, and rupture of terminal veins (Cole et al. 1974). Because *minor perinatal seizures* seldom induce impairment of consciousness and often mimic movements that are normal in the newborn, their diagnosis is sometimes missed (Volpe 1977). They may produce par-

oxysmal episodes of grimacing, pedaling, rowing, or swimming; oral-buccal-lingual movements such as sucking, drooling, or swallowing; paroxysmal movements of the eyes or eyelids; apnea, hyperpnea, dyspnea, pallor, or cyanosis. Because they sometimes go undiagnosed, perinatal seizures may evolve into status, with increased risk of mortality. Minor seizures occasionally occur in isolation, but they are more likely to be accompanied by major crises. *Major seizures* are generally of the motor type, especially focal seizures, and occur in order of decreasing frequency as follows: tonic, focal-clonic, multifocal clonic, myoclonic, tonic-clonic.

24.11 Spinal Cord Injury

Spinal injury in children is rare. As evaluated by Martin et al. (2004), during 1989–2000 of 19,538 pediatric trauma victims 527 (2.7%) suffered spinal column fracture/dislocation without cord injury and 109 with cord injury (0.56% of all children: 16.5% of spine-injured children). Thirty children (0.15% of all children; 4.5% of spine-injured children) sustained spinal cord injury without radiological abnormalities. The risk of cord injury was increased with reduced GCS, head injury (see Eleraky et al. 2000), and chest injury.

It was found that 9% of all spinal traumas observed in a special period of time in a hospital accounted for pediatric injuries (Osenbach and Menezes 1992). Early diagnosis of spinal cord injury can be difficult in such cases in which cord injuries are associated with brain injuries (Sneed and Stover 1988). Even in the absence of precise data (Burke 1976), it can be assumed that far fewer children are rendered paraplegic by mechanical violence than by congenital and non-mechanical causes, in particular spina bifida aperta (Meinecke 1972). The main postnatal cause of spinal cord injuries is motor vehicle accident (Burke 1974; Eleraky et al. 2000). Children younger than 9 years of age were more liable to suffer neurological injuries than older victims (Eleraky et al. 2000). The morphological sequelae are virtually identical to the changes described above for adults.

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Physical Abuse

25

25.1 Basic Principles

The present chapter will be restricted to physical abuse, i.e., mechanically caused brain damage as well as asphyxial and toxic brain injury, while the sequelae of neglect, especially by hunger (starvation and malnutrition – see pp. 606 ff) and thurst (dehydration – see pp. 608 ff) will be dealt with in chapter 30.

25.1.1 Sociopsychological/Forensic Considerations

Brain damage inflicted on a child by physical abuse as well as by physical and psychological neglect is an "avoidable injury" associated with high long-term morbidity or mortality (Duhaime et al. 1998; Mercon de Vargas 2000). Every instance of suspected physical abuse requires differential diagnostic clarification of whether the injury was accidental or the result of physical abuse. If it is determined that the injury was not accidental, it must be determined whether it resulted from intentional violence or (possibly unintentional) abuse. This will be the differential diagnostic consideration of the examination of injuries to dead (as well as of living) children by a doctor in the field of legal medicine and pathology or, of course, of a pediatrician.

Therefore, among the first aims of autopsy in suspicion of sudden death in infancy must be the exclusion of homicide (Byard and Krous 1999). Meadow (1999) describes 81 cases of infanticide, 42 of which had initially been attributed to SIDS. If prior instances of lethal violence have been misdiagnosed as SIDS, the victim's siblings are known to be at in-

Table 25.1. Obtaining a history in cases of suspected child abuse. Sources: Pearn 1989; Oehmichen and Meissner 1999

Unexplained delay in seeking treatment
Consultation of different pediatricians
Submitted history (presenting symptoms) is changed after initial presentation
Discrepancy in the stories given by each parent or caregiver separately
A history incompatible with (or very unlikely at) the age and development of the child
Ambivalence or hostility in the parent or caregiver
Injuries blamed upon a sibling or another child

creased risk of the same fate (Steinschneider 1972; Meadow 1990; Pinholster 1994; Firstman and Talan 1997; Oehmichen et al. 2000). In 1985 Emery (see Emery 1993) estimated the incidence of SIDS being filicide, or child homicide by either parent, as 2–10% (Emery 1985). In families with a recurrence of unexpected deaths, he (Wolkind et al. 1993) estimated the incidence at 55% (31/57 cases reported). This rate exceeds the balance of probabilities and would justify judicial care proceedings in all such cases. But none of the actual studies have investigated all babies as they were found dead, with the exception of Stanton (2003) who evaluated autopsies (n=72) in the Scarborough area since 1982. He concluded that the association of sudden unexpected death and maltreatment within families was at the lower end of previous estimates, 3–10%.

The presence of contusional injuries and hematomas as a result of bruises may be a simple symptom of abuse and has to be differentiated from non-abuse. Dunstan et al. (2002) developed a scoring system for discriminating bruising injuries by site, maximum dimensions, and shape. The presence of facial or generalized petechiae suggests asphyxiation (Green 1998; Oehmichen et al. 2000). Intra-alveolar hemorrhage may also be a finding in cases of suffocation; poisoning must be excluded by toxicological testing. If death has resulted from suffocation in soft bedding or a pillow, markers such as cutaneous petechiae or intra-alveolar hemorrhages – admittedly non-specific – will be lacking.

Children are constitutionally very vulnerable to violence and relatively few parents who shake, hit or slap a child do it with the intention of causing serious injury. If injuries do occur, it is usually because the carer has lost control of their temper under stress. Such loss of control however can prove fatal to the child; the outside observer is often shocked by the nature and extent of violence (and injuries) that out-of-control carers can inflict.

Injuries to children are always serious, even soft tissue injuries. It takes considerable force to cause bruising, which in turn inflicts pain and is almost always connected with a certain degree of emotional abuse in the form of harsh words, threats, and rejection. If violence is inflicted to the head, the consequent brain damage can have a wide range of long-term manifestations affecting the child's personality, learning, and functional skills (Levitt et al. 1994). Emotional abuse is hard to prove, although it is nearly always associated with considerable primary and secondary morphological changes (growth, development, stress ulcers, stress cardiomyopathy – Kirschner and Wilson 2001), and have diverse physiological and psychological sequelae (Gath 1989; post-traumatic stress disorder – Myers 1997).

Because the charge of child abuse can have devastating consequences for accused cares, false-positive diagnosis must always be excluded. Regardless of whether they lead to conviction or not, a charge of child abuse can make the accused a social outcast. The differential diagnostic considerations are therefore of utmost importance.

By the same token, a false-negative diagnosis can prove fatal to the child in question and/or to its siblings. The importance of an early diagnosis is evident because of the possibility of repeated abuse and because it is known that there is a higher incidence of poor outcome in groups suffering inflicted rather than accidental injury (Haviland and Russell 1997; Jayawant et al. 1998; Ewing-Cobbs et al. 1998).

It is therefore imperative that the clinician and neuropathologist seriously and carefully entertain the possibility of physical abuse. A number of diagnostic criteria have been put forth, which, while not definitive, do point to physical abuse (Table 25.1). Every child with a poorly explained injury of the body, head, or brain must be regarded as the possible victim of abuse. Moreover, epidemiologically evaluated criteria characterize the type of abused victim and give further evidence of the "abuse" or cause of injury (Table 25.2).

According to Stoodley (2002), in instances suspicious of physical abuse, skeletal surveys and radionuclide bone scans have been the mainstay of radiological investigations. Kemp (2002) suggests that a computed tomography (CT) scan of the head should be considered a routine part of the investigation of possible non-accidental injury in all infants under 6 months of age and in children aged 6 months to 2 years where there are other features such as retinal hemorrhages or unexplained neurological findings. The cranial CT scan should be followed by an MRI scan a few days later with a further MRI scan

Table 25.2. Differential diagnoses of some morphological changes encountered in the abused child. Source: Pearn 1989

Sign	Confounding diseases
Fractures	Osteogenesis imperfecta (Adams et al. 1974) Menkes' syndrome (Kirschner and Stein 1985) Atypcial skull suture line
Scars	Chickenpox lesions resembling cigarette burns
Bruising	Hemophilia (Schwer et al. 1982) Hypersensitivity vasculitis (Waskerwitz et al. 1981) Bacteremia with DIC (Kaplan and Feigin 1976) Folk medicine ("Pseudobattering syndrome") Oriental folk medicine phytophotodermatitis (Coffman et al. 1985) Mongolian spot Erythema multiforme (Adler and Kane-Nussen 1983)
Retinal hemorrhages	Resuscitation retinopathy (Purtscher's retinopathy) (Bacon et al. 1978)

at around 21 days (Collier 1998). Diffusion-weighted imaging may be the last exquisitely sensitive measurement to detect ischemic lesions in the brain.

In addition to active physical injury as an indication of physical abuse we have to consider the phenomenon of neglect and deprivation abuse as well as the phenomenon of Munchausen by proxy. *Neglect* is defined as the "neglectful" failure to supply the needs of the child, including emotional needs (Golden et al. 2003); neglect and deprivation may have its roots in ignorance of a child's needs and competing priorities; it is passive and usually sustained. Malnutrition and dehydration are the prime examples of neglect.

Munchausen by proxy is characterized by the following clinical presentation, motivation and prognosis (Ayoub et al. 2002; Schreier 2002): the mother falsifies symptoms in her child to get help either for herself (because she might be overwhelmed) or the child (because she truly believes that the child is not being treated adequately), or the mother has a delusional belief that the child is ill; this mother will pose quite different risks for that child than the mother whose motivation might be a compulsive need to repeatedly fool the doctor and/or garner attention for herself as an ideal parent. This is not an a priori belief; rather, it has been demonstrated that the recidivism rate of mothers suffering from Munchausen's syndrome is exceptionally high even in the moderately serious cases, as is the death rate of 6% (McClure et al. 1996). These mothers have even been known to kill their children on supervised visits.

25.1.2 Definition

Maltreatment of children encompasses a broad spectrum of abusive actions, some being acts of commission, others of omission or neglect that can result in severe pain, sickness or death of the child. Physical abuse can be narrowly defined as the intentional infliction of injuries to a child by a carer. In individual cases, a Munchausen's syndrome by proxy may be the background of injury or death. The (physical) types of injury inflicted by abuse include bruises, fractures, lacerations, stab wounds, burn wounds, suffocation, drowning, poisoning et cet. (Hobbs et al. 1999; Johnson 2000).

Within this definition, then, striking a child for the purpose of discipline does not constitute a prima facie instance of physical abuse unless it results in injury. Parents often strike their children, usually as an irritated or angry, rather than a considered, response to perceived provocation. Smith et al. (1995) showed that out of a sample of 403 families, 90% of the children had been smacked. The smacking in most instances was mild, but 15% were judged to be severe, with half the mothers saying it had been hard enough to inflict physical pain on the child.

Various forms of brain injury will be discussed in the following. The neuropathological changes secondary to dehydration and/or starvation attributed to carer neglect are discussed elsewhere (pp. 606 ff).

Table 25.3. Characteristic lesions in victims of accidental and inflicted violence. Source: Reece and Sege 2000

Lesions	Violence	
	Accidental	Inflicted
Mean age	**2.5 years**	**0.7 years**
Subdural hemorrhage	10%	46%
Subarachnoid hemorrhage	8%	31%
Retinal hemorrhage	2%	33%
Mortality rate	2%	13%

25.1.3 Incidence

Officially reported cases of child abuse and neglect account for only a fraction of all instances within a given population. It is estimated, for example, that from 200 to 300 non-accidental deaths of infants and children occur in Britain annually, and up to 2.0% of all children are subjected to physical abuse by the age of 17 years; even these numbers, however, are probably too low (Creighton 1985; Creighton and Russell 1995). In the USA, the Children's Protective Service registered 2.9 million abused children in 1992, 1,261 of whom died of their maltreatment (cited by Johnson 2000). In contrast to these findings, in 1997, 13.9 per 1,000 children were registered as victims of abuse or neglect in the USA, physical abuse accounting for 25% of cases. In the same year, 967 children died of their abuse (Johnson 2000). In Germany (Vock 1998), a total of 75 children died as a result of maltreatment and neglect in the years 1985–1989, i.e., 25 deaths annually. In all studies, nearly half of the victims were children aged 0–4 years.

Children with a handicap, premature infants, children with a chronic medical condition, colicky babies, and children with behavioral problems are reported to be at high risk of abuse (Smith and Hanson 1974; Johnson and Krishnamurthy 1996). Among physically abused children, 13.5% had handicaps (Johnson and Krishnamurthy 1996). The handicap is sometimes a result of the abuse (Buchanan and Oliver 1972), and this can give rise to a vicious circle in which the handicap provokes the very abuse, which in turn aggravates the handicap. A recent review of current research determined that from one-quarter to one-third of children diagnosed as having been physically abused were subjected to further abuse (Messages from Research 1995; Minnasch et al. 1999).

Brain injury is the principal cause of death due to physical abuse. Between 70% (Creighton and Russell 1995) and 95% (Billmire and Myers 1985) of serious head injuries in the first year of life are the result of abuse. Serious head injury in a baby alleged to have been caused by a minor fall should alert the clinician to the possibility of abuse (Billmire and Myers 1985; Bruce and Zimmerman 1989; Hobbs 1993 – see also pp. 507 ff). Multiple episodes of child abuse are common: evidence of prior injuries, from shaking episodes for example, is found in about 33–40% of all cases (Alexander et al. 1990; Ewings-Cobbs et al. 1998).

In a recent evaluation of case material on mechanical brain injury (MBI) including children aged >2 years (n=287) and children aged <2 years Reece and Sege (2000) found that the injury was accidental in 81% of instances in the elder children and inflicted by abuse in 19%. A comparison of the victims of accidental versus inflicted injury revealed differences as demonstrated in Table 25.3. Similar findings were obtained in a retrograde analysis of medical records submitted to the National Pediatric Trauma Registry between 1988 and 1997 (DiScala et al. 2000) integrating all types of injury by accident or abuse.

25.1.4 Types of Brain Injuries

We must differentiate four types of brain injuries as a consequence of child abuse:

1. Neglectful brain injury (pp. 606 ff)
2. Mechanical brain injury (p. 492)
3. Asphyxiant brain injury (pp. 510 ff)
4. Toxic brain injury (pp. 513 f)

25.2 Mechanically Caused Brain Injury

Cases of physical abuse including mechanically caused brain injury (MBI) involve three basic types of biomechanical mechanism (Hobbs 1993):

1. *Impact injury* of the head can result from directly striking the head, i.e., the relatively stationary head can be struck by hand or by a high-speed object, which probably represents the most common cause of abusive head trauma in children. Some examples of such violence are slapping, punching, hitting the head with a hand-held or thrown object. Impact injury of the head can result from the head striking another object or surface, e.g., by the infant being violently thrown against a wall or the floor. Direct impact head trauma can also result from negligence, such as failure to use proper safety restraints for children riding in an automobile.
   The reconstruction of such traumatic events, which result in injury of both the brain and its coverings, can be difficult sometimes, especially the determination of whether it was the head, the object, or both that were moving. If the high-speed impact leaves a patterned bruise or abrasion injury on the skin that corresponds to the shape of a particular implement or object, it is almost always the object that was moving relative to the head, rather than vice versa.
   Two examples may be described and documented:
   - By demonstrating at least three independent galea hematomas in an infant younger than 5 months a simple accidental fall could be excluded (Fig. 25.1).
   - Because of the localization of a calvarian depressed fracture of the skull at the top of the parietal bone (with the sequela of a binocular hematoma) a simple accidental fall could be excluded (Fig. 25.2).
2. *Penetrating injuries* caused by a high-speed object striking the head are almost always caused by firearms (AAP 1992), while those caused by low-speed objects usually involve knives, glass or spear-like objects such as stakes or posts.
   Non-accidental (abuse caused) MBIs such as "impact injury" and "penetrating injury" of the brain are described elsewhere and their neuropathological features do not differ from brain wounds caused by accidental violence in adults. Therefore, we must point the reader to Chapters 8 and 9. Only one type of MBI – the acceleration injury – will be dealt with in the present chapter.
3. *Acceleration injuries* caused by shaking. Such injuries result when a child is shaken back and forth repeatedly and violently while being held by the chest or shoulders. The child's relatively large and heavy head (high head:body mass ratio), which is given relatively poor support by the underdeveloped muscles and elastic spinal column, undergoes wide-amplitude whiplash-type flexion and extension movements, always accompanied by rotation. Rotational movements of the brain are particularly likely to injure the nervous system by creating shearing forces capable of causing diffuse axonal injury (DAI) with disruption of axons. Rotational motions can also tear bridging veins, giving rise to subdural and subarachnoid hemorrhages, and create internal shearing injury of the parenchymal white matter, retinal retinoschisis and retinal hemorrhages. Among the clinical consequences are diminished consciousness and respiratory distress. Shaking can also cause non-disruptive stretch injury of the axons at the craniocervical junction (see below, pp. 500 f).

This pattern of violence often involves no superficial injury or fractures of the head, skeleton or soft tissues. In some cases, however, rib and metaphysial fractures are found along with bruising injuries where the child was held. Injury of the cervical spine is uncommon.

Impact as well as acceleration injuries frequently coexist and overlap in their effects.

25.3 Shaken Infant Syndrome

25.3.1 Clinical Features

The doctor will be commonly confronted with a history of an accident while the shaking event will be kept secret. The suspicion of a non-accidental injury will arise when the story will not correspond to the infant's injuries. The common stories told by carers are summed up in Table 25.4 (p. 495). The real story is often based on the following scene:

Irritation at crying is cited as the stimulus to abusive violence to infants, who often cry without apparent or coherent reason, and who often do not heed initial attempts to comfort them. Crying is particularly prevalent in 6-week-old to 4-month-old infants (Barlow and Minns 2000), whose age coincides with the peak incidence of shaken baby syndrome (Dykes 1986).

The injury most likely to be fatal in shaken baby syndrome is an intracranial bleed as a result of the shaking mechanism. Clinical suspicion of intracranial hemorrhage arises from the symptoms exhib-

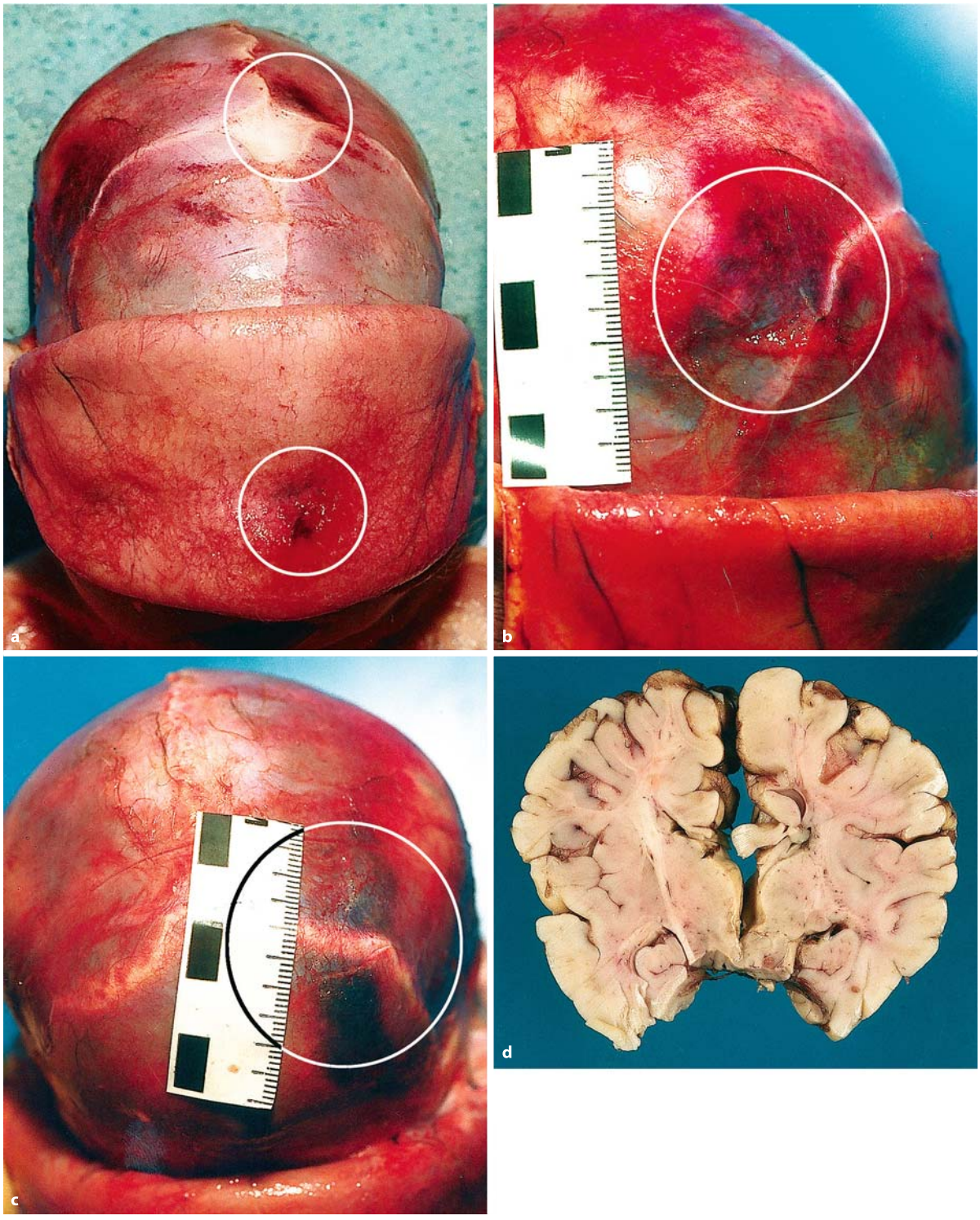


Fig. 25.1a–d. Exclusion of a simple accidental fall in an infant. **a–c** Three topographically different galea hematomas cannot be caused by a simple fall and are therefore characteristic of physical abuse. **d** No cortical hemorrhages are seen but an extraordinary edema

ited by the child: during the acute phase, the infant appears shocked, distressed, anemic. There can be vomiting, irritability, fits, poor responsiveness, coma, stupor, irregular breathing, and apnea. The fontanel is full or bulging.

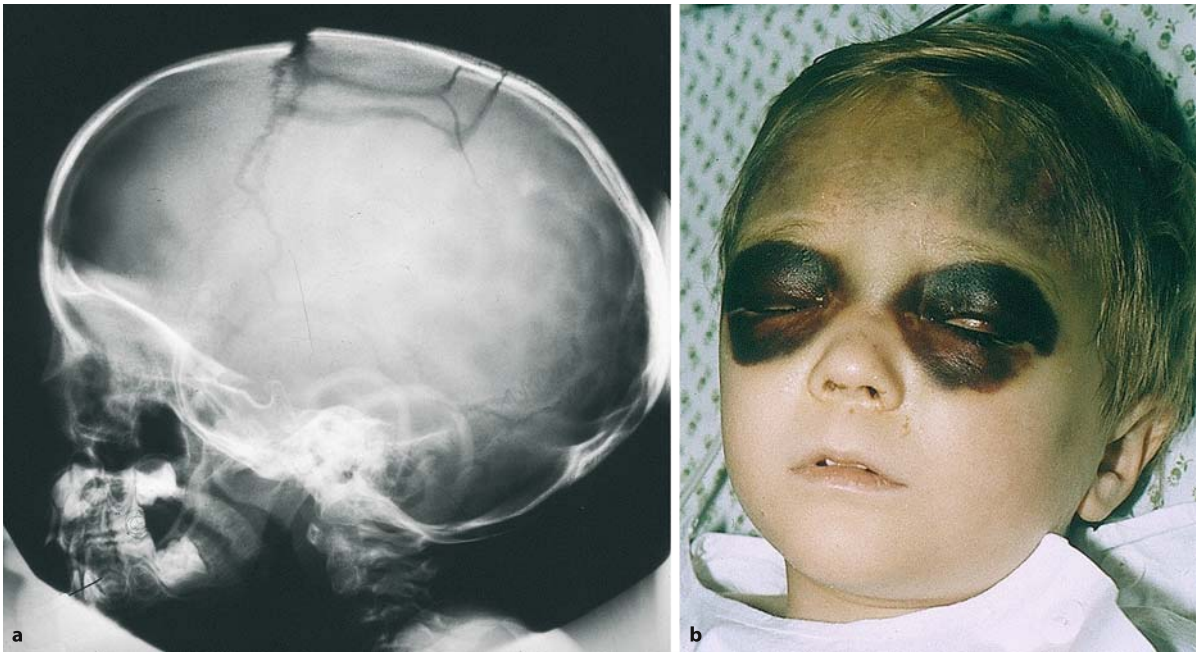


Fig. 25.2a, b. Exclusion of a simple accidental fall. **a** At the top of the parietal bone a depressed fracture excludes a simple accidental fall due to the localization of the fracture; **b** the binocular hematoma is secondarily caused by the (primary) hematoma at the site of the calvarian fracture

Table 25.4. Common stories told by carers to explain injuries suffered by infants or children under their care. Source: Kirschner and Wilson 2001 (CRP = cardiopulmonary resuscitation)

1. Child fell from a low height (<1.25 m or 4 feet) such as couch, crib, bed, chair or down stairs or a hard object fell on child (accident)
2. Alleged traumatic event, one day or more before death (accident)
3. Unexpectedly found dead (SIDS?)
4. Child choked while eating or suddenly turned blue or stopped breathing, and was then shaken (resuscitation)
5. Sudden seizure activity
6. Aggressive or inexperienced CPR to a child who suddenly stopped breathing
7. Injury inflicted by sibling

After fatal shaking the child suffers almost immediate loss of consciousness and rapidly escalating CNS dysfunction (AAP 2001). The interval between the traumatic event and death can be extremely short. Suspicion of shaken baby syndrome is underscored by detection of retinal hemorrhages, by morphological changes of the spinal cord, and by demonstration of subcutaneous hematomas (fingertip pattern bruises, Fig. 25.3) on the child's thorax or shoulders and/or of fractures of the ribs or humerus as signs of grasping. The presence of an intracranial hemorrhage will be confirmed by CT or MRI.

The physician must always suspect "shaken baby syndrome" if subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), intracerebral hemorrhage (ICH), or laceration of the brain parenchyma is detected in an infant. The most common symptom is SDH. If another cause can be ruled out for intracranial bleeding of this type (coagulation disease, birth trauma), a mechanical cause always lies behind the injury, either an intentional or unintentional blow to the head or acceleration of the head and brain.

The differential diagnoses for bruising injuries (crushing wounds) are surveyed by Vora and Makris

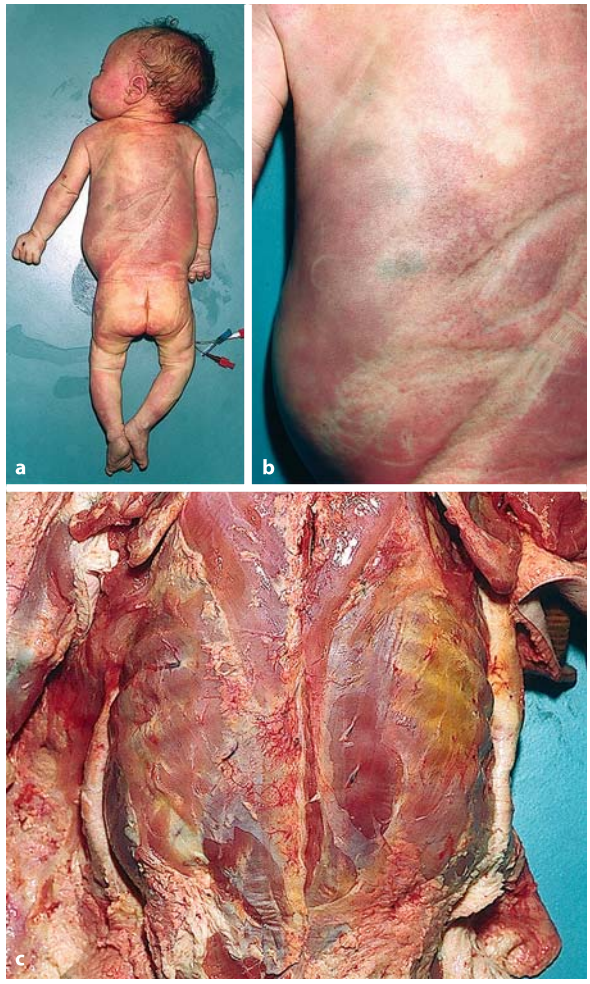


Fig. 25.3a–c. Shaken baby syndrome with fresh and old subcutaneous hematomas, i.e., finger tip pattern bruises on the child's thorax

(2001). The authors distinguish "normal" bruising injuries, which can be caused for example by an accidental fall, from "abnormal" bruising injuries. They point out the importance of the pattern of bruising injuries, any associated symptoms, and of the family history of drug abuse or domestic violence (see also Manno 1991). "Normal bruising" is generally limited to the lower limbs and is not associated with petechiae, purpura, or mucosal bleeding; the family history of drug abuse or domestic violence is negative. Bruising injuries resulting from accidental falls are not uncommon at about the age of 1 year, the age at which most infants begin "cruising."

A wide variety of rare diseases cause coagulation disturbances associated with spontaneous intracranial hemorrhages (SAH, SDH or ICH) in childhood: hemophilia, *Haemophilus influenzae* and pneumococcal meningitis, arteriovenous malformation/aneurysm, malignancy, glutaric aciduria type I, post-cardiopulmonary bypass (Hoffman and Naughten 1998), disseminated intravascular coagulation, Menkes' disease, Ehlers–Danlos syndrome (Nuss and Manco-Johnson 1995), hemophilia (Schwer et al. 1982), and vitamin K deficiency (Schaible et al. 1996). In the absence of such disease, intracranial hemorrhage is invariably of mechanical origin in infants.

It is not uncommon for infants with SAH, SDH or ICH to have no signs of skull fracture or other indication of impact to the head. If the medical history or symptoms exclude birth trauma or accidental trauma and the above-mentioned coagulation disturbances, it is now generally assumed that the child has been violently shaken (Guthkelch 1971; Caffey 1972). As perhaps overstated by Lloyd (1998): intracranial hemorrhages in infants are almost always due to abuse, but abuse is often not recognized. Violent shaking usually produces SAH and/or SDH.

Subarachnoid Hemorrhage (SAH). Spontaneous SAH is extremely rare in childhood. In a review of 10,000 cases reported between 1966 and 1973, Newton (1989) found not a single instance of spontaneous SAH in children under 1 year of age (see also Matson 1965). Prahlow et al. (1998) observed a single case with a ruptured berry aneurysm. SAH is, however, a common result of mechanical violence associated with birth, or it is seen as part of a wider pattern of injury from other types of violence, often in association with SDH.

Subdural Hemorrhage (SDH). In children under 2 years of age SDH has a reported annual incidence of 12.8 per 100,000 children (95% confidence interval 5.4–20.2); in children less than 1 year old, it is 21.0 per 100,000 children (confidence interval 7.5–34.4). The average child has a 1:4,761 risk of developing a SDH within the first year of life (Jayawant et al. 1998).

As described above, acceleration of the soft, pliable skull and brain leads to stress on the bridging veins, which are attached to the sagittal sinus, causing disruption and bleeding into the subdural space, often over a wide area bilaterally. A SDH can be survived or can lead to sudden or even delayed death. A child will sometimes exhibit multiple SDHs of different ages, or can have an acute SDH associated with the vestiges of older trauma of a different type. The median survival time of fatal SDH is reported to be <24 h in 80% of cases (Gilliland 1998).

25.3.2 Autopsy Findings

The typical autopsy findings in shaken infant syndrome are characterized by six features:

1. Intracranial hemorrhage, especially SDH, SAH, ICH and/or laceration injury
2. Retinal hemorrhage

3. Brain edema
4. Dural hemorrhage of the cervical cord
5. Hyperextension hemorrhages within the neck muscles
6. Fingertip pattern bruises on shoulders or chest

25.3.2.1 Intracranial Hemorrhage

With few exceptions (see above) intracranial hemorrhages are caused by mechanical violence. The most common type of intracranial hemorrhage as a result of shaking is SDH. As mentioned above (pp. 127 ff) SDH results from tearing of the bridging veins, which extend from the cortical surface to the dural venous sinuses. Isolated bleeding limited to the intracranial spaces (SAH, SDH, ICH) without extracranial hematoma is always highly suspicious of a shaking mechanism.

Violent shaking of a child often produces a combination of intracranial hemorrhages, SDH being combined with SAH, ICH, and/or laceration injuries of the brain parenchyma, usually in the transition zone between the cortex and white matter (subcortical white matter). Microscopic features include axonal injury, which becomes evident after survival times of 1.5–3 h.

SDH is the most frequent type of intracranial hemorrhage. One of the hallmarks of shaking will be the phenomenon that the bridging veins have been torn by the forces created by the shaking; the bleeding is usually bilateral (Fig. 25.4), less often unilateral (Fig. 25.5); unlike the injuries in older children and adults, the contusion injuries of the brain are rare and do not correspond to the point of impact, but extend along the lines of force through the brain.

In contrast to SDH in adults, SDH in infants or children is not necessarily a "massive" lesion (Caffey 1974; see also Duhaime et al. 1998; David 1999). The bleeding often appears to form a film of blood covering the cerebral hemispheres without a space-occupying tendency that would warrant neurosurgical intervention ("smear subdural hematoma" due to the resemblance of blood smeared on the brain). The hematoma may consist of only 2–3 ml of blood and the prosector personally has to inspect the subdural space as the calvarium is being removed as recommended by Case et al. (2001).

The associated subarachnoid bleeding is usually without clinical significance. These hemorrhages arise from tearing of arachnoid vessels at the same time as bridging veins are torn.

25.3.2.2 Retinal Hemorrhage

Retinal hemorrhages are both clinical and postmortem signs of shaking (Andrews 1996) (Table 25.2).

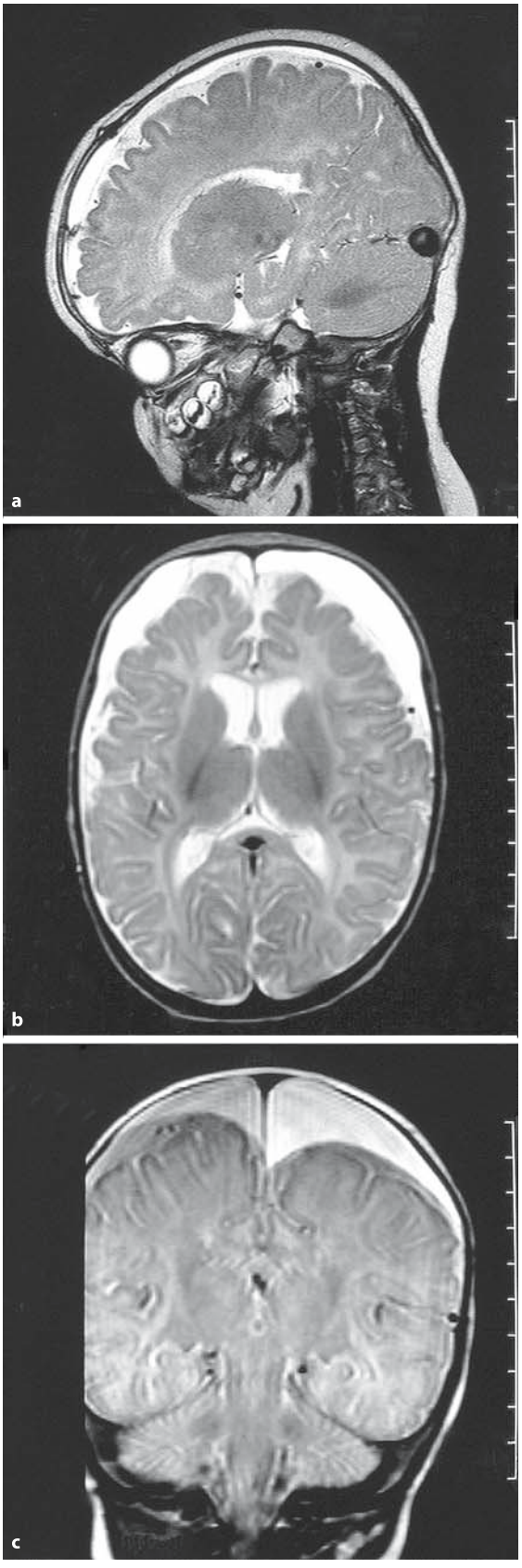


Fig. 25.4a–c. Bilateral subdural hemorrhages covering the frontal lobe of both hemispheres as demonstrated by MRI

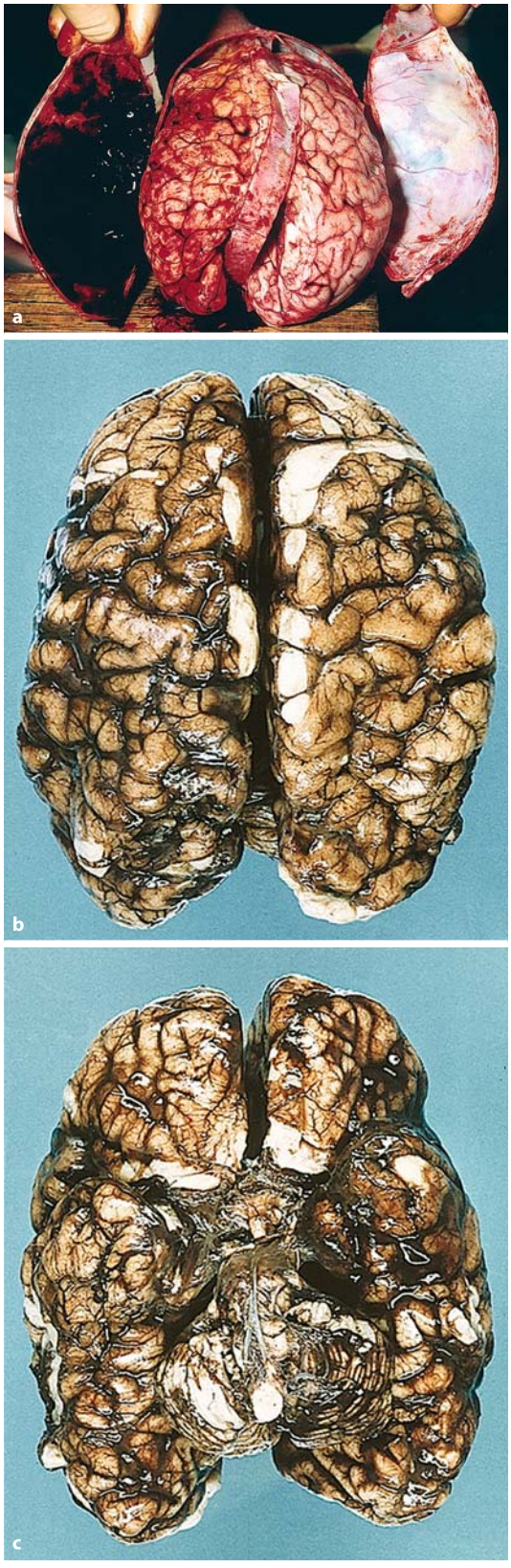


Fig. 25.5a–c. Unilateral (left-sided) subdural hemorrhage at autopsy (**a**) and – in the same case – characterized by a slight subarachnoid hemorrhage on the left hemisphere and a bilateral congestion – (**b, c**) after formalin fixation

They occur in cases with and without impact. Geddes et al. (2001a) found that every case of retinal bleeding they investigated also included SDH (see also Reece and Sege 2000; for review of the literature, Gilliland 2003). Another question will be whether retinal bleedings are specific to shaking, especially in cases without intracranial hemorrhage. Budenz et al. (1994) supposed that infant victims of shaking with no intracranial hemorrhages exhibit optic nerve sheath abnormalities on histopathology. Butler-Sloss and Hall (2002) described one case: the baby was found unconscious in his cot and died. The baby had retinal bleeds, but no intracranial hemorrhage. The local authority asserted that the retinal hemorrhages could on their own amount to proof, on the balance of probabilities, of a violent non-accidental death caused by shaking the baby. That view was supported by the majority of experts appointed in the case although other experts were of the opinion that the cause of death could not be definitively ascertained.

Retinal hemorrhages can cover the retinal surface (Fig. 25.6) (preretinal hemorrhage), lie beneath the retina (subretinal hemorrhage), or occur within the retinal tissues proper (intraretinal hemorrhage). They can be detected according to various studies in 65–95% of infants after shaking (Billmire and Myers 1985; Luerssen et al. 1991), in 75–90% (AAP 1993), or in approximately 80% of shaken babies (Levin 2001; Morad et al. 2002).

For differential diagnosis it is important to know that retinal hemorrhages are non-specific to shaking, also being an extremely rare consequence of acute leukemia and other hematological disorders, of hypertension, of raised intracranial pressure, of meningitis (cf. Kaur and Taylor 1990), and of cardiopulmonary resuscitation with chest compression (Kanter 1986; Gilliland and Luckenbach 1993; Levin 2000) as well as following a convulsive episode (Mei-Zahav et al. 2002). A prospective study of 100 consecutively admitted head-injured patients under 24 months of age revealed some retinal hemorrhages in patients with serious accidental head injury, but more were encountered in victims of inflicted injury (Duhaime et al. 1992). Although intracranial pressure or hemorrhage alone is often associated with intraocular hemorrhage in adults (Terson syndrome), it is observed in fewer than 5% of children with intracranial bleeding (Levin 2001). Moreover, perinatal retinal hemorrhages are described in 15–40% of newborn infants, and retinal iron (see below) was not seen with the same frequency in non-injured children in a review of iron staining in the eyes of 169 children examined in a prospective study (Gilliland 2001).

As most full-term neonates after vaginal delivery have retinal hemorrhages it is important to know the time of resorption. Commonly the neonatal retinal hemorrhages completely resolve by 5–6 days, although a few persist longer (Levin et al. 1980; Berger

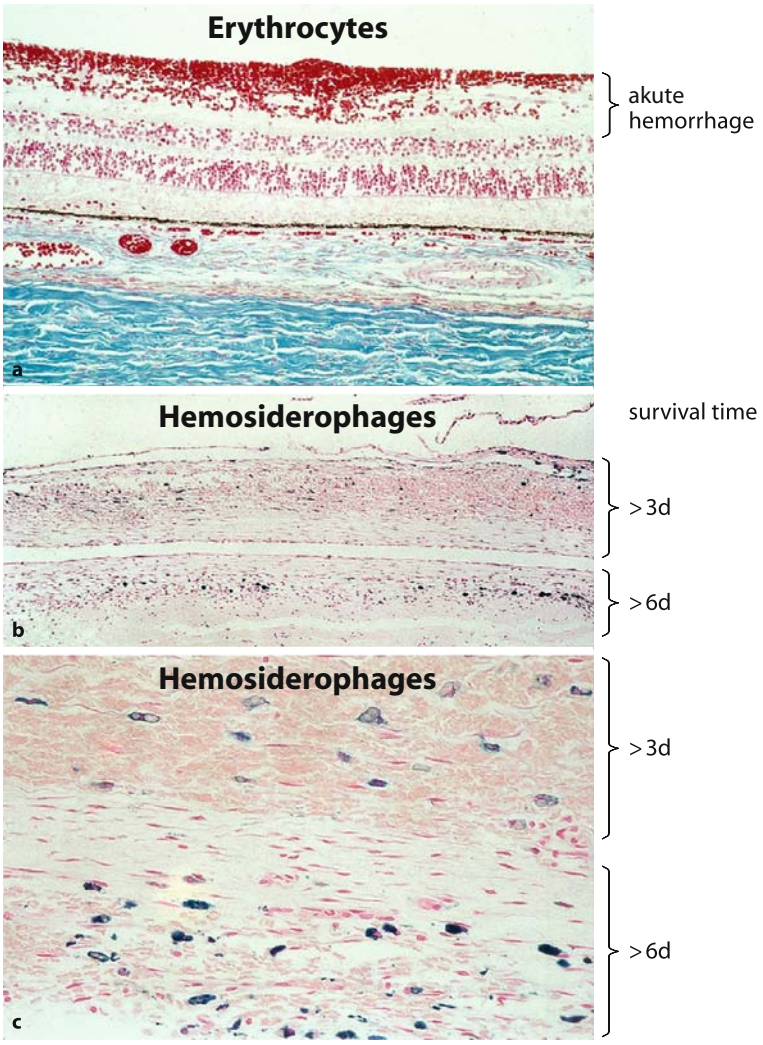


Fig. 25.6a–c. a Retinal hemorrhage which covers the retinal surface. **b, c** Hemosiderophages within the retina of the same case as an indication of a repeated shaking event. The two layers of different staining features in the Prussian blue reaction allow the differentiation of at least three shaking events: an acute hemorrhage and old hemorrhages twice before (**a** trichrome stain, **b, c** Prussian blue reaction; magnification **a**, **b** ×100, **c** ×500)

and Margolis 1985). In children older than 30 days who have retinal hemorrhages, the great majority have abusive head injuries (Case et al. 2001).

How rapidly hemorrhages clear can be quite variable. Small birth-related hemorrhages may clear in a few days while large deep-seated hemorrhages may take a small number of weeks to clear (Emerson et al. 2001). Iron has been detected as early as 2 days after wounding (Elner et al. 1990; Gilliland et al. 1991, 1999, 2005), but documented survival beyond 48 h is often associated with no stainable iron. The rate of resolution of hemosiderin seems to take several months (Luther 2003; see also Gilliland et al 2005: up to 16.8 months as demonstrated by animal experiments). If the interval between the traumatic event and death is less than 48 h and iron is present, a previous episode of hemorrhage seems likely. A previous hemorrhage at birth is not excluded in all cases. Reactive changes (Luther 2003) are characterized by an upregulation of GFAP in the radial glia (Müller cells) seen after a survival time of 24 h. It takes 12 h and longer for macrophages to be present as demonstrated by macrophage markers such as CD68.

It is commonly supposed that retinal hemorrhages arise from shearing forces between the vitreous and retina. The arguments are summed up by Luther (2003):

- Shaking may generate rotational forces within the eye.
- Rapid deceleration can generate retinal hemorrhage.
- Retinal hemorrhages are seen in ophthalmologic procedures associated with vitreous traction.

But Luther (2003) gives critical evidence of this hypothesis: rotational loading may be important but convincing data are not available.

According to Amberg et al. (1995) as well as Morad et al. (2002) there are two alternative *biomechanic explanations* for retinal hemorrhages; the last of the explanations seems to be the most probable:

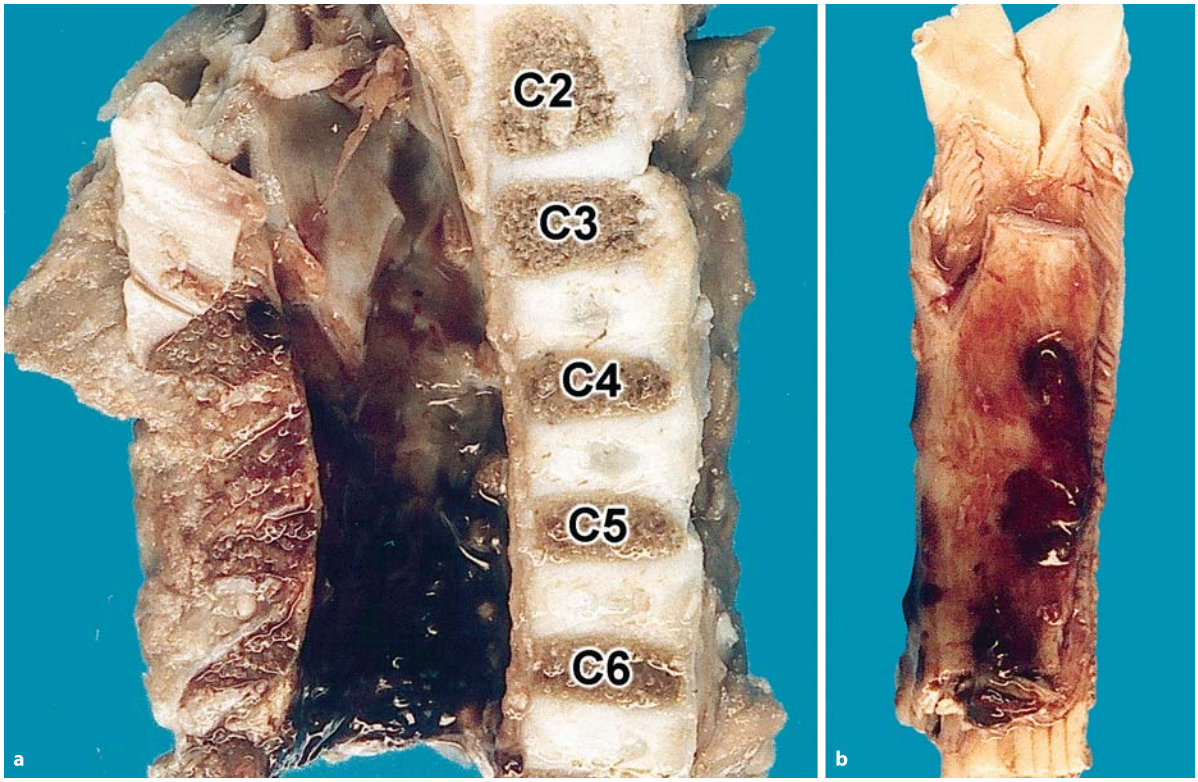


Fig. 25.7a, b. Epidural hemorrhage of the cervical cord. An epidural hemorrhage may develop as a result of the shaking event

- Extranial compression, i.e., elevated intrathoracic pressure, or direct impact on the eye by a blow.
- Compression of the central retinal vein, with a rise in pressure at the choroidal anastomosis of the optic disc (Müller and Deck 1974; Hobbs et al. 1999; Uscinski 2002) as a result of an elevated intracranial pressure, direct tracing of blood from the intracranial space; blockade of the circulation leads to leakage of blood from ruptured intraretinal capillaries into the retinal tissue.

Some other explanations are given by Luther (2003) but he concludes that we do not know how retinal hemorrhages form in most cases of alleged non-accidental injury. Therefore, he states that the presence of retinal hemorrhages is not compelling evidence for a shaking injury per se. He cites single cases of retinal hemorrhages following simple falls (Plunkett 2001) or direct impact without shaking (Budenz et al. 1994; Christian et al. 1999).

In contrast, the phenomenon of "retinoschisis,"i. e., severe bilateral retinal hemorrhaging with retinal folds or detachments, is highly specific to shaken infant syndrome, never having been described in any other condition of infants or young children (Greenwald et al. 1986; Levin 2000). If shaking forces are applied indirectly to the vitreous, the resulting shearing forces exerted on the retina, especially the macula, cause a splitting of its layers to form a cystic cavity that can fill partially or completely with blood (Levin 2001).

25.3.2.3 Brain Edema

Brain edema – as described above – is a morphological alteration characterized by a large increase in brain volume and in brain mass with the clinical sequelae of herniation symptoms. This non-specific phenomenon can be caused by intracranial hemorrhages, by the mechanical (shaking) effect of acceleration on the brain tissue or by ischemia. An important – possible additional – cause may be a very rapid onset of the secondary ischemic effect (Geddes et al. 2001a, b).

25.3.2.4 Cervical Cord Injury: Dural Hemorrhage and Cord Lesion

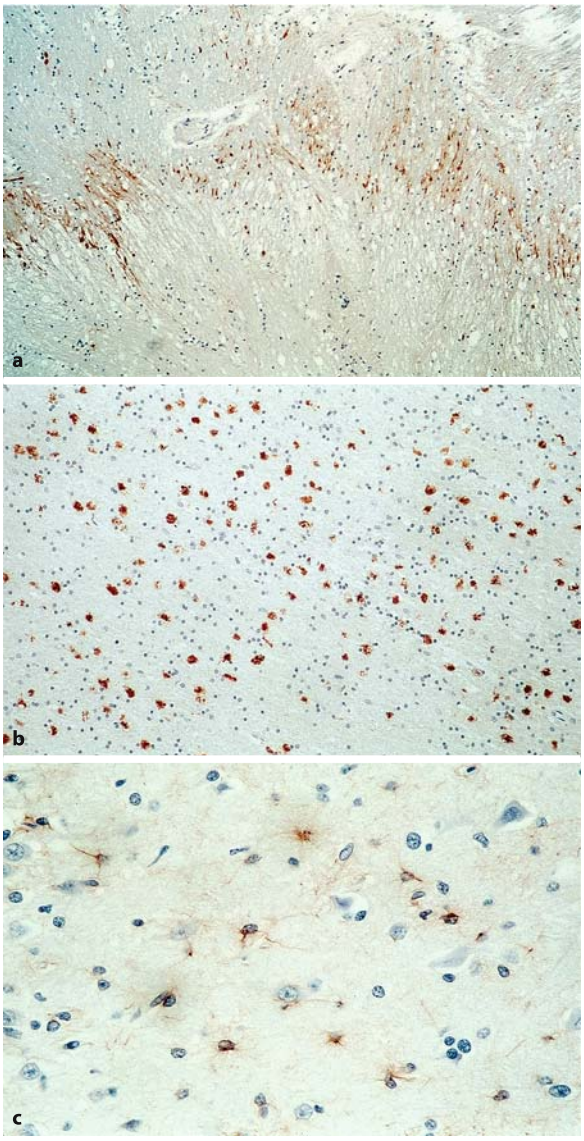
While shaking rarely results in injury of the cervical spine, spinal epidural and/or subdural hemorrhages at the level of the craniocervical junction are more common (Fig. 25.7). This type of injury is obviously a variable feature of "shaking infant syndrome," while macroscopic spinal cord injury is unusual (Caffey 1974; Johnson et al. 1995; Hart et al. 1996; Geddes

et al. 2001b). Leestma (1997) by contrast described focal hemorrhages and gray matter injuries in the spinal cords of victims of violent shaking, which in non-fatal cases occasionally resulted in a transverse myelopathy.

In the first careful examination of the spinal cord at the cervico-medullary junction in SIDS autopsies, Towbin (1967) found four victims with cervical cord injury and hemorrhaging into the epidural space, meninges, and spinal cord parenchyma. The author suggested the injury was caused by a forceful delivery. More recently, Hadley et al. (1989) discovered injury of the spinal cord at the cervico-medullary junction in five of six victims of shaking. Leestma (1989, 1997) points specifically to cervical cord injury caused by violent shaking, in particular epidural hemorrhages. Extradural hemorrhages around the craniocervical junction, while not a common feature in adult head injury, have also been reported in non-accidental head injury in 3 of 53 infants by Geddes et al. (2001a). However, no definitive clinical investigations (CT, MRI) or studies by forensic pathologists have yet described the actual frequency of this phenomenon.

At the microscopic level, cervical cord injury is detected in the form of axonal injury (see Fig. 25.8a) at the level of the craniocervical junction (Shannon et al. 1998). The staining in the corticospinal tracts is quite distinct, bilaterally affecting variable numbers of axons in the fiber bundles, and appears to indicate localized mechanically caused axonal injury at the craniocervical junction. Geddes et al. (2001b) attributed this pattern to non-disruptive stretch injury of the axons.

Shaking-induced spinal cord injury can be explained by the oscillating motion of the head relative to the thorax. Gleckman et al. (1999) described a single case with cervical spine ligament hemorrhages between C1 and C4 with corresponding luminal compression of the vertebral arteries. However, injuries of the cervical spine and cervical soft tissues are surprisingly rare.



500Fig. 25.8a–c. Histological findings in shaken baby syndrome. **a** Axonal injury; focal aggregation of **b** macrophages and **c** astrocytes as an indication of an old, i.e., a repeated, parenchymal injury (immunoreactivity to **a** β-APP, **b** CD68, **c** GFAP; magnification **a** ×50, **b** ×200, **c** ×300)

25.3.2.5 Skull Fracture

In particular, the phenomenon of skull fracture has been discussed repeatedly. Hobbs (1984) showed that accidents resulting in single narrow, linear fractures of the skull especially of the parietal bone, with no associated intracranial injury, usually remain without clinical consequence. This observation suggests that for skull fractures in young children alleged to have been caused by a minor fall, examination of the fracture alone can confirm or exclude abuse. Although linear fractures were occasionally seen in the abuse victims, the author stated that the presence of even one of the following criteria is suggestive of abuse:

- Multiple or complex skull fractures
- Depressed fractures
- Fracture widths of 3.0 mm or more
- Growing skull fractures
- Fracture involving more than a single cranial bone
- Non-parietal skull fracture
- Associated intracranial injuries

Table 25.5. Grading the seriousness of head and eye injury in victims of shaking. Sources: Hobbs et al. 1999, see also Green et al. 1996

Grade of injury	Head injury	Eye injury
Less severe	Subdural hemorrhage	Subhyaloid and intraretinal hemorrhage
More severe	Intracerebral subarachnoid hemorrhage	Optic nerve sheath hemorrhage
Most severe	Cerebral laceration	Retinal detachment Choroidal and vitreous hemorrhage

25.3.2.6 Further Morphological Alterations

A number of additional morphological changes characteristic of shaken infant syndrome can be identified by careful examination, including typical fingertip pattern bruises, rib fractures, cervical cord injuries, and intraparenchymal shearing injuries in the brain (Duhaime et al. 1998; Case et al. 2001). Autopsy should include thorough inspection of the upper limbs, shoulders, the brachial nerve plexus and muscles close to the scapula. Hemorrhages caused by hyperextension are found in the transition zone between the thoracic and cervical spine and at insertions of the sternocleidomastoid muscle (Saternus et al. 2000). DAI, a reliable marker of angular acceleration of the brain (Fig. 25.8a), may be detected by immunohistochemical staining (Li et al. 1998; Shannon et al. 1998; Gleckman et al. 1999), but only in cases with survival times of at least 1.5–3 h or more (Oehmichen et al. 1997). Geddes et al. (2001b) observed that DAI occurs in severe cases but not in all cases; the vast majority of infants with fatal head injury caused by abuse have *"little" or "no"* mechanical brain damage.

25.3.2.7 The Repeated Shaking

In cases where there is a suspicion of shaken baby syndrome, the forensic neuropathologist has to demonstrate (or to exclude) morphological features which give evidence of repeated physical abuse. He has to exclude old hemorrhages in dura, leptomeninx, and brain parenchyma as well as in the cervical spine or the retina (Fig. 25.6b, c) by application of the Prussian blue reaction; he has to search for focal scavenger and scarring processes by specific demonstration of macrophages (Fig. 25.8b) and activated astrocytes (Fig. 25.8c).

Moreover a grading of the seriousness of head and eye injury in victims of shaking is possible in order to get comparable information as proposed by Hobbs et al. (1999) and documented in Table 25.5.

25.3.3 Shaking Impact Syndrome

Duhaime et al. (1987, 1998) point out that the term "shaken infant syndrome" is not an accurate description of the biomechanical features and morphological findings in many cases. They propose instead the name "shaken impact syndrome." The authors provide empirical documentation of cases exhibiting intracranial lesions typical of an acceleration mechanism (SDH, laceration injuries, retinal hemorrhages) plus extracranial lesions associated with impact, e.g., subgaleal hemorrhages and laceration injuries or fractures of the skull. They especially cite the biomechanical experiments of Gennarelli and Thibault (1985) and conclude that DAI cannot be induced by shaking alone (see discussion above, pp. 508 ff). The postulated combination of impact and acceleration accords with the findings of other authors (Alexander et al. 1990; Gilliland and Folberg 1996; Hymel et al. 1998).

25.3.4 "Tin-Ear" Syndrome

Tin-ear syndrome (Hanigan et al. 1987) is a variation of shaken infant syndrome characterized by contusion injury of the ear, ipsilateral cerebral edema, ipsilateral SDH, and retinal hemorrhage. It is produced by a blow to the side of the head that causes the head to rotate around the x-axis of the neck (rotational acceleration, around the frontal-dorsal axis). The spinning motion of the head after the blow is thought to compound the direct impact with angular momentum. The blow must be delivered with such velocity that a single impact is capable of inflicting severe intracranial injuries with only minimal external bruising injuries.

25.3.5 Cause of Death

Death in cases of shaken infant syndrome can result from the following processes (Shannon and Becker 2001), which can occur in isolation or combination:

1. A *space-occupying process* with SDH-induced shift and herniation is rarely seen since in victims of shaken infant syndrome, the SDH in most cases is only slight. Still, the space-occupying process in combination with the loss of blood and secondary edema and ischemia can lead to death.
2. *Diffuse brain injury in the sense of DAI* caused by acceleration usually involves additional rotational movements of the head (Vowles et al. 1987; Shannon et al. 1998; Gleckman et al. 1999; Case et al. 2001). However, the majority of the cases described by Geddes et al. (2001b, 2003a, b) did not exhibit the phenomenom of DAI. Moreover, based on biomechanic calculation, Duhaime et al. (1987) even excluded this mechanism of injury as a cause of death in most cases. But undoubtedly in cases with survival times of more than 100 min, this phenomenon may be demonstrated, at least in single cases.
3. *Brain swelling* may be either a direct result of the trauma (primary edema) or a result of a hypoxic–ischemic process or SDH (secondary edema) that may induce rapid apnea and respiratory and cardiac arrest. If the victim survives for long, generalized edema and hypoxic–ischemic neuronal damage can be demonstrated.
4. *Injury of the cervical cord* and lower brain stem is most likely the result of hyperextension. Such injury can induce apnea and hypoventilation (Johnson et al. 1995), which could ultimately lead to the hypoxic–ischemic brain edema described by Geddes et al. (2001b, 2003a, b; Kemp et al. 2003). Although Geddes et al. thought this type of damage was survivable, it may cause hypoxia and/or transient ischemia and therefore may be one significant factor contributing indirectly to death.

The death of an infant from violent shaking will be in most cases the result of several mechanisms, i.e., as of hypoxic–ischemic brain damage combined with primary and/or secondary edema, a space-occupying lesion and anemia, possibly aggravated by episodes of apnea secondary to minor axonal lesions of the lower brain stem and upper craniocervical junction. In some cases DAI may be the primary cause of death.

25.3.6 Clinical Outcome

The clinical outcome of shaken infant syndrome was assessed by Jayawant et al. (1998; see Bonnier et al. 1995) in a retrospective study of 33 cases of SDH in children under 2 years of age over a period of 3 years. Nine infants (27.3%) died, 15 (45.5%) were left with profound disabilities; only 9 infants were considered to be normal after 1 year of follow-up. Other authors report mortality rates ranging from 15% (Ludwig and Warman 1984) to 38% (Alexander et al. 1990). Sixty percent of infants who were comatose at initial examination died or suffered profound mental retardation, spastic quadriplegia, or severe motor dysfunction as a result of their injuries; other infants presented with seizures, irritability, or lethargy (Sinal and Ball 1987).

A common cause of infantile post-traumatic cortical atrophy is the injury (axonal injury and/or ischemia) inflicted by shaking. Infants who have suffered such trauma typically present with an altered level of consciousness, seizures, retinal hemorrhages, and bulging fontanel. CT scans reveal punctate hemorrhages in the white matter and signs of intraventricular or subarachnoid bleeding (Zimmerman et al. 1978). Once the child has recovered from the acute injury, the fontanel softens and head growth ceases. This is accompanied by progressive enlargement of the ventricles, sulci, and subarachnoid cisterns (Luerssen et al. 1986). If the child survives, it may be cortically blind and suffer from microcephaly, spasticity, seizures, hygromas, hydrocephalus or porencephalic cysts (Figs. 25.9, 25.10) (Sato et al. 1989).

Recently a case report was published with neuropathological findings of two infants who survived an episode of violent shaking for 7 and 9 years, respectively (Marín-Padilla et al. 2002). The shaking injuries included cortical and subcortical hemorrhages, hypoxic/ischemic and axonal damage, and severe edema. By 6 months, the original injuries were repaired and resulted in encephaloclastic encephalopathies (e.g., multicystic encephalomalacia, porencephaly, generalized white matter attenuation, diffuse cortical atrophy, microgyria, ulegyria, and hydrocephalus ex vacuo). By neuropathological investigation it could be demonstrated that the reorganization included progressive cortical dysplasia with cytoarchitectural disorganization, laminar obliteration, morphologic and functional (synaptic reorganization) transformation of some neurons, preservation of layer 1 intrinsic fibers and Cajal–Retzius cells, and the presence of large (hypertrophic) intrinsic neurons with intense neurofilament immunoreactivity.

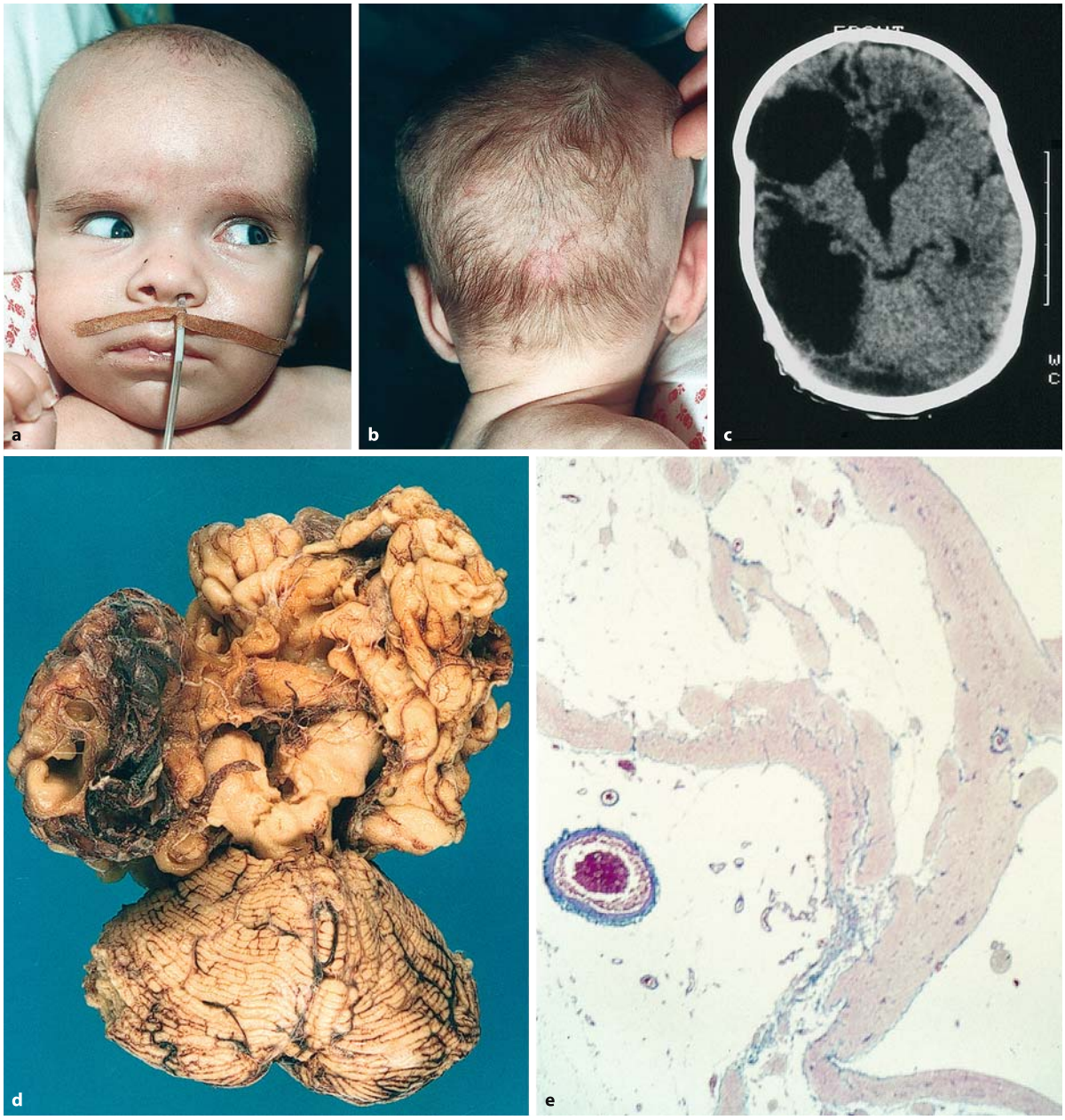


Fig. 25.9a–e. Clinical outcome. At the time of clinical examination the distinct neurological deficits (**a**) contrasted with discrete external lesions (**b**), but were supported by imaging techniques (MRI – **c**). The child suddenly died 1 year later; the autopsy revealed a cystic and collapsed brain without cortical structures (**d**) held together by a glial–collagenous scar (**e**) (**e** trichrome stain; magnification ×50)

25.3.7 Differential Diagnosis

Common explanations given by accused carers or parents for the child's injuries are listed in Table 25.2. The most frequent explanation provided is that the injuries were caused by a mishap, such as a fall (p. 507). A detailed survey of this topic and exhaustive review of the literature was made by Bays (2001; Oehmichen et al. 2005). The major types of violence will be discussed below, special attention being paid to those most frequently offered in expert testimony to explain intracranial injuries in children. The differential diagnosis is oriented on the cardinal symptom, the SDH.

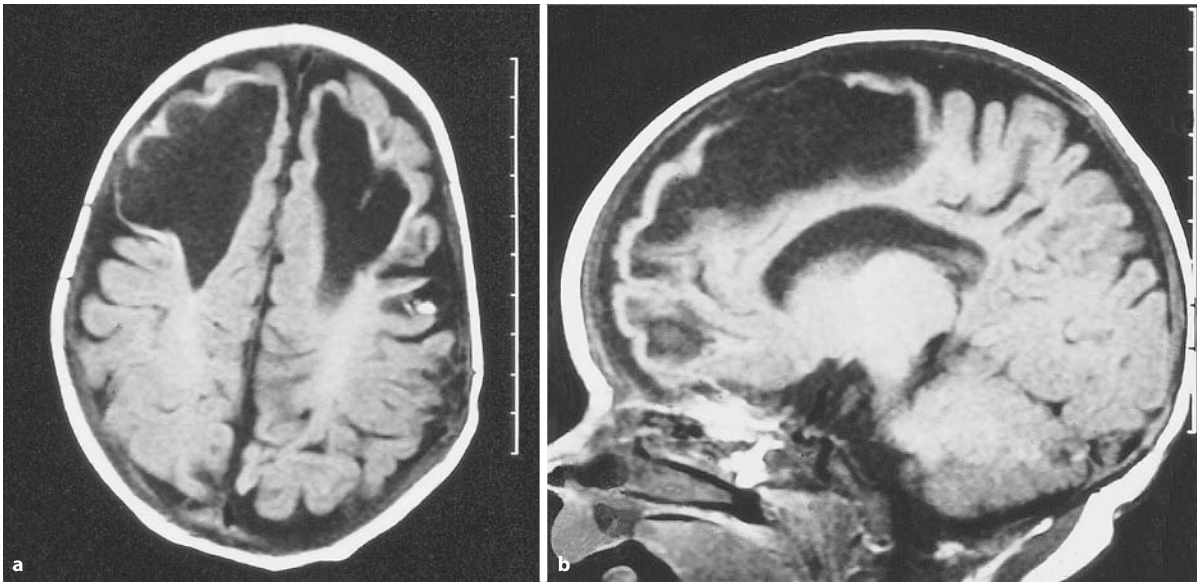


Fig. 25.10a, b. Clinical outcome with extreme porencephaly as a sequel of subdural and bilateral parenchymal hemorrhage after shaking

25.3.7.1 Wounding by Birth

SDH may be a result of an injury sustained at delivery but not recognized at the time. Therefore, it seemed to be necessary to establish the frequency of clinically silent SDH in live-born term infants as a result of delivery, and the natural history of these hematomas. Whitby et al. (2004) included 111 babies in their study. Nine babies had subdural hemorrhages: three were normal vaginal deliveries (risk 6.1%), five were delivered by forceps after an attempted ventouse delivery (27.8%), and one had a traumatic ventouse delivery (7.7%). All babies with subdural hemorrhages were assessed clinically but no intervention was needed. All were rescanned at 4 weeks and hematomas had completely resolved.

Violence by birth is a major cause of acute intracranial hemorrhages in newborns despite improvements in obstetric methods (Choux et al. 1986; Hayashi et al. 1987; Towner et al. 1999). Although full-term and premature infants are both at risk, the risk to mature babies is greater (Hovind 1986; Hayashi et al. 1987; Towner et al. 1999). The main obstetrical events associated with acute SDH are breech presentation, protracted labor, vacuum extraction, and forceps delivery (Hayashi et al. 1987; Romodanov and Brodsky 1987; Takagi et al. 1982). In contrast, SAH caused by birth is common, very minor SAH being perhaps universal.

To distinguish birth trauma from shaken baby syndrome, the individual birth process and the child's clinical appearance from birth during the postnatal period must be evaluated. If traumatic violence during delivery can be excluded, the SDH must be attributed to another cause. If the child is found to have developed normally postnatally, birth trauma is unlikely. The macroscopic and microscopic timing of the SDH should also be ascertained: if the SDH is recent and did not occur at birth, then birth trauma can be reliably excluded. The same is true of retinal bleeding, which can also occur during the birth process though it is usually only slight.

As a general rule, birth-induced intracranial bleeding (as well as sinus thrombosis) becomes manifest clinically within the first 24 h of life; recognition however may take up to 4 days if the ongoing hemorrhage is only slight (Menezes et al. 1983). The birth history, the dynamics of the carers, and the review of postnatal care all yield clues.

25.3.7.2 Dehydration

Infants with severe diarrhea, comparable other generalized disease or neglect suffer from subdural effusions, subdural hemorrhages, and neomembrane formation (Williams and Stevens 1954; Freundlich et al. 1956; for review see Friede 1989). Infants are particularly liable to SDH secondary to dehydration-induced shrinkage of the cerebral hemispheres. The skulls of infants are subject to much greater stretching and deformation of parasagittal structures than is possible in adults due to their open fontanels. Twelve infants with gastroenteritis and malnutrition were reported by Herzberger et al. (1956) to have subdural effusions. Seven of the infants had developed neomembranes, two cerebral phlebothrombosis. In

2 of 11 patients, Satoh et al. (1982) reported subdural effusions secondary to massive shrinkage of the brain from adrenocorticotrophic hormone (ACTH) treatment.

25.3.7.3 Physiotherapy in Premature Infants

Two series of investigations gave evidence of the consequence of postnatal encephaloclastic porencephaly (ECPE) in English neonatal units. The authors recognized the similarity between ECPE and shaking injuries in older children (Cross et al. 1992; Harding et al. 1998). Two neonatal units stated an association between ECPE and rigorous chest physiotherapy and its disappearance with a change of practice. In 2001, Knight et al. reviewed the chest physiotherapy between 1985 and 1998 looking at ECPE in a population of 2,219 premature babies weighing less than 1,500 g. There were no new cases of ECPE other than the 13 cases reported between 1992 and 1994. The editors of the Journal *Archives of Disease in Childhood. Fetal and Neonatal Edition* (Rosenbloom and Ryan 2002) questioned the association of physiotherapy and ECPE (and their answer was "no") as promulgated by Williams and Sunderland (2002).

25.3.7.4 Sudden Infant Death Syndrome (SIDS)

Because some victims of shaking exhibit no or only discrete external injuries, it is possible that deaths attributed to SIDS are sometimes in fact caused by shaking (Meadow 1995). Bass et al. (1986), for example, found two definite and one probable case of shaken baby syndrome among 24 consecutive cases of suspected SIDS. An autopsy should therefore be performed on every SIDS victim to exclude mechanically caused non-accidental death.

In contrast, during testimony in court, carers often attribute the SDH to their attempts to waken or revive a child by shaking after finding it lying apparently lifeless in bed. The possible validity of such claims is supported by the observations of Meny et al. (1994, 1996 – see also Poets et al. 1999), who used memory-equipped cardiorespiratory monitors to retrospectively analyze the agonal process in SIDS cases. As expected, they found that most of the deaths were sudden, i.e., they occurred within 20 min of the onset of agony. The agony, however, was prolonged in two SIDS cases, taking almost 2 h in one case (Meny et al. 1994), 4 h and 12 min in the other (Meny et al. 1996). In nine SIDS cases examined by Poets et al. (1999), the monitor alarm was set off by bradycardia in all but two infants. None of the cases exhibited heart block or ventricular tachycardia. Three of the infants were already gasping when the monitor sounded, while gasping began within 2.7 min of the first alarm in another four infants. The gasping lasted from 3 s to 11 min in five infants in whom it was not interrupted by resuscitation.

If the cases just described did represent true victims of SIDS, the following can be said: SIDS victims do not suffer primary acute asystole, but primary respiratory arrest; circulatory arrest may always be delayed. If a child is taken to be "dead" during this phase and an attempt is made to revive it by shaking, it can be assumed that the child's circulation has not stopped and that the shaking could cause an intracranial hemorrhage.

This "theoretical" consideration however is contradicted by the fact that no single case of confirmed SIDS has been found to include SDH and/or retinal hemorrhages, even in cases where a parent or caregiver had attempted to revive the victim by shaking. Moreover, a primary respiratory arrest immediately will lead to brain edema and, therefore, to a secondary reduction or total interruption of cerebral blood flow, which is not compatible with intracranial hemorrhages. It can also be assumed that the shaking administered by distressed caregivers (cf. Sect. 25.1.1) is never of sufficient force to cause the intracranial injuries encountered in shaken infant syndrome. A caregiver would not dare to apply the massive force necessary to produce SDH. The first author to describe shaken baby syndrome (Caffey 1972) attributed the SDH to "mild" shaking, but this could not be confirmed by subsequent authors and apparently only reflected the descriptions of the perpetrators. Moreover, it is questionable whether the cases described by Meny et al. (1994, 1996) and Poets et al. (1999) did in fact represent SIDS victims and not cases with entirely different underlying pathophysiological mechanisms. Each of the infants they described had a history of apnea or other breathing abnormality, which had led to their being monitored in the first place. However, it can be assumed that each of the victims had extremely low blood pressure corresponding to a "vita minima," so that any bleeding would be minimal and insufficient to cause intracranial and retinal hemorrhages as well as cervical epidural hemorrhages.

25.3.7.5 Resuscitation

Resuscitation by health care professionals should not be capable of causing SDH. In very rare instances retinal hemorrhages are found after cardiopulmonary resuscitation in patients with non-traumatic illness. In a prospective study of 43 pediatric patients, Odom et al. (1997) found that punctate retinal hemorrhages occurred in only one eye (see also Amberg et al. 1995).

Other suspected causes of SDH include practices such as tossing a baby into the air to resuscitate it or while playing, acts generally assumed to be inca-

pable of injuring an infant's brain (Case et al. 2001) or cervical cord or of causing retinal hemorrhages.

25.3.7.6 "Rebleed" of Chronic Subdural Hematoma

The death of a child is sometimes attributed to "rebleeding" of an organizing and/or chronic SDH occasioned by repeated episodes of shaking or other mechanical violence. Some infants are shaken on more than one occasion and many are found to have SDHs of varying ages even in the absence of external evidence of abuse (Jenny et al. 1999; Minnasch et al. 1999; Morris et al. 2000). Findings of a rebleeding phenomenon may be evident which may be induced by a non-significant impact. It is important to remember that the natural history of chronic subdural hematoma involves rebleeding from the granulation tissue that is part of the repair process. The acute hemorrhage could be the cause of a significant space-occupying lesion, and may be invariably associated with extreme cerebral injury and bilateral retinal hemorrhages.

But according to recent literature the event of rebleeding after trivial impact or a spontaneous rebleeding from a preexisting chronic SDH is extremely rare (Chadwick et al. 1998), but undoubtedly exists (Hymel et al 2002). A chronic SDH very rarely follows severe head impact in a previously normal person (Case et al. 2001). The hemorrhage is readily resolved and rapidly organized (Duhaime et al. 1996; Lee et al. 1998; Parent 1992) as the resorption process seems to be more rapid and more complete in children than in adults (Gean 1994).

25.3.8 Shaking versus Fall

Persons accused of causing shaking trauma in a child usually state that the child was injured in an accidental fall. If the coverings of the brain exhibit signs of impact, it can be extraordinarily difficult to establish the exact cause of the trauma because the intracranial injuries typical of acceleration are almost identical. This gives rise to the aforementioned dilemma of distinguishing between inflicted and accidental causes of brain injury, especially in the absence of other signs of abuse or objective corroboration of the alleged accidental fall.

In infants and young children, according to Duhaime et al. (1998), the household falls that cause head injuries usually generate low-velocity translational forces; rotational (angular) acceleration is rare (Duhaime et al. 1992). To determine if a child's injuries were caused by a fall, it is important to ascertain the following physical and physiological information (Wilkins 1997 – modified):

- The height from which the child fell.
- The type of surface the child landed on.
- The integrity of the child's forwards and/or sideways protective reflexes.
- Whether the child propelled himself.
- The absolute and relative masses of the child's head and body.
- The proportion of total kinetic energy that was absorbed in deforming the skull, the brain or the rest of the body, and in compressing the ground.
- Whether any kinetic energy was dissipated in causing fractures.
- Whether the child fell flat on the ground or "head first," and/or whether the child landed on a level surface or a pointed or angled object.
- Whether secondary brain damage might confuse the primary injury-induced state, i.e., ischemic encephalopathy from an ischemia from cerebral edema or an unprotected airway. While hypoxia alone does not damage the brain, it exacerbates ischemic brain damage (Miyamoto and Auer 2000) such as might be seen in a compressed brain underlying a subdural hematoma or resulting directly from the impact.

Cory et al. (2001) recently published an extensive biomechanical study on freefall-induced head injuries in infants. They employed a head-impact injury model to examine the basic engineering principles that must be considered to calculate the force of a head impact after freefalls from different heights. Such models may at least indicate whether it is likely that a given injury could or could not have been sustained in the event reported in the case history (provided the event can be "simulated" by a model).

In addition to the above-mentioned morphological changes and basic biomechanical information required in the individual case, both the epidemiological data and further biomechanical considerations associated with falling and shaking are worthy of consideration.

25.3.8.1 Epidemiologic Evaluation

Systematic studies comparing head injuries caused by different types of accidents in children can aid in establishing criteria for differentiating between accidental and inflicted injuries (for survey see Levitt et al. 1994; Alexander et al. 2001). Falls especially from low heights at home very seldom cause serious brain injury (Chadwick et al. 1991; Duhaime et al. 1992). Basically, falls are rarely the cause of death in children (Rivara et al. 1993); severe head injuries – unless caused by motor vehicle accidents – are more often the result of abuse, especially if they are ascribed to a fall from a short height. Last but not least, it is more difficult to distinguish between accidental

and abusive injury if the head injuries are less severe (Hall et al. 1989; Reiber 1993). There are reports however of serious injury or death being caused by falls from slightly greater heights outside or away from the home (Adams et al. 1984; Williams 1991) and rarely also in the home (Hall et al. 1989; Reiber 1993).

Chadwick et al. (1991) reviewed a total of 317 children and noted that falls from heights of less than 1.2 m were never fatal. A study of 45 children who had fallen from a building (a height of 3 m or more = one to six stories) found that only 19 had suffered a head injury and that there was no correlation between the severity of the injury and the distance fallen (Roshkow et al. 1990). Duhaime et al. (1992) found a high incidence of features suggestive of inflicted injury among 34 children with head injury alleged to have been suffered in household falls of under 1.2 m. Some of the toddlers had SDH or retinal hemorrhages and two died. Similarly, two other studies found that severe injuries can be incurred in falls from heights of 1.5–12 m, but never in falls of 1.5 m or less, and that death is very rare even in lengthy falls (Barlow et al. 1983; Roshkow et al. 1990; Williams 1991).

In 1977, Helfer et al. (cf. Nimityongskul and Anderson 1987; Lyons and Oates 1993) reviewed the injuries suffered by 246 children less than 5 years old in a total of 314 falls. The children fell at home in 219 of the falls, at hospital in the remaining 95. The children generally fell from beds or sofas that were elevated 90 cm or less, although several fell from heights of up to 1.5 m. Two of the children sustained linear skull fractures, but none suffered central nervous system injury. In a study of 363 children who had fallen down the stairs, Joffe and Ludwig (1988) found that 22, all 2 years old or younger, had sustained skull fractures.

In contrast, Lehman and Schonfeld (1993) found that 7 of 100 children alleged to have fallen 1.2 m or less had died, but none of 65 children who had fallen 1.5–2.7 m. The total mortality rate was low (0.7%); however, 10% were left with neurological impairment. The alleged cause of death in the children who had died after falling 1.2 m or less proved to be false; all of them had died of physical abuse.

Alario and Duhaime (1990) evaluated the cases of 50 children less than 2 years old, who had been injured under clearly documented circumstances. Half the children were hurt in falls down the stairs, one-third in falls from heights of less than 1.2 m, a few in falls from greater heights. Fourteen of the children sustained uncomplicated skull fractures, six intracranial injuries, and two epidural hemorrhage. Two of the children who fell further than 1.2 m suffered SAH. None of the children developed retinal hemorrhages, and all recovered without neurologic sequelae.

Finally, in their study of 100 young children hospitalized due to injuries incurred in household falls, Duhaime et al. (1992) found isolated epidural hematomas in 3 children who had fallen from a height of 1.2 m or less. Falls from heights greater than 1.2 m produced focal parenchymal cortical hemorrhages in 4 children, focal SAH in 2 others. The clinical course of these children was benign. Of the 24 children with SDH or diffuse SAH, 13 were found to have been the victims of abuse; 3 of these children died of their injuries.

In general, children who fall at home sustain simple linear fractures without significant neurological sequelae. A prospective study of head trauma in 608 infants disclosed a 2% risk of intracranial injury in falls of 0.9 m or less, but no risk of unfavorable outcome (Greenes and Schutzman 1999). Reece and Sege (2000) found the following ratios of accidental to abuse-related injuries in children alleged to have fallen from heights of 1.2 m or less: SDHs were accidental in 8%, caused by abuse in 38%; SAH were 2% accidental, 38% abuse related; retinal hemorrhages were 9% accidental, 25% abuse related.

Another way to establish criteria for distinguishing accidental from non-accidental head injuries is to review cases of proven abuse. Merten et al. (1984) reported that 8% of physically abused children had skull fractures. Hahn et al. (1983) reviewed 621 abused children and found a 12% incidence of head injuries. There is also no doubt that head injury causes the highest incidence of morbidity and mortality among cases of abuse (Weston 1980; Calder et al. 1984).

These observations on the causes of skull fractures in children, especially of linear fractures, are opposed – somewhat surprisingly – by the findings of Weber (1984, 1985) (cf. discussion by Leestma 1989), who dropped dead infants from an average height of 82 cm onto stone, carpets, and linoleum floors. The invariable result was skull fracture. An obvious explanation for this finding is that the children were "dead" and their brains were not perfused by blood.

25.3.8.2 Biomechanical Aspects

According to Williams and Sunderland (2002) during the inquiry, many parents gave evidence of their children being shaken and their concerns:

- "…hanging the baby's chest with the baby shaking like a jelly on a plate…."
- "…my baby was bouncing around on the bed and the head and parts of the body which were not restrained were all moving, it was like they were on a little trampoline."
- "The baby's head would move a lot, it looked to me as though the baby had little spasms running through the body."

It is not known how many times, nor for how long a child must typically be shaken to inflict clinically rel-

evant injury. Because retinal hemorrhages are almost never caused by accidents producing a single oscillation of the head, by automobile accidents for example (Billmire and Myers 1985), two or more shaking-induced oscillations are required. It has been estimated that a child with a mass of 3.8–4.5 kg is typically shaken for 20 s or less during an abusive episode, receiving up to 40 or 50 shakes (Levitt et al. 1994). To inflict brain damage sufficient for clinical detection severe force must be applied. To lift and shake an infant clearly requires the strength of an adult.

The biomechanical result of the shaking process will be best described as a shearing injury (Case et al. 2001). Shearing injury results in shearing stress in the brain induced by rotational movement of the head caused by impact or impulsive loading (Committee on Child Abuse and Neglect Shaken Baby Syndrome 2001). Impact is more likely to produce shearing injury of the immature brain rather than the typical cortical hemorrhages that might occur in older children and adults. The paucity of myelination, the large number of neurons without glial or dendritic connections and the small axonal size predispose the young brain to shearing injury.

Mechanical violence to the head that produces brain injuries is primarily associated with translational and rotational movements, velocities and accelerations of the head. Rotational accelerations are generated by either impact or non-contact inertial mechanisms (impulsive loading), such as whiplash or shaking, which produce accelerations of the head with sudden changes of sign. To investigate the relative contributions of the translational and rotational components of inertial loading to brain damage, Gennarelli et al. (1972) carried out series of experimental tests with monkeys. They found that both components are associated with focal injuries of the brain, while diffuse injuries were seen only when a rotational component was present (Ommaya 1995).

The investigations of Ommaya et al. (1967, 1993) provide experimental verification of the cause of cerebral concussion and intracranial hemorrhages. Anaesthetized Rhesus monkeys were exposed to rotational acceleration of the head without impact to the head. The authors could demonstrate that rotational acceleration of the head exceeding 10,000 rad/s^2 for >20 ms was sufficient to produce experimental cerebral concussion in 50% of the Rhesus monkeys subjected to whiplash. For scaling this animal data to humans, they used an inverse relationship between injury level and brain mass raised to the 2/3 power. The authors deduced that levels of head angular acceleration required to produce cerebral concussion injuries in adult men (brain mass of about 1,300 g) with a probability of 50% are in the order of 1,800 rad/s^2. For infants with a brain mass of 600 g this would mean 3,000 rad/s^2, all for accelerations with durations exceeding 20 ms.

Another experimental investigation was done by Duhaime et al. (1987), who showed that human models, shaking dolls with hinge necks and equivalent massed heads, generated mean angular accelerations of 1,138 rad/s^2, whereas impacts against a hard surface generated a mean of 52,475 rad/s^2. The mean peak tangential acceleration of the head (vertex) was nearly 50 times greater (430 g within a mean time interval of 21 ms) if the head was forcefully stuck against a surface at the end of a shaking series than over the half oscillation of one single shake (9 g within 107 ms). Injury thresholds for infants were only attained at the moment of impact. The same team cited the biomechanical studies of Gennarelli and Thibault (1985) in stating that forces producing a translational or straight-line movement of the center of gravity are generally less injurious to the brain, the effects depending largely on the specific focal contact forces.

Biomechanical studies of brain injury have shown that rotation of the brain about its center of gravity can cause DAI (likely via an internal swirling motion of the normal semi-liquid brain tissue) and SDH. Consistent with these findings, Duhaime and her team (1987) suggest that shaking is not capable of producing the forces needed to cause DAI.

The experimental data of Duhaime et al. (1987) in particular led to the conclusion that pure angular acceleration is an inadequate explanation of the phenomenon of SDH associated with shaking baby syndrome (Geddes et al. 2001a, b; 2003a, b; Uscinski 2002; see also Donohoe 2003). But neither the experimental circumstances using adult primates (Ommaya et al. 1993) nor the calculation based on experiments with a doll necessarily truly resemble the immature human infant skull and brain (Brenner and Fischer 1988; Case et al. 2001) especially as the oscillating movements and forces are not quantified in the biomechanical reconstructions. At this point we additionally have to state that up to this time we do not really know the minimum forces necessary to cause SDH and/or retinal hemorrhage in infants (Kemp 2002; Geddes et al. 2001b, 2003a, b). However, one issue that can definitely be resolved by different experts is that the tossing of a baby into the air or other playful maneuvers cannot cause brain damage as caused by a shaking mechanism (Case et al. 2001).

Alexander et al. (1990) described 24 victims of shaking, 12 of whom exhibited additional external head trauma. In 71% of the cases, they found evidence of prior abuse, neglect or both, and 33% of the children were known to have been shaken previously. Gilliland and Folberg (1996) claimed that 11.3% of the 80 head traumas sustained by the children they studied were caused exclusively by shaking, while 37.5% were induced by shaking combined with blunt impact. Duhaime et al. (1998), in contrast, showed

that almost 85% of cases of shaking also exhibited evidence of impact. Although shaking with impact definitely creates greater force than shaking alone (Duhaime et al. 1987; Hymel et al. 1998), confessions, statements by witnesses, and the absence of morphological signs of blunt violence to the head (Alexander et al. 1990; Gilliland and Folberg 1996; Block 1999) all provide ample evidence that shaking alone can result in fatal brain injury.

The theoretical considerations of Duhaime et al. (1987) contrast with the findings of Ryan et al. (1994), who assert that vehicle-pedestrian collisions generating peak linear accelerations of the pedestrian head of 150 *g* can lead to brain injury with cortical hemorrhages, sometimes even to death, especially if the impact was to the side of the head. Another group described three toddlers who died of alleged blows to the side of the head, with bruising injury in the pinna, ipsilateral SDH, brain swelling, and retinal hemorrhage (Hanigan et al. 1987). They calculated (by extrapolation from adult data) that the acceleration required to produce such injury was much less than that suggested by Duhaime et al. (1987).

In their study mentioned above, Geddes et al. (2001a, b) showed that DAI is not present in the brains of most victims of shaking they examined. In the few cases in which it was found, the axonal injury was interpreted as being secondary to hypoxia–ischemia and/or edema. The same authors, however, supposed cervical cord and low brain stem injuries on the basis of axonal injury at the craniocervical junction (see also Johnson et al. 1995). Like Shannon et al. (1998), who were the first to demonstrate axonal injury in the high cervical cord, Geddes and her team think this pattern is a product of non-disruptive stretch to the neuraxis. They (Geddes et al. 2001b) cite, among others, authors Bohn et al. (1990) and Koch et al. (1998), who showed that infants appear to be liable to high cervical cord injury without evidence of bony injury. Autopsy studies have described bleeding into the perispinal tissue and epidural or subdural hematomas of the spinal cord (see above), testifying to the traumatic effect shaking can have on the craniocervical junction.

Recently Geddes and Whitwell (2004) pointed again to the difficulty that no formal neuropathological studies exist of accidental or non-accidental infant head injury, i.e., there is no definite evidence of any shaking event. In most cases the diagnosis is based only on the clinical or autoptic phenomena of subdural and retinal hemorrhages. The histological study of dura from 50 autopsied children, of whom none suffered a head injury, leads the authors to the suggestion that the subdural and retinal hemorrhages may rather be caused physiologically than by external mechanical violence. The authors indicated the critical role of determining the response of the individual brain to a given insult (Graham et al. 2000), and they emphasized that in a genetically susceptible child any factor may be present that triggers an episode of apnoe sufficiently to cause severe hypoxic brain damage resulting in a subdural and retinal hemorrhage.

In contrast to this hypothesis we have to state that in several cases the offender confess a shaking event. In several cases additional symptoms give further evidence of an impact (see pp. 496 ff). As described above, the absence of signs of axonal injury will be explained by their delayed morphological expression. In contrast, spontaneous intracranial and retinal hemorrhages may only be present in infants with coagulation diseases.

25.3.8.3 Conclusion

Based on the foregoing, the following conclusions can be drawn regarding the shaken infant syndrome (cf. Kirschner and Stein 1985; Duhaime et al. 1998; Oehmichen and Meissner 1999; Kirschner and Wilson 2001):

- Trivial injuries are produced by trivial forces; it takes significant events (blows, shaking, violent impact) to cause life-threatening injuries.
- A lethal injury is characterized by almost immediate onset of severe symptoms: there is virtually no "lucid" or asymptomatic interval.
- If a carer attributes severe head trauma in a child to a fall in the home, the claim should be regarded as false until proven otherwise.
- If an infant is injured in a fall, the carer will immediately seek medical help and exhibit anxious concern about the fate of the child; by contrast, if the child is injured by intentional violence, i.e., physical abuse, the responsible carers will usually wait to see whether the symptoms spontaneously improve; if they do seek medical help for the child it is often after a marked delay.

The diagnosis of shaken infant syndrome will be based – on the one hand – on the explanations and story given by the carer as well as the plausibility of the story, i.e., whether the injuries correspond with the story. On the other hand, we have to accept that the above-mentioned lesions are nearly always specific to shaking-caused injuries, especially in cases with more than one lesion (cf. Sect. 25.3.2). Sometimes bruises of the scalp and/or of the truncus/chest are seen as well as fractures of the skull or of ribs. But these lesions are not common and are non-specific.

Table 25.6. Features seen in suffocated infants but not seen in SIDS victims. Source: Meadow 1990

Features	Suffocation (%)	SIDS (%)
Previous apnea	90	<10
Previous unexplained disorder	44	<5
Greater than 6 months old	55	<15
Dead sibling	48	2

25.4 Asphyxiant Brain Injury

After mechanical head injury, the second most common result of physical abuse of children is asphyxia, which, like shaking, can result in death. Choking at the neck, prolonged squeezing of the chest, gagging of the mouth, or soft smothering or covering of the airway with a plastic bag (Jones et al. 2000) are all capable of inducing potentially lethal asphyxia. Cases of Munchausen syndrome by proxy have been reported in which a parent has repeatedly covered a child's mouth with a hand to induce apnea symptoms (Rosenberg 1987, 2001). As mentioned above in the discussion of Munchausen by proxy, a parent or carer will persistently and secretly simulate and produce illness in a child and repeatedly present the child for medical care (Rosenberg 2001). It is discussed that survived anoxia or repeated episodes of ischemia in children can produce cerebral atrophy and neurological damage, with ventricular enlargement and cortical brain tissue changes; microcephaly is sometimes the result (see below).

25.4.1 Types of Violence

Usually no or only discrete external signs of violence are found on the face, the mouth or nose, or on the throat or thorax. Injuries of the head or trunk may be barely evident as the violence necessary to produce such injuries is comparatively slight. In rare instances discrete scratches or hematomas of the face, throat or thorax can be assigned to lethal suffocation. Such traces however can be so discrete as to be overlooked or wrongly interpreted. Death can also be caused by accidental stenosis or occlusion of the airways, for example if the child swallows a toy or other object (death by bolus). In rare cases accidental strangulation can occur. The death being attributed – like cases of shaken infant syndrome without signs of external injury (see above) – to SIDS instead (cf. Meadow 1990, 1999; Reece and Krous 2001) (Table 25.6). The finding of conjunctival or dermal petechiae is highly suspicious of accidental or intentional asphyxia.

The traumatic effect varies; for example, there may be choking at the neck causing a primary ischemia of the brain or a cardiovascular instability resulting from acute central hypoxia causing secondary compromise of circulation to the brain. If prolonged, obstruction of the carotid arteries will lead to unconsciousness and eventually death. CT scans or autopsy of the neck may reveal characteristic signs of hemorrhages in the muscles and soft tissues of the neck or a major vessel occlusion. The neurologic deficits at the cellular level are related to the cutoff of the oxygen supply to neurons and the resultant inability of mitochondria to continue the molecular cascades of respiration (see Chap. 13, pp. 273 ff).

25.4.2 Compression of the Chest

As already mentioned, accidental death due to asphyxia can result from external compression of the chest that prevents the respiratory thoracic excursions. In children, this can happen if a parent or older sibling lies on top of them while sleeping with them in bed or a child can suffocate after being buried in the sand during play.

The compression of the chest that kills a child can also be intentional (Oehmichen et al. 2000). Petechiae in the face and on the skin of the shoulders and upper limbs are an indication of chest compression. The petechiae are caused by diminished or arrested venous blood flow within the area drained by the superior vena cava. Intentional strangulation of the neck almost always causes facial petechiae only. If petechiae or other signs of injury are absent, suffocation may have been caused by a pillow covering the face. It can be extremely difficult or impossible to distinguish such a death by suffocation from SIDS.

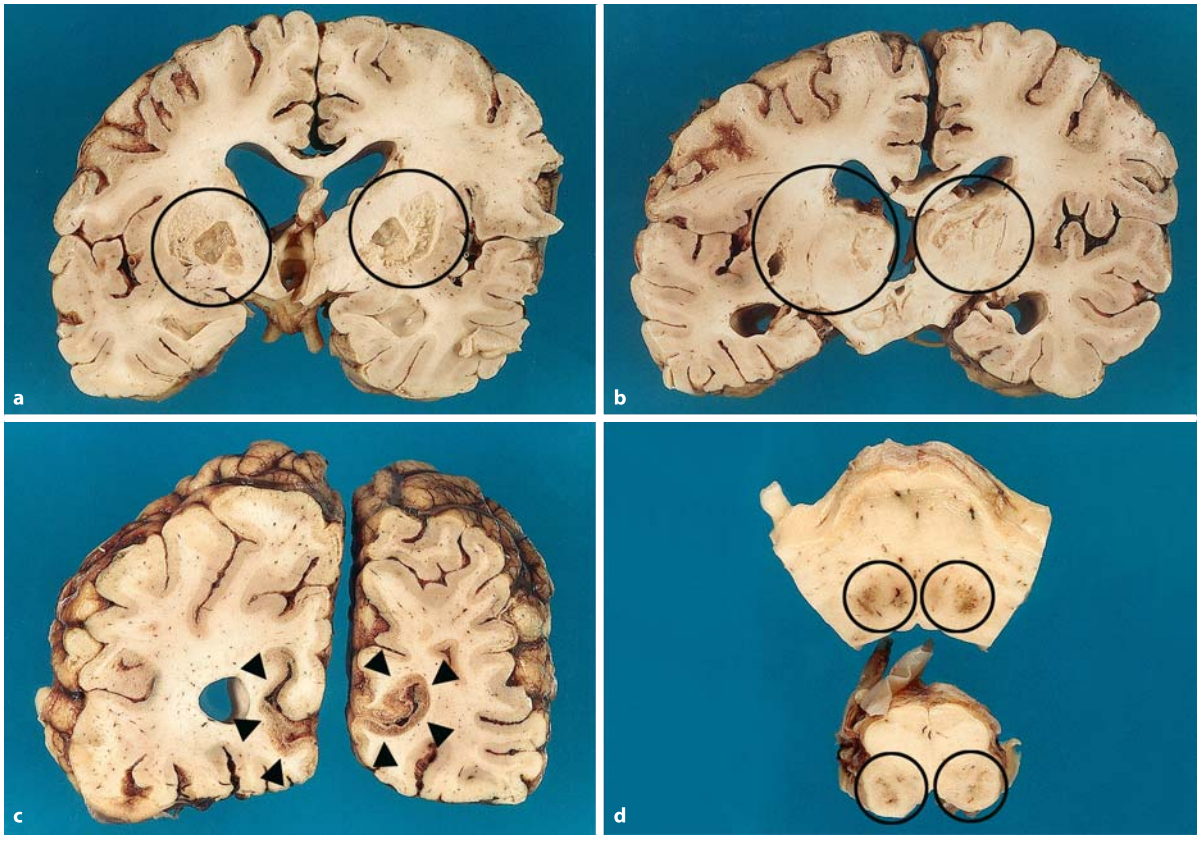


Fig. 25.11a–d. Macroscopic alterations as late sequelae of non-accidental ischemic–hypoxic brain injury in children: bilateral cystic alterations of the basal ganglia as well as generalized external and internal atrophy and hemorrhagic infarction of the occipital lobe (**c**) and discolored brain stem nuclei (**d** – *circles*)

25.4.3 Drowning

Accidental drownings of children are noted with extraordinary frequency in the statistics. It was estimated that in 1998 almost half a million deaths worldwide were caused by drowning, 57% of which were among children aged up to 15 years old (Krug et al. 2002). In the United States, King County, Washington, for example, has annual incidence and mortality rates of 5.5 and 2.6 per 100,000 children (Quan et al. 1989); Florida records an annual incidence of 93 per 100,000 children aged 12 years or younger (Rowe et al. 1977). In 2000, more than 1,400 US children younger than 20 years drowned. Most of these deaths (91%) were unintentional and were not related to boating (National Center for Health Statistics 2000; see also Brenner 2003).

It is noteworthy, however, that many drownings involving infants and young children occur in bathtubs (Feldman 2001). The majority of cases involve accidents for which the carers are – at least in part – responsible (Cohle 1994). As illustrated by the recent case of a mother in Texas who drowned her five children (ranging in age from 2 to 7 years), such deaths can also be intentional (http://edition.cnn.com/SPECIALS/2001/yates/, In-Depth Special, The Case of Andrea Yates).

Non-accidental drownings of this type are termed abusive drowning (Feldman 2001). They usually involve children outside the 8- to 15-month-old age group and histories are inconsistent, including late referral to hospital because a resuscitation is not desired. Gillenwater et al. (1996) determined from other evidence of abuse or inconsistencies in the carer's story that 8% of 205 drownings were, in fact, inflicted. The victims of abusive drowning had a mean age of 2 years and drownings in bathtubs tended to be inflicted. Kamp et al. (1994) reviewed accidental and intentional drowning of children. They found that 20% of bathtub immersions and drownings were suggestive of abuse. Most bathtub submersions, i.e., near drowning, thought to be accidental happened to children aged 8–15 months. In one epilepsy-related drowning, a child with known seizures aged over 24 months was left alone in the bath. The holding of a child's head under water was recently described as a physical control strategy (Smith 1995). Also worthy of mention are drownings in the commission of neo-

natal infanticide, a practice which has deep historical roots (for review see Feldman 2001).

In the absence of consistent or specific external findings, a drowning may be impossible or at least very difficult to diagnose except by autopsy. Moreover, the victim may have died of natural causes before or after entering the water. In a review of 58 childhood drowning deaths, Smith et al. (1991) discovered no homicides, but six deaths due to natural causes unrelated to drowning. In four cases, a prior epileptic event led to immersion. One child had died of a coronary anomaly, another of a ruptured intracranial aneurysm.

25.4.4 Neuropathology

The morphological sequelae of the brain's ischemia are described above (pp. 280 ff). The alterations depend on the duration of the ischemia and on the survival time (reperfusion time). Late macroscopic alterations following a long survival time are seen in Fig. 25.11 (see also Fig. 25.9, 25.10): bilateral cystic alterations of the basal ganglia, external and internal atrophy, and grayish coloring of nuclei in pons and medulla. But during the very early period of the survival time there are no characteristic features. We know that in adults systemic histological changes, evident on hematoxylin and eosin staining, take at least 4–6 h to develop (Adams and Graham 1994), but in infants and children no comparable time interval is described. Pronounced brain edema is generally apparent. In most instances, morphological features are absent: there are no specific symptoms or signs of ischemic injury.

25.5 Toxic Brain Injury

25.5.1 Incidence

In contrast to accidental poisoning (Riordan et al. 2002) abusive poisoning of children is a rare occurrence (for review see Tenenbein 1986). In the US, the American Humane Association reported 222 cases of child abuse by poisoning in 1981 (Fischler 1983). In another study, 31 cases of intentional, non-suicidal, and non-accidental poisoning were found among more than 10,000 cases of toxic exposure, 11 (0.1%) involving children 15 years or younger. None of the victims died as a result of the poisoning (Yamamoto et al. 1991). The number of deadly poisoned children is reviewed by Oehmichen et al. (1994).

Dine and McGovern (1982) reviewed 48 cases of intentional poisoning of children and gave evidence on the type of drugs. A current list of toxic agents is published by Bays and Feldman (2001). With regard to the poisoning of children, however, it is true to a certain extent that only the more severe or unusual cases are published. The literature therefore probably vastly under-reports the number of cases of intentional poisoning of children. Intentional childhood poisoning is usually more lethal than accidental poisoning (Meadow 1989). Rivara et al. (1988), for example, examined 156 victims of poisoning less than 1 year old and found only five fatalities. Only two of the deaths were intentional. Moreover, poisoning is also a common component of Munchausen's syndrome by proxy (Zumwalt and Hirsch 1980).

Among cases of homicidal poisoning, iatrogenic deaths pose a special challenge to investigators. A series of unexplained deaths in a pediatric intensive care ward in San Antonio, for example, was traced to a nurse by a systemic investigation. A number of the deaths were attributed to poisoning with such drugs as digoxin, potassium, phenytoin, chloral hydrate and phenobarbital, administered both singly and in combination. Although the nurse was never charged with any of these deaths, she was later convicted of giving an overdose of non-prescribed insulin to a child in the same hospital (Istre et al. 1985). In Toronto, a suspiciously high number of deaths due to intravenous digoxin intoxication in a children's hospital were all found to have occurred during the work shifts of one particular nurse (Buehler et al. 1985); subsequent investigations however failed to identify the perpetrator.

Much more common than intentional poisoning is exposure of the child to poisons originating from the carer, e.g., to the nicotine in cigarette smoke (nicotine poisoning), or administered by the caregiver, e.g., alcoholic beverages given to a child to promote sleep or as a sedative.

Special problems arise in newborns of alcohol- or drug-dependent mothers. They develop withdrawal symptoms after delivery. With breast-fed infants the question arises as to whether relevant amounts of alcohol can be transmitted via the mother's milk (Tolis 1965). A calculation of the amount of alcohol an infant would ingest in this manner [100 ml of milk with a 4‰ alcohol concentration ingested by an infant weighing 5 kg produce 0.064‰ alcohol concentration of serum in the child (Oehmichen and Schmidt 1984)] shows that it would be insufficient to induce intoxication. It cannot be excluded, however, that chronic exposure to alcohol in breast milk could have a harmful effect on the motor development of an infant (Little et al. 1989).

Accidental iatrogenic poisoning of children is certainly much more common than once thought (Brockstedt 1994) (see Chap. 16). Even today, the dos-

Table 25.7. Clinical features suggestive of abusive poisoning. Source: Bays and Feldman 2001

Age
Younger than 1 year or between 5 and 10 years
History
Non-existent, discrepant, inconsistent or changing
Does not fit child's development
Previous poisoning in this child
Previous poisoning in siblings
Does not fit circumstances or scene
Third party, often a sibling, is blamed
Delay in seeking medical care
Toxin
Multiple toxins
Substances of abuse
Bizarre substances
Presentation
Unexplained seizures
Life-threatening events
Apparent sudden infant death syndrome
Death without obvious cause
Chronic unexplained symptoms that resolve when the child is protected
Other evident of abuse or neglect

ages for many medications administered to infants and children are based on guidelines originally established for adults. Because the specific physiological and metabolic situation of the child is not taken into consideration, overdosing – or even underdosing – is possible, sometimes resulting in death.

25.5.2 Clinical Features and Neuropathology

The signs and symptoms of abusive poisoning are summarized (Table 25.7). Poisoning should not be excluded as a possible cause of death without toxicological screening for prescription drugs or illicit substances. Such screenings, however, may raise more questions than they answer because the toxic effect of particular levels of substances in infants is often unknown (Naumberg and Mony 1988). Moreover, screening for a panel of toxicological agents does not exclude missing other possibly lethal substances.

Poisoning often leaves no or only discrete morphological signs. Suspicion therefore requires an investigation of the scene of the poisoning, a thorough case history, and a drug screen. Forcing a substance into the mouth of a child, for example, may produce injuries in the buccal mucosa and the frenulae of the upper and lower lips. The neuropathological findings are described above (Part IV: Intoxication, Chaps. 17–19).

25.6 Obligations of an Expert Witness

The task of the physician who is called as an expert witness to examine living injured infants differs from that of the pathologist examining a child at autopsy. The medicolegal aspects of dealing with living victims of child abuse and the duties of the physician as expert witness are described in detail elsewhere (Oehmichen and Meissner 1999; Myers 2001). They include among other things assessment of the child's own testimony (exclusion of statements suggested by the interviewer), physical examination of the child and interpretation of the results, radiological examination, and thorough documentation of all findings.

The physician also has obligations with regard to civil authorities (youth welfare department, public health department, public prosecutor's office, etc.). What are the circumstances under which a physician is obliged by law to inform the police or other appropriate authority of suspected abuse and when is a physician justified – or obliged – to remain silent? The primary consideration here should be whether informing the police or civil authorities will help the child or possibly expose it to greater danger from its abuser(s).

Independent of specific laws, the primary concern of the physician as expert witness is always the physical and mental well-being of the child. The physician must always assume that the child does not choose to suffer physical or mental abuse or sexual assault. The duty to remain silent, if for example the child's carers insist they have provided confidential information that should not be reported to the authorities, is always of only secondary importance. The responsible physician should always report abuse or neglect to the proper authorities if there is "cause to believe," or "reasonable cause to believe," that abuse has occurred, or in the event of "known or suspected abuse," or after "observation or examination which discloses evidence of abuse" (Myers 2001).

The pathologist as expert witness has cause to suspect abuse or neglect if at autopsy he detects the

Table 25.8. Questions to be answered by the forensic pathologist as an expert witness. Source: Kirschner and Wilson 2001

1. Was death due to injury, neglect, or complications of injury or neglect?
2. If related to injury, what was the mechanism of injury?
3. Was the injury consistent with the alleged history or circumstances of injury? If not, why not?
4. When did the injury occur in relation to the time of death?
5. Did a delay in seeking medical care contribute to death? If so, could the delay be considered unreasonable?
6. Did death result from a single episode or multiple episodes of injury?
7. Were drugs or poisons involved in the death?
8. If neglect was involved, what form did it take?
9. If there is evidence of failure to thrive, was this due to metabolic disorder, other disease, or neglect?
10. To what extent did environmental, nutritional, and social factors contribute to death?

changes listed in Table 25.8 and will be called upon to answer the questions given in the same table. These questions must also be answered by the forensic neuropathologist as expert witness, with particular reference to specific organic findings and the general pathological findings.

The basic task of the forensic neuropathologist, however, is to differentiate between accidental and non-accidental injury. In cases of non-accidental injury, he must determine whether the injury was voluntary or involuntary. The decisive criteria in making these determinations are:

- The number of injuries
- The localization of the injuries
- The type of injuries
- The age of the injuries
- The plausibility of the explanation provided by the carer

If it is determined that a child has died from non-accidental injury, the victim's siblings are at risk if the perpetrator is not aware that his acts led to the death. The question of "punishment" is thus always also a question of preventing further misdeeds.

To avoid legal and/or procedural difficulties with scientific and medical evidence, the Royal Commission on Criminal Justice has recommended that scientific matters of direct forensic bearing be sorted out and defined (Shepherd 1993) prior to trial. The expert has to consider the following scenarios (cf. Roberts 1999).

Before trial, a case is mistakenly pursued due to unwarranted reliance on medical evidence that turns out to be weaker than the lawyers had thought it to be (or were led by expert to believe).

At trial, the medical evidence is challenged and found wanting; a physician for example has relied too uncritically on his own conclusions while failing to admit the existence of other, equally likely, explanations for the clinical or autopsy findings. After trial, the surviving victim may continue to suffer not only from the physical injury, perhaps for life, but may also have to endure the social isolation and psychological consequences of a shattered family life.

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Clinical Neuropathology VI

Basic Principles

26

It is not the intention of the present chapter to present clinical neuropathology in all of its complexity. Instead the focus will be mainly on *sudden and unexpected death* attributable to intracranial disorders and/or functional disturbances of the CNS in adults. Similar naturally occurring processes in children are discussed elsewhere (pp. 451 ff). C*erebral diseases* coincidentally associated with sudden, unexpected death or resulting from initially survived external violence such as impact or intoxication are additionally treated here. Because the neuropathologist is often confronted with such disorders in connection with forensic questions, they are relevant to the topic of the present volume. Diseases of the latter type can lead to death due to generalized cerebral or extracerebral processes or events. Typical chronic or acute neurological disease processes that do not lead directly to death, i.e. multiple sclerosis will be shortly discussed, but the usual spectrum of neurological diseases whose pathology is the subject of textbooks on clinical neuropathology, will not be described here.

26.1 Sudden, Unexpected Death

26.1.1 Definition

Sudden, unexpected death is a death that occurs in persons in apparently good health or after rapid worsening of a minor illness. Mason (1995) defines it as follows as "an unexpected death following so rapidly from the onset of symptoms that the cause of death could not be certified with confidence by a medical practitioner familiar with the patient." Black and Graham (2001, 2002) have discussed the different uses of the terms "sudden" and "unexpected" death. What interval between the onset of symptoms and death can be described as "sudden?" The World Health Organization accepts a maximal interval of 24 h (Knight 1996). This is regarded as being too long by some authors who prefer a much shorter interval of "within a few hours of apparently good health" (Simpson 1947) or of "one hour" (Knight 1996).

The definition applied in a given instance is dependent to a large part on the circumstances of the particular case. If one is seeking information for insurance purposes as to the statistical risk of an acute death occurring during hospitalization (Shafer et al. 1990), different criteria will apply than if information is being sought for purely forensic-diagnostic reasons. Shafer and his team (1990) prefer applying an operational classification for a neurology service by using specific predictors developed and validated for such a service.

The definition we use places less weight on the time interval than on the "surprise effect" (Berg and Fricke 1992), i.e., "sudden" is used in the sense that any death with a very rapid onset is unexpected. An "unexpected" death, by contrast, can occur slowly over a prolonged period of time, the victim being discovered dead to everyone's "surprise" at a time when the death is not expected. Hecht and Löffler (1984) speak therefore of the "expectation improbability."

Though the terms "unexpected death" and "unexplained death" are partly synonymously used, the term "unexplained" needs a further clarification. "Unexplained" does not designate cases that remain unexplained after full postmortem examination, but cases that are unexplained at the time of death, i.e., before autopsy and final analyses have been completed.

26.1.2 Epidemiology

The first (very early) epidemiological study was done by Kuller (1966; Kuller et al. 1967) while the most extensive study was carried out by Janssen and Naeve (1975). In their study of 40,444 deaths they found that 22,321 (55.2%) could be classified as unexpected deaths from natural (non-traumatic) causes. This finding agrees with that of a smaller study of about 1,000 cases which also reported about 50% of the deaths to have been acute and unexpected (Berg and Fricke 1992). If the cause of death is assigned to the principle organ system involved, all studies [as summarized by Berg and Fricke (1992)] found the heart and circulatory system to predominate (40–70% of cases), with the central nervous system following far behind (4–24% of cases).

Among the CNS diseases that are most likely to lead acutely and unexpectedly to death, epilepsy is listed as being absolutely predominant by the aforementioned Glasgow studies (Black and Graham 2001, 2002), followed by spontaneous subarachnoid hemorrhage. A somewhat older study (Shafer et al. 1990), which assumes an interval of 30 days between onset of symptoms and death, reported the following diseases, necessary medical measures, and/or symptoms, to be associated with acute death:

1. AIDS with central nervous system involvement
2. Intubation in or out of the emergency room
3. "Found on floor" at age >64 years
4. Coma with structural lesion on cranial CT or lateralizing exam if CT not done
5. Stroke with hemiplegia
6. Stroke with loss of consciousness
7. Subarachnoid hemorrhage, not induced by external violence
8. Status epilepticus
9. Intracranial hemorrhage, any cause, any size
10. Cancer primary to CNS or metastatic to brain or cord or cauda equina
11. Deep coma of any cause
12. Bacterial meningitis
13. Severe quadriplegia

26.1.3 Classification

We have already referred above to the following differentiation:

1. Sudden death from intracranial diseases
2. Sudden death with an accompanying cerebral disease in cases of generalized and/or extracerebral processes

This differentiation should be compared with another classification referred to elsewhere (Oehmichen and Gerling 1992).

26.1.3.1 Neuronal-Mediated Death

Neuronal-mediated deaths have already been discussed elsewhere in this volume, including Chap. 2. The cortical regions are known to have a direct effect on the hypothalamic nuclei, while in the hypothalamus and pituitary gland regulation occurs at the neurohormonal and immunological level [see Adinolfi (1991) among others]. Feedback mechanisms are also able to directly influence the cortex. This functional network allows the thesis that an acute death can also result from cerebral-somatic and cerebral-psychological causes (Angell 1985; Williams 1990; Pedal et al. 1996; Kernbach-Wighton et al. 2003).

The burgeoning field of neurocardiology, the study of brain–heart interactions (Cechetto 1994), has been of great assistance in our understanding of sudden death. It is clear that autonomic control of the heart rate and rhythm extends above the spinal, brain stem, and hypothalamic axis (Cechetto and Saper 1987; Cechetto and Chen 1990), and that the highest level of autonomic control is the cerebral cortex (Yasui et al. 1991; Butcher and Cechetto 1995). Studies of cardiac chronotropic sites in the posterior insular cortex, for example, have shown tachycardia represented rostrally and bradycardia caudally (Oppenheimer and Cechetto 1990). Cortical stimulation can produce lethal cardiac arrhythmias (Oppenheimer et al. 1991). Cerebrogenic cardiac arrhythmias and their role in sudden death have been reviewed (Oppenheimer et al. 1990). Cerebral arrhythmogenesis is a topic most germane to the medicolegal pathologist faced with a paucity of anatomical findings to explain asphyxial, hypoxic, athletic or epileptic deaths, or deaths where there is brain disease on first glance insufficient to explain death.

We know from sudden death in athletes, sudden death in epileptic patients (SUDEP), sympathetic dyadic death in the elderly (where death of one spouse is followed shortly by the death of the other), cardiac arrest in subarachnoid hemorrhage and from the inevitable heart stoppage in respirator brain (brain

death) (Auer and Sutherland 2002), that coronary occlusion or other heart structural abnormality is not necessary for the heart to stop. Cases of delayed death 4 days after hanging (Hausmann and Betz 1997) or 2–3 days after CO poisoning (Opeskin and Drummer 1994) can be considered neurocardiac death. Brain disease or brain injury must act via a final common pathway of either heart stoppage or cessation of breathing in order to cause death. These forms of death seen with antecedent brain injury, or with overstimulation of the heart caused by the brain, attest to the powerful trophic influence of the brain on the heart for its continued normal rhythmicity and long-term function.

But we must state: a neurocardiac death as described above will never occur in healthy young patients other than highly exertional athletes. The prerequisite will be a primary cardiac pathology (athletes, elderly) or a primary brain pathology (epilepsy, subarachnoid hemorrhage, brain damage caused by hanging or CO poisoning).

Moreover we know of centrally induced *pulmonary edemas* which are especially common as a result of mechanical brain injury (MBI) in the form of so-called neurogenic edema of the lung (Graf and Rossi 1975). An *acute central respiratory arrest* is regularly seen after herniation secondary to an intracranial space-occupying process or compression of the respiratory center. The *swallowing reflex* can be disturbed by injury of the CNS: individuals under the influence of alcohol or toxic agents, or with traumatic or age-related cerebral atrophy are particularly at risk of asphyxia due to aspiration of vomitus into the respiratory tract or from alimentary bolus (Mallach and Oehmichen 1982).

26.1.3.2 Death Associated with Vascular Diseases

Vascular diseases will be discussed below. Here only the following will be mentioned:

Luminal stenosis or luminal occlusion and/or reduced or arrested perfusion can lead via local or generalized O_2 deficiency to an acute and unexpected central regulation failure, in the sense of hypoxia or ischemia. A typical example of sudden, unexpected death is massive intracranial bleeding, which can lead via an acute space-occupying process to herniation. Rapid tumor growth accompanied by tumor hemorrhage in primary neurogenic tumors – more often however in metastases – can quickly result in a space-occupying event, even if the tumor had previously produced no neurological deficits. Tumors especially prone to bleeding include oligodendroglioma, glioblastoma, metastatic melanoma, and the rarer choriocarcinoma. Hypoxia and bleeding can have many causes. According to the Harvard Study (Mohr et al. 1978), predominant among brain vessel diseases are thrombosis (53%), embolism (31%), intracerebral bleeding of unknown cause (10%), and subarachnoid bleeding due to aneurysm or angioma (6%).

26.1.3.3 Death Associated with Inflammatory Diseases

Inflammation of the CNS is usually accompanied by systemic clinical and pronounced somatic, neurological or psychopathological symptoms, which usually require emergency medical or clinical treatment before death. Despite this fact, inflammation of the CNS is often a diagnosis, sometimes even surprising and unexpected, that is first made at autopsy.

For death to be unexpected under these conditions there must be an absence of prior symptoms, a misunderstanding of the true nature of the illness, or poor observation by others. Inflammation can lead to acute death in infants or children, in isolated elderly persons, the homeless, alcoholics, and drug addicts.

26.2 Further Cerebral Diseases of Forensic Significance

There are numerous types of death that, while not being sudden or unexpected, must still be diagnosed and assessed by the forensic neuropathologist:

- Delayed (secondary) death resulting from injury or intoxication
- Deaths, the causes of which cannot be explained clinically or by autopsy alone
- Deaths due to neglect and/or failure of medical treatment

We will not present the entire spectrum of such diseases and their sequelae here, but limit our comments to the following two disease groups:

1. Nutritional and metabolic insults
2. Degenerative diseases of the elderly

In both groups the same questions must be addressed by the forensic scientist:

1. Which disease of the CNS is present (diagnosis)?
2. Is there a causal connection between the disease and the death?
3. Could the disease have been prevented under distinct conditions?
4. Was the death itself preventable?

Since a large percentage of the diseases are accompanied by dramatic psychopathological changes, the forensic neuropathologist must often answer a number of other questions as an expert witness; for example,

was the deceased able to act or to think clearly, i.e., legal capacity for the last will, to decide, etc. Since the number of such cases is on the increase both in the clinic setting and in the context of forensic autopsy, an interpretation of the neuropathological findings in terms of cerebral (intellectual) function appears to be unavoidable (Stewart et al 2004).

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Seizures and Epilepsy

27

Seizures are abnormal episodic events regarded as a pathological functional state of the CNS. They are sudden, acute, and involuntary disturbances of consciousness that are usually combined with sensory and/or motor paralysis or abnormal reactions such as prickling sensations, aching/tenderness, and/or clonic or tonic cramps or spasms. *Epilepsy* by contrast is a chronic disease of variable pathogenesis that is characterized by paroxysmal sensory or motoric events, i.e., by seizures. Although seizures are characteristic of epilepsy, they are not specific to the clinical diagnosis of epilepsy. Epilepsy is the most common neurological disorder in clinical medicine, while seizures represent a non-specific "symptom."

27.1 Classification

Seizures and epilepsy can be classified according to a number of criteria, including the cause, phenomenology, age at onset, the pathogenetic background, and the topography of the focus stimulating the electrical excitation.

Depending on the pathogenetic background, seizures can be of idiopathic or of symptomatic type. The *phenomenology* (Lothman and Collins 1990) involves a basic distinction between focal, i.e., partial, and generalized seizures. There are two types of *partial seizure*:

1. Simple partial seizures, which do not impair consciousness (also known as focal motor, sensory seizures or as Jacksonian motor seizures or psychomotor seizures).
2. Complex partial seizures, which do involve an alteration or loss of consciousness (alteration of emotion, cognition or memory), or an impairment of consciousness (blank stare and/or automatisms).

There are two types of *generalized seizures*:

1. Non-convulsive seizures, usually seen in children, are sometimes associated with no motor or sensory deficits (petit mal) or atypical absence. Whether an absence is typical or atypical can be determined by the type of EEG abnormalities.
2. Convulsive seizures, marked by bilateral motor convulsions and sometimes combined with tonic-clonic (grand mal) manifestations or myoclonic movements.

Pathogenetically, a seizure is defined as a dysfunction in the gray matter of the brain. Seizures are caused by an excessive abnormal paroxysmal, synchronous discharge in neurons and they may become so generalized as to involve all neurons of the brain. Rarely

do seizures last more than 1 or 2 min and they are often followed by a postictal state of depressed neurological function lasting for minutes or hours.

A variety of acute insults can induce seizure and, because *seizures have many causes*, one of the main tasks of the physician is to identify – if possible – the specific etiology of the seizure. A seizure is always a very serious symptom of CNS disease the cause of which must be elucidated. Seizures can be associated with almost any CNS disease or with generalized disease such as metabolic encephalopathies (Lothman and Collins 1990; Honavar and Meldrum 1997).

Regarding *pathogenetic aspects*, three different types of epilepsy have been distinguished, each associated with partial or generalized seizures. These three types can only be differentiated on the basis of extensive diagnostic measures, including a thorough check of the family history and the patient's medical history combined with neurological, EEG, and CCT examinations. In some cases of inherited, i.e., familial epilepsy in the sense of infantile or childhood epilepsy, supplementary genetic investigations should be performed (Leppert et al. 1993; Rees and Gardiner 1994). The three types of epilepsy are as follows:

1. *Idiopathic epilepsies*, i.e., obviously genetically caused epilepsies, which occur mainly in infants and children. These account for as many as 40% of all epileptic diseases in childhood, and are characterized by oligogenic or multifactorial inheritance (Steinlein 1999). Recently specific gene defects have been linked to certain epileptic syndromes. Mutations in the CHRNA4-gene, which codes for the α4-subunit of the neuronal nicotinic acetylcholine receptor, have been linked to autosomal dominant nocturnal frontal lobe epilepsy, while defects in the voltage-gated potassium channel gene KCNQ2 are known to cause benign familial neonatal convulsions.
2. *Cryptogenic epilepsies* of unknown etiology.
3. *Symptomatic epilepsies* are associated with perinatal asphyxia or hemorrhages, malformations, tumors, infectious and metabolic insults, mechanical violence and intoxications, and arteriovenous malformations and stroke. They constitute about 80% of all epilepsies in adults (Peiffer 1963).

Epilepsies can be differentiated according to the affected age group as follows:

- *Neonatal period*
  The predominant cause of epilepsy in this age group is hypoxic–ischemic encephalopathy (40%), followed by infections (16%) (Kellaway and Mizrahi 1990). The prognosis depends on the extent of the brain damage, hypoxic–ischemic encephalopathy being associated with a positive outcome in only 16–50% of patients; subarachnoid hemorrhage-induced seizures, by contrast, have a normal outcome in 85–90% of patients, late-onset hypocalcemia in 95–100%. Preexisting developmental defects and intraventricular hemorrhage are associated with a very poor outcome (Aicardi 1986). Idiopathic convulsions are associated with a good prognosis, as are isolated postasphyxial seizures observed on less than 2 days and not involving severe clinical and EEG abnormalities (André et al. 1990).
- *Febrile seizures in infants up to age five*
  Febrile illness in infants up to the age of 5 years can lead to generalized seizures. Febrile seizures have a higher incidence (about 2.7%) than epilepsy (cf. Hauser et al. 1985; Verity and Golding 1991). They must be differentiated from convulsions secondary to CNS infections (meningitis, encephalitis). Simple febrile convulsions are of short duration and have no appreciable sequelae. If a convulsion lasts longer than 15–30 s or if two, three or more convulsions occur within 24 h, or if there are sustained focal features, it is more likely that there will be neurological or behavioral impairment, or the occurrence of subsequent complex partial seizures (Annegers et al. 1987). Generalized epilepsies with febrile seizures have a dominant inheritance with a specific defect in cerebral sodium channels; they vary widely in severity within affected members of the same kindred group (Camfield and Camfield 2002).
- *Seizures during adolescence* (<30 years of age)
  These seizures are predominantly trauma induced or they occur secondary to tumors and infectious diseases.
- *Seizures in adults* (>30 years of age)
  As a rule, seizures in adults are caused by tumors, vasogenic processes or infectious diseases. Another frequent cause is alcoholism – acute intoxication and alcohol withdrawal both being able to trigger a seizure. Because epileptics often have difficulty in social adjustment, they have a tendency to alcoholism. Thus, for a number of reasons the combination of epilepsy and alcoholism is relatively common.

Symptomatic seizures can also be classified according to the *site of the focus* giving rise to the electrical discharge, as follows:

1. *Frontal lobe seizures*: frontal lobe injuries are associated with a predisposition to generalized seizures, especially status epilepticus.
2. *Temporal lobe injuries* predispose especially to psychomotor seizures.
3. *Occipital lobe epilepsy* is a benign epilepsy.

27.2 Clinical Features

Not all seizure-induced changes will be discussed here, at most examples of only the main types.

Simple partial seizures affect sensory or motor functions without disrupting consciousness; they are characterized by flashing lights in a visual field or by jerking of a single extremity.

Complex partial seizures are synonymous with limbic system or psychomotoric temporal lobe seizures. Consciousness is disturbed but not necessarily lost. The seizure often begins with an aura, i.e., the victim is briefly aware of an abnormal sensation such as a strange odor, intense fear, or a rising feeling in the abdomen. This is followed by a phase of unconsciousness in which the patient remains immobile and has a blank stare. Some victims experience automatisms, i.e., involuntary stereotyped motor activities such as fumbling with clothes or lip smacking.

Absence seizures (petit mal) are most common in children and adolescents. They feature attacks of impaired consciousness lasting 2–10 s and are associated with blinking, rolling of the eyes, etc. Absence seizures are associated with a three per second spike and wave EEG abnormality.

Generalized convulsive seizures (grand mal) sometimes begin with a loud cry. The victim falls down in rigid extension for 15–20 s, becomes cyanotic, salivates, and often loses bladder and bowel control. The primary tonic phase blends into a clonic phase of rhythmic-limb contractions lasting another 20–30 s. The victim then slowly regains consciousness over a period of several minutes, but remains drowsy for several hours. Postictal headache and muscle soreness are not uncommon.

Status epilepticus designates seizure activity that may be continuous or intermittent without intervening recovery and can last as long as 60 min (or longer) in adults or 30 min in infants and children. Status epilepticus if generalized constitutes a medical emergency that even today has a high morbidity and mortality. It strikes individuals that have been seizure-free or with known epilepsy. The most common cause of status epilepticus in the latter group is non-compliance in taking anti-epileptic medication. In patients with no history of epilepsy the usual causes include cerebrovascular diseases and drug overdose, but mechanical brain injury (MBI), tumor, cardiac arrest, and withdrawal from alcohol are also common. Poor outcomes are associated with precipitating circumstances such as cardiac arrest and MBI, with hyperpyrexia and seizure lasting more than 2 h (Aminoff and Simon 1980), at which time epilepsy-induced neuronal necrosis becomes significant, even if oxygenation is upheld (Nevander et al. 1985).

Myoclonus epilepsy involves precipitous shock-like involuntary movements of short duration triggered by muscle contractions or muscle inhibitions arising from the CNS. The jerks may be single, multiple or repetitive and involve a single muscle or groups of muscles. The underlying diseases are heterogeneous and uncommon.

27.3 Etiology of Symptomatic Epilepsy

Demonstration of brain disease or brain malformation may explain the induction of seizures or the cause of epilepsy in cases of symptomatic epilepsy.

Bacterial or parasitic (meningitis, encephalitis, and brain abscesses) *brain infections* are often associated with epilepsy (Annegers et al. 1988), whereas viral infections rarely induce seizures.

Brain tumors (Büttner et al. 1999) and cerebral infarcts were the most frequent causes identified by Dam et al. (1985) in 221 patients aged >25 years. Epilepsy in the presence of *cerebral neoplasms* has an incidence of 35% (LeBlanc and Rasmussen 1974). According to Ketz (1974 – see also Kasper et al. 1999) seizures are associated with oligodendrogliomas (71%) and astrocytomas (59%), followed in order of frequency by meningiomas (37%) and glioblastomas (29%). According to Wolf and Wiestler (1993), gangliogliomas predominate (47%), then piloid astrocytomas (20%), astrocytomas grade II (10%), oligodendrogliomas grade II (11%), and dysembryoplastic neuroepithelial tumors (7%). Seizures may be caused by *vascular processes* (arteriosclerotic strokes, etc.) and *vascular malformations*. Indeed, any cause of GABA-ergic neuron destruction or inhibition may cause epilepsy, since the brain is dependent on the balance between excitation and inhibition to avoid epilepsy, and GABA is the chief inhibitory neurotransmitter.

The risk of developing *post-traumatic epilepsy* is related to the severity, type, and localization of the injury. A study of 500 soldiers from World War II suffering non-missile closed head injury found that 6% had post-traumatic epilepsy (Philips 1954). In 820 men who had suffered gunshot wounds with depressed skull fractures and dural penetration the incidence was 54% (Russell and Whitty 1952).

Depressed skull fractures, dural penetration, cortical laceration, intracerebral hemorrhage, loss of brain tissue, and foreign materials (e.g., fragments of bone or bullets) embedded in the brain can all increase the risk of post-traumatic epilepsy (Salazar et al. 1985). Seizures that occur soon after a traumatic event indicate an increased risk of late epilepsy. Russell and Whitty (1952) found the incidence of epilep-

sy to be highest if the parietal lobe and motor area were injured.

27.4 Pathogenesis

Epileptogenesis involves multiple factors such as trauma, healed abscess scars, ischemic lesions, and surgical interventions (Pollen and Trachtenberg 1970). Hoeppner and Morrell (1986) showed that the collagenous component of a scar played a greater role in epileptogenesis than the glial component. It is difficult to diagnose and classify cases where there is *perinatal brain damage* or *cerebral malformations* rather than distinct brain diseases. In such cases the epilepsy may be explained by cortical architecture defects and aberrant neuronal arrangement or other types of defective neuronal migration (Peiffer 1993; Honavar and Meldrum 1997). The malformations also include cortical malformations that can be identified by MRI (Barkovich et al. 1996) or microscopy (see Kasper et al. 1999): neuronal clustering throughout cortical layers II through VI, prominent perivascular clustering of oligodendroglia in white mater, proliferation of single heterotopic neurons in white matter, and glioneuronal hamartomas. Cortical malformations were found to be a major cause of epilepsy in children (Lagae 2000).

27.5 Pathophysiology

Convulsive and non-convulsive epilepsies have complex pathophysiologies. Recent findings have been provided mainly by animal experiments (Ure and Perassolo 2000).

Both GABA-ergic inhibitory postsynaptic potentials (IPSP) generating high-rate action potentials and the absence of focal epileptogenic depolarizing shifts have been recorded in the cortex and thalamus during spike and wave discharges in experimental epilepsy. Long-term activation of *N*-methyl-D-aspartate (NMDA) receptors with agonist has been shown to block absence attacks, produce a tonic depolarization of thalamic neurons, and to decrease the occurrence of low-threshold calcium current (Snead 1995). Such depolarization conductance can be activated by the NMDA receptor, which is one of three classes of excitatory amino acid receptor present in the human brain. Conductance activated by the NMDA receptor has a number of unique characteristics compared to those activated by the other two classes of excitatory amino acid receptors (the kainate and quisqualate receptors) or by the inhibitory amino acid GABA. The channel is coupled to the NMDA receptor and to several regulatory sites.

The full sequence is as follows: (1) IPSP mediated by NMDA; (2) slow IPSP mediated by $GABA_A$ and $GABA_B$ receptors; (3) low-threshold calcium current; and (4) renewed depolarization and start of a new cycle.

An essential element of the cycle is hyperpolarization, which improves the conductivity of voltage-dependent calcium currents (T channels), thus producing sodium-dependent action potentials and repolarization via voltage-dependent potassium currents. Depolarization opens the calcium channels, hyperpolarization of the membrane potential closes them. When open they allow calcium to flow into the cell, creating further depolarization and activating potassium channels that allow potassium ions to move out of the cell, thus hyperpolarizing the cell and inactivating the calcium channels.

Each complex of spike and wave discharges is thought to originate in the cerebral cortex. Oscillatory patterns require the integrity of the thalamocortical circuits that comprise specific and non-specific thalamic neurons. Epilepsy is thus not so much a single derangement of some nerve cells but a network dysfunction.

Temporal lobe attacks are generally thought to arise in the hippocampus, where most patients have an astrocyte proliferation and loss of CA1 and CA3 neurons. In adult animals proconvulsive treatments can induce recurrent discharges that start in CA3 and spread to CA1, whereas ictal events are generated when the hippocampal area undergoes an increase in potassium or a decrease in calcium or magnesium (Traynelis and Dingledine 1988). Due to their very high calcium conductance and profuse disposition of recurrent axonal collaterals, pyramidal CA3 cells can act as interictal spike pacemakers. The CA1 region itself can maintain seizures without previous interictal spikes (Lothman and Collins 1990).

27.6 Epidemiology

With an incidence of 20 to 70 per 100,000 per annum (Sander and Shorvon 1987), seizures are among the most common neurologic disorders in clinical medicine (Lothman and Collins 1990). Their incidence is highest in the first year of life (Ellenberg et al. 1984), and decreases thereafter until rising again after the age of 60. In the USA, seizures occur in approximately 1.8/1,000 to 5/1,000 live births and can be triggered by any condition affecting neonatal brain function (Tharp 2002). Epilepsy has a high prevalence in developing countries that is attributed to perinatal brain damage, intracranial parasitic infections, head

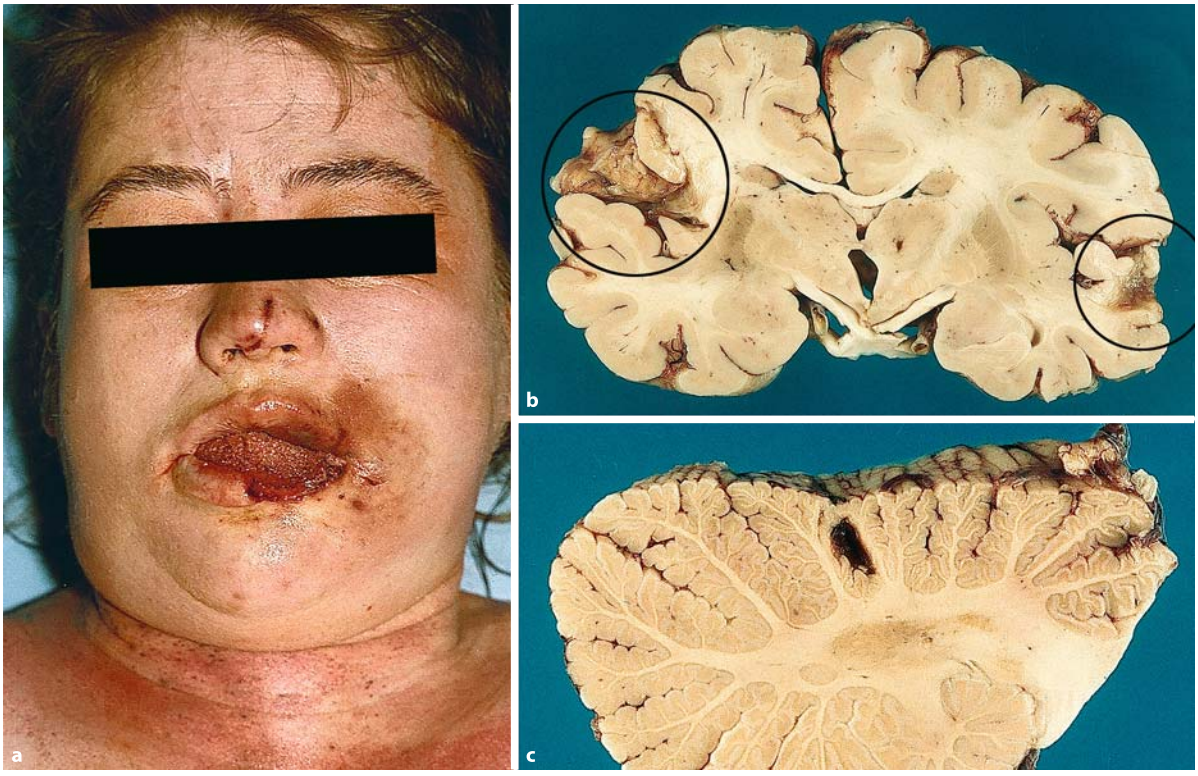

Fig. 27.1a–c. Macroscopic findings in death caused by seizure. **a** On autopsy a bite on the victim's tongue may raise suspicion of a sudden unexpected death in epilepsy. **b** The macroscopic neuropathologic findings are limited to visible old injuries of the temporal lobe, hardening of the hippocampus and **c** minor atrophy of the cerebellar cortex

injury, and toxic agents (Senanayake and Román 1993). It should be noted however that in children, post-traumatic epilepsy is uncommon, even if they have severe brain injuries (Appleton and Demellweek 2002). In general the *prognosis* for epilepsy is better if onset is before the age of 10 years (Annegers et al. 1979) unless neurological deficits are present at birth or there is mental retardation.

Epilepsy entails an increased risk of traffic accidents, burns, drowning, etc. A recent international study (Beghi et al. 2002) found a moderately higher risk of illness and accidents in patients with idiopathic, cryptogenetic or remote symptomatic epilepsy than in the general population.

A prospective study (Lhatoo et al. 2001) reported that more than 70% of a cohort of 792 patients experienced lasting remission from seizures but that their long-term mortality rate was double that of the general population. Significantly elevated long-term mortality rates were found in patients with acute symptomatic epilepsy, remote symptomatic epilepsy, or epilepsy due to congenital neurologic deficits, but not in patients with idiopathic epilepsy. The increased mortality was particularly notable in the years immediately following diagnosis.

27.7 Neuropathology

There are two types of lesion:

1. Primary brain lesions that give rise to seizures, i.e., extrahippocampal pathology is associated with epilepsy.
2. Secondary brain lesions that result from (repeated) seizures or epilepsy, i.e., hippocampal pathology is associated with epilepsy.

It is usually difficult to determine whether epileptic brain damage is the cause or the consequence of seizures (cf. Meldrum 1997; Sutula and Pitkänen 2001; Peiffer 2002). Primary brain lesions with a convulsive focus feature changes in tissue texture, i.e., neuronal degeneration, dendrite swelling, plus an astrocytic, and microglial reaction (Blumcke et al. 1999).

Mechanical injury of the brain caused by a *seizure-induced fall* can be regarded as a secondary brain lesion (Zwimpfer et al. 1997). The incidence ranges from 11% to 36% (Sano and Malamud 1953; Margerison and Corsellis 1966). These lesions can be recognized macroscopically and may themselves cause the epilepsy. Microscopic changes greatly complicate the differentiation of primary from sec-

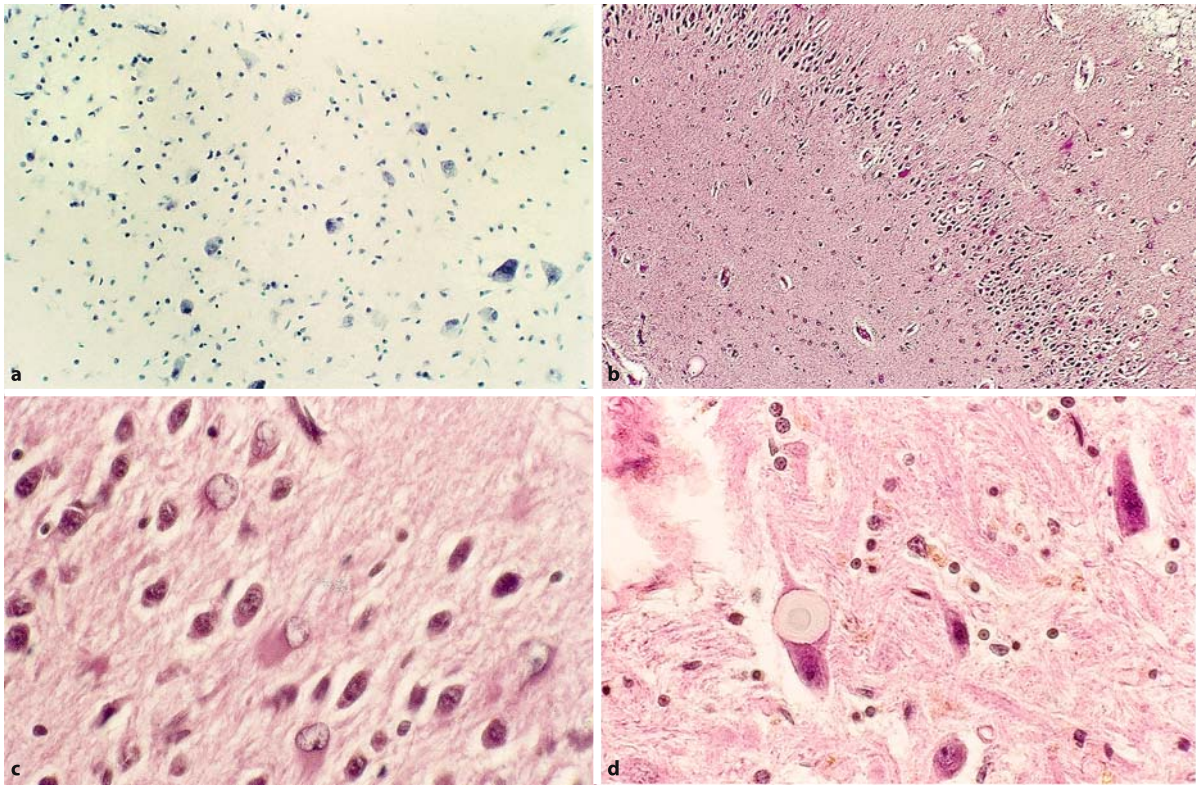

Fig. 27.2a–d. Macroscopic findings in death caused by seizures. Reduction of nerve cells in the CA1 segment of Ammon's horn (**a**) and replacement of the neurons lost by astrocytes (**b**, **c**). The second type of "myoclonic epilepsy" is characterized by spherical inclusions in the perikaryon and/or the process of nerve cells, so-called Lafora bodies (**d**) (**a** Nissl stain; **b–d** H&E; magnification **a** ×200, **b** ×100, **c**, **d** ×1,000)

ondary lesions, especially in the hippocampus and cerebellar cortex. It must be assumed that seizures cause damage to neurons, leading to neuronal loss and a reactive gliosis (Dam 1982). Pyramidal cells in the hippocampus, neocortical neurons of laminae II and III, and Purkinje cells are all susceptible to such damage. Cases of long-lasting epilepsy exhibit subpial fibrillary gliosis (Chaslin's gliosis), periventricular subependymal and perivascular gliosis in the white matter.

27.7.1 Hippocampal Pathology

Sommer (1880) first described selective neuronal loss in the CA1 segment of the hippocampus followed by a fibrillary gliosis. Because hypoxic events lead to neuronal loss in the same localization, it was thought that the neuronal loss is caused by a cerebral ischemia secondary to seizure-induced vasospasm (Spielmeyer 1927). This hypothesis is supported by, for example, the lobular pattern of cerebellar damage and the laminar pattern of neuronal loss in the neocortex, Purkinje cells being the most vulnerable followed by granule cells. This hypothesis is opposed by the more recent theory of an association between seizures and vasodilatation and enhanced blood flow. According to this theory Scholz (1951) and others suggest a "consumptive hypoxia." Moreover, Siesjö and co-workers showed that seizures induce neuronal loss even in the presence of normal pO_2, normal levels of glucose and lactate and even under normal temperature conditions (Nevander et al. 1985; Auer et al. 1986).

The macroscopic findings may give evidence of a mechanically or inflammatorily induced scar process, especially in the temporal lobe (Fig. 27.1b) which may be the cause of the epileptic disease (see also Sect. 27.7.2). Moreover in single cases the hippocampus feels hardened as an indication of gliosis. A minor atrophy of the cerebellar cortex may be visible (Fig. 27.1c). The microscopic findings are characterized by a neuronal loss in the CA1 region (Sommer's sector) of Ammon's horn (Fig. 27.2a). The lost neurons are replaced by astrocytes (Fig. 27.2b, c).

Fifty-five percent (n=55) of the cases have hippocampal sclerosis, 45% cerebellar changes, 27% changes in the amygdaloid nucleus, 25% in the thalamus, and 22% in the cortex as evaluated by Margeri-

son and Corsellis in 1966. In contrast, hippocampal sclerosis was reported by Schnabel (1986) (n=61) in only 31% of cases and cerebellar atrophy in 33%, as was confirmed by Peiffer (1993), who demonstrated neuronal loss in the hippocampus (34.1%), cortex (18.9%), basal ganglia (13.6%), and cerebellar cortex (22%) in selective case material. Two-thirds of his cases exhibited no neuronal loss.

27.7.2 Temporal Lobe Epilepsy

In epilepsy patients or in patients with temporal lobe epilepsy, Ammon's horn sclerosis is the major neuropathological substrate. In an extensive study, Rushing et al. (1997) found unilateral sclerosis of Ammon's horn in only 1 of 43 cases of primary epilepsy, but in 15 of 35 cases of secondary epilepsy, the sclerosis being unilateral in 7 cases, bilateral in 8 cases.

Meldrum (1997) was able to show a vicious circle in animal experiments supporting the hypothesis that the hippocampus and other limbic structures are damaged by prolonged generalized or limbic seizures in early life, initiating an epileptogenic process that gives rise to spontaneous limbic seizures after a latent period. Other findings show that experimentally induced seizures are associated with hypertrophic and proliferating astrocytes and microglia–macrophages in the CA3–CA4 fields of the hippocampus and dentate hilus (Niquet et al. 1994). Blumcke et al. (2002) in a recent molecular neuropathological study on temporal lobe epilepsy disclosed evidence that a neurodevelopmental component contributes to the induction of Ammon's horn sclerosis. This disease's association with an increased susceptibility to segmental loss in the hippocampus and a lowered seizure threshold during the long course of the disease may comprise further elements in a pathogenetic cascade. A tectonic malformative abnormality has recently been described in epileptic hippocampi, an abnormality that may have been previously overlooked (Sloviter et al. 2004).

27.7.3 Myoclonic Epilepsy

Sudden brief, shock-like involuntary movements are caused by muscle contractions or muscle inhibitions arising from the CNS. Though myoclonic seizures are non-specific, this phenomenon especially occurs in Lafora body disease and in Unverricht–Lundberg disease. The first type of disease is characterized by Lafora bodies, which are intracytoplasmic spherical inclusions found in nerve cell processes and apparently free in the neuropil (Fig. 27.2d). Lafora bodies are concentric-lamellar basophilic balls with a basophilic core surrounded by a pale amphophilic zone; the pale outer zone may show dark radial stria (Honavar and Meldrum 2002).

27.7.4 Status Epilepticus

Neuropathological findings in adults dying shortly after *status epilepticus* are sparse. They show acute cell loss in the hippocampus, ischemic neuronal changes, laminar necrosis in the neocortex, and Purkinje cell loss in the cerebellum (Corsellis and Bruton 1983). It is now generally thought that NMDA-receptor activation during epileptic discharges is crucial to the increased calcium entry and consequent cell death. The entry of calcium and sodium into neurons seem to be the principal factors (Meldrum 1983; Wasterlain et al. 1993). Neuronal excitation in experimentally induced seizures triggers a set of immediate early genes (IEG) (for review, see Kiessling and Gass 1993). The gene products of *fos*, *jun*, and *krox* participate in the regulation of gene transcription, a fundamental biological control mechanism. Investigations of IEG expression at the mRNA level by in situ hybridization and Northern blot analysis, and at the protein level by immunohistochemistry and Western blot analysis have shown rapid and transient neuronal IEG induction with peak levels in the hippocampus. *Krox-24* and *c-fos* show a simultaneous rapid rise, reaching peak levels after 2 h of postictal recovery and a return to control levels by 8 h post-seizure. IEG-encoded proteins exhibit an identical sequence of induction in different hippocampal subfields in the order dentate gyrus, CA1, and CA3.

27.8 Cause of Death

Epileptics have a threefold elevated mortality rate compared with the general population (Lund 1968). Death in most cases however is due to the underlying disease, such as a known brain tumor, an acquired or congenital metabolic disease, severe brain injury, suffocation, drowning, aspiration of food, and status epilepticus. A recent population-based study on "death in children with epilepsy" (Camfield et al. 2002) determined that death from epilepsy is rare unless there is a severe neurological disorder sufficient to cause functional neurological deficits (cf. Breningstall 2001).

An early study on mortality in epileptics (Schwade and Otto 1954) determined that death occurred from seizure-induced heart failure in 31%, during status epilepticus in 20%, and as a result of seizure-related

injuries or suffocation in 17%. Though such figures may not represent today's reality given the dramatically improved therapeutic possibilities, it remains true that epilepsy per se increases the risk of motor vehicle accidents, drowning, and fatal asphyxia (gastric contents).

It is noteworthy though that sudden unexpected death is relatively frequent in both adults and children with epilepsy.

27.8.1 Sudden Unexpected Death in Epilepsy (SUDEP)

A 1996 workshop on SUDEP proposed the following *definition* (Nashef and Shorvon 1997): a "sudden unexpected witnessed or unwitnessed non-traumatic and non-drowning death in patients with epilepsy with or without evidence of a seizure and excluding documented status epilepticus where necropsy does not reveal a toxicological or anatomical cause of death" (see also Annegers and Coan 1999).

Various *epidemiological studies* have found that about 10–13% of epileptic patients suffer SUDEP, which is the major form of death in epilepsy patients between the ages of 20 and 40 years (Ziegler and Kamecke 1967; Zielinski 1974; Leestma et al. 1989; Earnest et al. 1992; Cockerell et al. 1994). In recent studies (for review see Langan and Sander 2000) the incidence of SUDEP was found to vary from 1:370 to 1:1,100 (Leestma et al. 1989), 1:650 (Kirby and Sadler 1995), and 1:680 (Langan et al. 1998). Two other studies reported annual incidences of 3.5:1,000 (Leestma et al. 1997) and 1.21:1,000 (Derby et al. 1996; O'Donoghue and Sander 1997; Walczak et al. 2001; see also Tennis et al. 1995). All these studies included both adults and children. In sum, the epileptic population is at 25 times greater a risk of SUDEP than the general population (Ficker et al. 1998; McGugan 1999).

27.8.1.1 Risk Factors

Among the identified risk factors are male sex, antiepileptic drug polypharmacy, poor compliance with medications, antipsychotic drugs, and alcoholism. It is difficult to compare the different studies due to the considerable variability of populations, reliability of records, and definitions of SUDEP.

SUDEP also occurs in epileptic *children* (Appleton 1997; Camfield and Camfield 1999). In one study the cause of death could be determined in all but 4 of 954 cases (=0.4%) (Molander 1982). It is estimated that 10–20% of children with neurological and cognitive deficits die by the age of 15, 20–30% by the age of 25. Although the mortality is generally attributable to the underlying condition rather than the epilepsy itself, a significant proportion result from suicide, accidents, and sudden unexpected death (Gordon and Wilmslow 2001). A large systematic analysis of 27 cases of SUDEP in children under 18 years of age (Donner et al. 2001) found that 63% were male, 52% had symptomatic epilepsy, 18% cryptogenic epilepsy, 30% idiopathic epilepsy, 46% had been treated with one anti-epileptic drug, and 35% had serum levels below the therapeutic range. It was concluded that for adults there is at least one risk factor for SUDEP, namely low serum anti-epileptic drug levels at the time of death while anti-epileptic drug polytherapy does not appear to be significant in children.

A recent study (Nilsson et al. 1999) gives evidence of the relative risk of SUDEP which increases with the number of seizures per year. The estimated relative risk was 10.16 (95%, Ci 2.94–35.18) in patients with more than 50 seizures per year, compared with those with up to 2 seizures per year. The risk increases with increasing number of anti-epileptic drugs taken concomitantly, the early-onset versus late-onset epilepsy, and frequent changes of anti-epileptic drug dosage compared with unchanged dosage.

Few studies have been done on *neuropathological changes* in victims of SUDEP. Shields et al. (2002) recently investigated 70 cases, the findings in which turned out to be non-specific for SUDEP but characteristic of epileptic brains in general: neuronal clusters, gliosis, cystic gliotic lesions, increased perivascular oligodendroglia, decreased myelin, cerebellar Bergmann astrogliosis, and folial atrophy.

27.8.1.2 Pathogenetic Considerations

The explanation of the pathogenetic basis of death remains controversial. In most cases, especially in the elderly, a seizure-related event is suggested (Nashef and Brown 1996) though it is very difficult to prove, as recently published by Thom et al. (2003). In children, Sillanpää (1992) was able to show a significant association between co-morbid conditions and SUDEP. During adolescence and adulthood, death often results from respiratory failure (apnea) or cardiac arrhythmia, during or immediately following a seizure (Hirsch and Martin 1971; Earnest et al. 1992; Hewertson et al. 1994). Ventricular arrhythmias, however, are not more frequent in epileptics than in the general population (Liedholm and Gudjonsson 1992). However, it is thought that seizure-induced cardiac dysfunction, i.e., ventricular arrhythmia or asystole, could cause death, and that these deaths can be considered a form of neurocardiac death (see pp. 526 f). Histomorphological studies of the heart disclosed signs of perivascular and interstitial fibrosis (Natelson et al. 1998). Two postmortem studies on the other hand found pulmonary edema of neurogenic origin in the majority of cases (Terrence et

al. 1981; Leestma et al. 1989). The role of centrally induced respiratory failure was supported by the finding of a marked hypoventilation with a precipitous drop in arterial pO_2 after induction of seizures in animals which experienced sudden death. Epileptic seizures in young children are definitely associated with prolonged and repeated pauses in breathing movements that in some cases result in hypoxemia/ischemia (Hewertson et al. 1994).

SUDEP is rarely witnessed. Of the 15 SUDEP cases reported by Langan et al. (1998, 2000), 12 were associated with convulsive seizures or respiratory difficulties. It was concluded that both central and obstructive apnea contribute to such sudden deaths. The development of apnea, however, does not exclude the possibility of cardiac arrhythmia, such as sinus arrest or bradycardia (Gordon and Wilmslow 2001).

27.8.1.3 Diagnosis of SUDEP

The main forensic–pathological problem of SUDEP has still not been resolved: currently there is no known reliable indicator of acutely lethal seizure activity. A bite on the victim's tongue (Fig. 27.1a) or injuries as a consequence of a fall may raise suspicion of SUDEP (Ulrich and Maxeiner 2003). However, in most instances no morphological criteria explain the sudden death. The immunohistochemical demonstration of prolactin in hippocampal neurons failed to become a morphological criterion (Miller et al. 2003), though clinical studies recorded a relationship between recent (within 10–40 min) seizure activity and elevated serum prolactin levels (Whalley et al. 1982).

27.9 Additional Forensic Implications

When *working on or with machinery* or when *driving*, individuals liable to frequent seizures are placed at risk by the sudden and unexpected loss of consciousness or by their own involuntary movements (Krumholz et al. 1991; Lings 2001). Most countries have laws prohibiting epileptics from driving motor vehicles and/or from working in situations that could endanger their own lives or those of others. A danger of course always exists for the epileptic during activities that would otherwise not be life threatening. But the risk of losing consciousness renders leisure activities in water, in the air, or in traffic particularly dangerous for individuals with epilepsy.

The *psychopathological changes* associated with epileptic disorders can lead to alcoholism, aggressive behavior (Treiman 1990), or sexual deviation. In rare cases, epileptics exhibit psychopathological changes in the sense of episodic dyscontrol syndromes with paroxysmal outbursts of rage and violence far exceeding that of the precipitating stimulus. The question of culpability arises in such cases if injuries are inflicted or if someone is killed. Epileptics are also poor at compliance due to their poor understanding of the nature of their illness. If a patient with epilepsy takes anti-epileptic medication at below recommended doses, he is not only at risk of a paroxysmal outburst, but also of SUDEP. This again gives rise to the question of whether the patient was fully, partially, or not at all at fault.

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Vascular Diseases 28

Acute and unexpected death can result from the spontaneous (i.e. not induced by external violence) fatal cerebrovascular disturbances known as "*stroke*." Sacco (1994) defines stroke as an "abrupt onset of focal or global neurologic symptoms caused by ischemia or hemorrhage." Symptoms that are only transitory or that "resolve within 24 hours" (Kalimo et al. 2002) are characteristic of a "*transient ischemic attack*" (TIA).

Both stroke and TIA have *pathogenetic backgrounds* including a variety of diseases affecting global circulation as well as local arteries and veins (for review see Zülch and Hossmann 1988). Their sequelae are attributable to the reduction of cerebral blood flow or rupture of vessels, i.e.,:

- Cerebral *infarct* is a consequence of reduced or stopped cerebral blood flow: according to Futrell (1998) this is referred to as:
  - "Embolic" (definite only if a source of embolism was proven, suspected if cerebral infarcts were bilateral).
  - "Hemodynamic" (if there was a tight carotid stenosis thought to produce stroke by decreased flow past the stenosis or if there was decreased cardiac output or decreased blood pressure).

  - "Lacunar" (implying "hypertensive small-vessel disease") if the stroke was small and deep, even though the patient may not have a history of hypertension.
  - "Thrombotic" (if none of the other three "mechanisms" could be demonstrated), which was thought to be the major mechanism for stroke.
- Cerebral *hemorrhage* is usually caused by the rupture of an arterial or venous wall, less often by arterial or venous occlusion.

The *effect of stroke* is damage of brain tissue (*infarct*) or impairment of CNS function secondary to an intracranial space-occupying hemorrhage and/or edema with consequent displacement of brain parenchyma.

The *clinical symptoms* of stroke are dependent on:

1. The extent of the rupture in the vascular wall and whether an artery or vein is involved
2. The size of the occluded artery
3. The age of the patient
4. The suddenness of the event
5. The site of the affected brain parenchyma
6. How early therapeutic measures are initiated

Strokes can be *caused* by a number of cerebrovascular diseases or by extracerebral disturbances (see below), as shown by the *epidemiological data*. Stroke is the third leading cause of death in the industrialized Western world (Jörgensen and Torvik 1969; Wolf 1990; Sacco 1994). As a major cause of long-term disability, it is the number one cause, representing an economic problem of enormous proportions. The age-adjusted *annual incidence* of all first-ever strokes varies between 90 and 350 per 100,000 (Terent 1993). The mortality rate of stroke depends largely on age: the age-specific death rates by stroke calculated from the 70th year of life double after every 5 years (Millikan et al. 1987). The main *risk factors* for stroke are hypertension, diabetes mellitus, and obesity; additional factors include alcohol abuse, cigarette smoking, oral contraceptives, atrial fibrillation, etc.

The most common result of *cerebral vessel disease* is *cerebral ischemic infarct* (60–80%), followed by intracerebral hemorrhages (10%), and subarachnoid hemorrhages (5–10%) (Kalimo et al. 2002). The Framingham Study found that about 400 out of a population of 5,184 persons over 26 years of age suffered stroke, 223 of whom died. Eighty-two percent died after spontaneous intracerebral hemorrhage, 46% after subarachnoid hemorrhage (SAH), 16% after cerebral embolism, and 15% after infarction (Sacco et al. 1982; see also Bamford et al. 1990). We also have to draw attention to the possibility of transformation of an acute ischemic infarct into a hemorrhagic stroke. This may be the consequence of thrombolytic therapy, which is suggested to be of benefit to patients with acute ischemic infarct (Larrue et al. 1997). On the other hand a spontaneous hemorrhage may occur that can be explained by a parallel loss of three basal lamina components, which contribute to a loss of microvascular integrity (Hamann et al. 1995).

The vascular diseases associated with stroke are described below. In most cases stroke is followed by a slow disease course, sometimes however by acute, unexpected death. The morphological changes in the brain parenchyma after vessel occlusion or rupture are also described, i.e., the cerebral *infarct* (pp. 564 ff)and the cerebral *hemorrhage* (pp. 569 ff). For information on the non-natural causes of stroke and/or hemorrhage the reader is referred to Parts II and V (for ischemic and hypoxic changes of the brain, see Part III). The following description is based primarily on Kalimo et al. (2002).

28.1 Physiology of the Cerebral Circulation

The physiology of the cerebral circulation is described in greater detail in Part III. Only the data relevant to vascular diseases and their sequelae are discussed here.

Under normal conditions, the adult human brain receives 15–20% of the cardiac output. The average blood flow to the brain as a whole is 750 ml/100 g per min (for review see Powers 1990), the gray matter receiving approximately 80 ml/100 g per min, and the white matter 20 ml/100 g per min. The cerebral venous pressure is usually equal to the intracranial pressure. The force driving blood to the brain is the cerebral perfusion pressure. The pressure can change if an obstruction causes a 70% reduction in the diameter of the major arteries to the brain (carotid and vertebral arteries) distal to the obstruction for which the collateral circulatory pathways are unable to compensate. Carbon dioxide is a known vasodilator of cerebral blood vessels. Reduced hematocrit and hemoglobin are associated with an increase in cerebral blood flow (for further information, see pp. 561 f).

A drop in cerebral perfusion pressure results in an automatic dilation of cerebral arterial vessels, thus reducing resistance and maintaining blood flow. A rise in perfusion pressure to the cranium, in contrast, causes cerebral arteries and arterioles to constrict. An increase in intracranial pressure therefore creates a vasodilation resembling that ensuing upon a decrease in arterial blood pressure.

Autoregulation is effective under normal conditions for intracranial pressures between 60 and 150 mmHg. A reduction in pressure below 60 mmHg exceeds the vasodilatory capacity of vessels, with a

consequent drop in cerebral blood flow. If pressure exceeds 150 mmHg, the vasoconstrictive capacity of vessels is inadequate to prevent a rise in cerebral blood flow that further increases intracranial pressure.

Brain metabolism depends almost entirely for its energy needs on the ability to generate high-energy phosphate compounds via glucose oxidation. Glucose consumption is normally about 30 µmol/100 g per min, oxygen consumption about 165 µmol/100 g per min. Approximately 90% of glucose is metabolized to carbon dioxide and water.

Cerebral metabolism affects blood flow depending upon cerebral activity. At rest, the brain utilizes only about one-tenth of the glucose and one-third of the oxygen supplied by arterial blood flow. An increase in local neuronal activity (e.g., voluntary hand movement) induces a dramatic rise in local cerebral blood flow. Oxygen metabolism is known to increase much less than cerebral blood flow. The rise in local glucose metabolism is similar to that in cerebral blood flow.

28.2 Anatomy of Cerebral Vessels

The *extracranial arteries* possess multiple collateral circuits that can guarantee sufficient blood flow to the brain if a single vessel becomes occluded. The most common anastomosis following occlusion of the extracranial portion of the internal carotid artery is the external carotid, external maxillary, ophthalmic, intracranial internal bypass (Dudley 1982). If the proximal part of the cerebral arteries becomes occluded, blood can be shunted in compensation from the external carotid artery through the thyroid and occipital arteries to the distal vertebral circuit (Fisher 1970). Deficits in collateral circuits can be detrimental to the brain. The salient example is *subclavian steal syndrome*, which is characterized by reduced pressure within the ipsilateral vertebral and distal subclavian arteries secondary to total occlusion of the subclavian artery at its origin.

The large *intracranial arteries* are connected to one another by the circle of Willis via the basilar artery, creating a special pattern of collateral blood supply. Gradual narrowing of the lumen of the large cerebral arteries, therefore, rarely leads to neurologic deficits, whereas acute and sudden occlusion does. The cerebrum, cerebellum, and brain stem including the medulla oblongata are supplied via this ring of vessels at the base of the brain. Figure 28.1 provides a rough diagram of the blood flow to the individual areas of the brain. For further details the reader is referred to textbooks of anatomy or clinical neuropathology (e.g., Kalimo et al. 2002; Roggendorf 2002). The spinal cord has its own, separate source of blood supply.

Microscopically and *functionally*, intracranial vessels and extracranial vessels differ only slightly: intracranial vessels have walls that are thinner per unit diameter. They possess a relatively robust internal elastic lamina but no, or only a rudimentary, external elastic lamina. The brain lends little adventitial support. Rich anastomoses are localized in the gray matter, end arteries and terminal venules in the white matter.

The *intracerebral capillaries* differ functionally from extracerebral capillaries in being responsible for maintaining the blood–brain barrier. This task is accomplished mainly by the specialized endothelial cells (see Chap. 4).

Venous drainage is accomplished via the superior sagittal sinus, the inferior sagittal sinus, the straight sinus, the great vein of Galen, the internal jugular vein, and the sigmoid portion of the lateral sinus. The veins of the cortex enter the subarachnoid space and drain towards the dural sinus, especially in the paramedian and suprasylvian regions. Veins of the parasylvian region drain towards the cavernous and sphenoidal sinuses, while veins on the lateral and inferior surface drain towards the transverse sinuses. Veins of the superficial system within the brain parenchyma anastomose extensively with the internal cerebral and basal veins of the deep network.

28.3 Pathology of Cerebral Arteries

The following changes are common to the various vessel diseases:

1. Thickening and hardening of vessel walls with narrowing of the lumen (causing a reduction or cessation of blood flow).
2. Thinning of vessel walls due to overload or malformation (weakening the wall and increasing the risk of dilation and/or rupture).

28.3.1 Cerebral Atherosclerosis

Epidemiology and Topography. The most common arterial disease is atherosclerosis, which is associated with – and possibly partly caused by – diabetes mellitus, hypertension, cigarette smoking, dyslipidemia, etc. Atherosclerosis is the predominant underlying cause of stroke.

Compared to extracerebral systemic atherosclerosis, brain vessels are affected in a relatively small percentage of cases (5%) (Jellinger and Neumayer 1964). About 20% of patients with distinct athero-

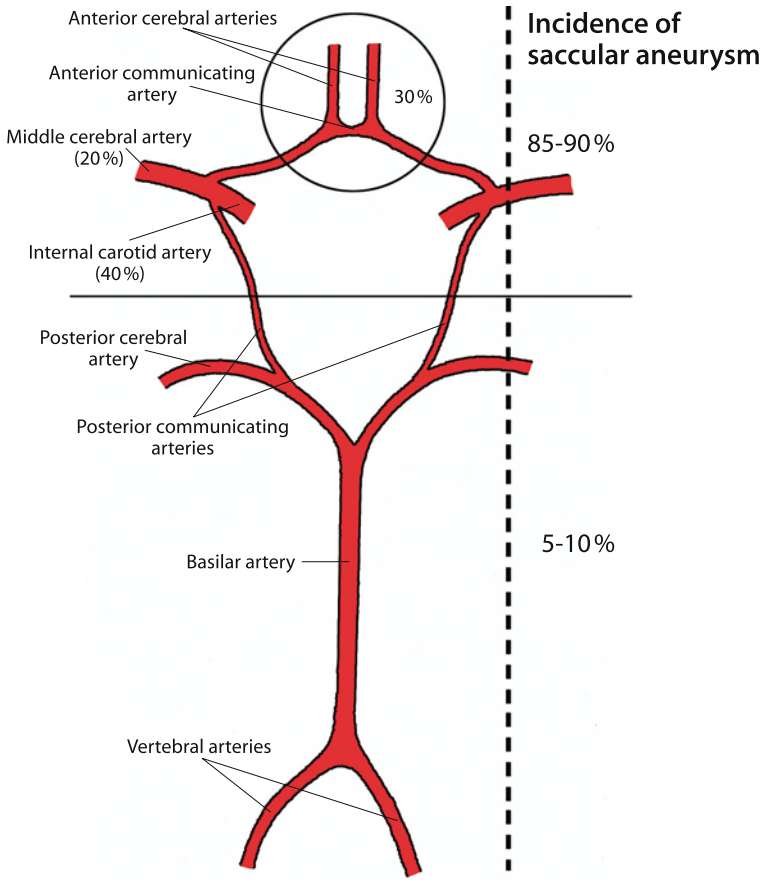

Fig. 28.1. Circle of Willis. Schematic demonstration of the anatomy of large basilar arteries of the cerebrum including data on the incidence of the topographic distribution of saccular aneurysms

sclerosis of the basal arteries exhibit no atherosclerosis of the intracerebral arteries. Conversely, 50% of patients with intracerebral atherosclerosis show no changes to the vessel walls of the large basal arteries (Baker and Jannone 1959; Reed et al. 1988).

The extracerebral carotid arteries are affected relatively early, especially the carotid siphon. The intracranial portion of the vertebral arteries and both ends of the basilar artery become involved later (Moossy 1966). The frequency of atherosclerosis, especially of the vertebral vessels, increases with age. By age 75 this type of vessel change affects about 95% of cases (Ule and Kolkmann 1972).

Risk Factors. As already mentioned, a variety of risk factors are known, some associated with pathological mechanical overloading, others with pathological biochemical blood constituents capable of inflicting endothelial damage. Atherosclerosis is associated with elevated blood pressure, which can lead in turn to mechanical vessel wall lesions such as recurrent vascular spasms triggered by nicotine consumption or stress. On the other hand, increased cholesterol, low density lipoproteins (LDL), high density lipoproteins (HDL), and the entire group of saturated fats are all closely associated with atherosclerosis. A combination of several factors increases the incidence of this disease. The extent to which additional genetic factors play a role in this multifactorial disease remains unclear.

Pathogenesis. Initially atherosclerotic disease represents a disruption of the endothelial barrier function secondary to endothelial cell injury (Ross 1993) caused in most cases by hemodynamic stress. Lipoproteins (LDL, HDL) invade the intima and lamina media, where they are modified in the extravasal compartment. Intravascular blood monocytes leave the blood stream and by migration invade the vessel's wall and ingest – like smooth muscle cells – LDL cholesterol. Monocytes transform into foam cells, which appear as fatty streaks in the large vessels. A fibrosis develops, eventually producing fibrous plaques. A variety of additional factors also play a role, including chemokines and free radicals, which participate in a secondary inflammatory process (Koenig 2003). The formation of fibrous plaques, which are sometimes accompanied by calcium deposition and precipitation of crystalline cholesterol, can take years or decades. Despite narrowing of the lumina, the blood flow remains sufficient in the early stages, in many patients averting the development of functional deficits of the nervous system. Extensive detachment of the intima sometimes does occur, with a consequent

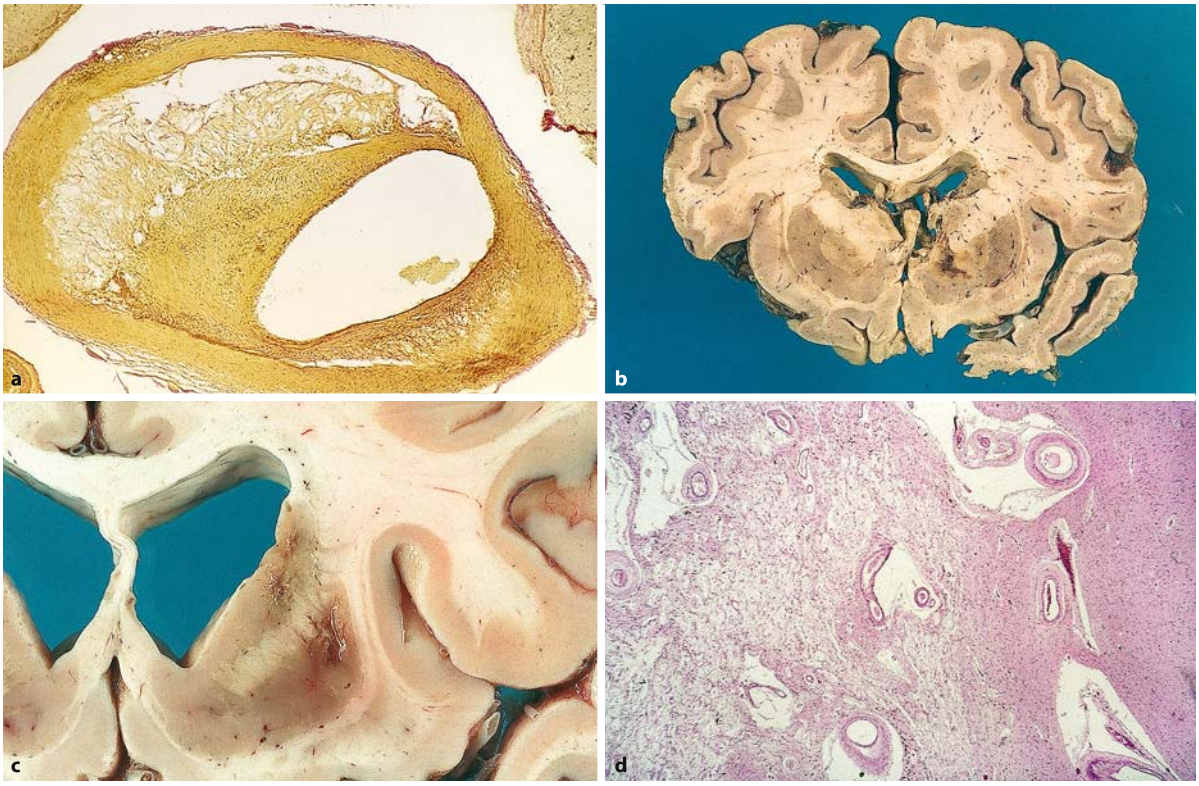

Fig. 28.2a–d. Arteriosclerosis cerebri. **a** Narrowing of the lumen of an artery by an atheromatous plaque; **b** focal cystic necrosis at the internal capsule involving pallidum and thalamic nucleus as well as **c** putamen and caudate; **d** histological demonstration of a cystic scar as the result of an arterial occlusion (**c**: van Gieson stain; magnification ×100)

risk of thrombosis giving rise to acute vascular occlusion, which in turn can lead to neurologic deficits.

Morphology. Atherosclerosis features disruption and splintering of the internal elastic lamina and destruction of the media (Fig. 28.2a). Fibrosis causes scarring of the media and deposition of calcium and crystalline cholesterol. A simultaneous proliferation of foam cells as well as of the medial fibroblasts produces narrowing of the lumen with elevated risk of thrombotic vessel occlusion. The reduction or halt of blood flow in an artery leads to necrosis of the tissue that is supplied by this artery, i.e., most often a necrosis of the internal capsule as a consequence of obliteration of the lenticulostriate artery (Fig. 28.2b, c). The thrombosis of the basilar artery as a result of atherosclerosis (Fig. 28.3a) will lead to necrosis in the center of the pons (Fig. 28.3c).

Though there is a direct correlation between the atherosclerosis of brain arteries and stroke, obviously the stroke will not be caused by an atherosclerotic occlusion of intracerebral arteries. In most cases the sclerosis-induced narrowing of the arterial lumen leads to an occlusion by an additional thromboembolic event or by a cardiac-induced reduction of blood pressure.

28.3.2 Brain Calcinosis

In cases free of neurologic deficits, calcification of the lamina media of arteries, and of perivascular tissue of arterioles and capillaries is a process that is usually detected as an incidental finding by radiologists and neuropathologists. They occur in the putamen, globus pallidus, caudate nucleus, dentate nucleus, and lateral thalamus (striato–pallido–dentate calcification – see Fig. 28.4a, b) as well as in the cerebral cortex and cerebellar folia. Microscopically they partly appear as extracellular globular, basophilic material of varying diameter, mainly in conjunction with pericytes and astrocytic processes (Kobayashi et al. 1987). They can also be detected as "isolated" deposits within the media of arteries or of veins and capillaries, and as massive lobulated or spherical concretions (Nakano et al. 1984). Biochemically the deposits contain polysaccharides, proteins and metals, phosphate and bicarbonate ions (Nakano et al. 1984; Kobayashi et al. 1987).

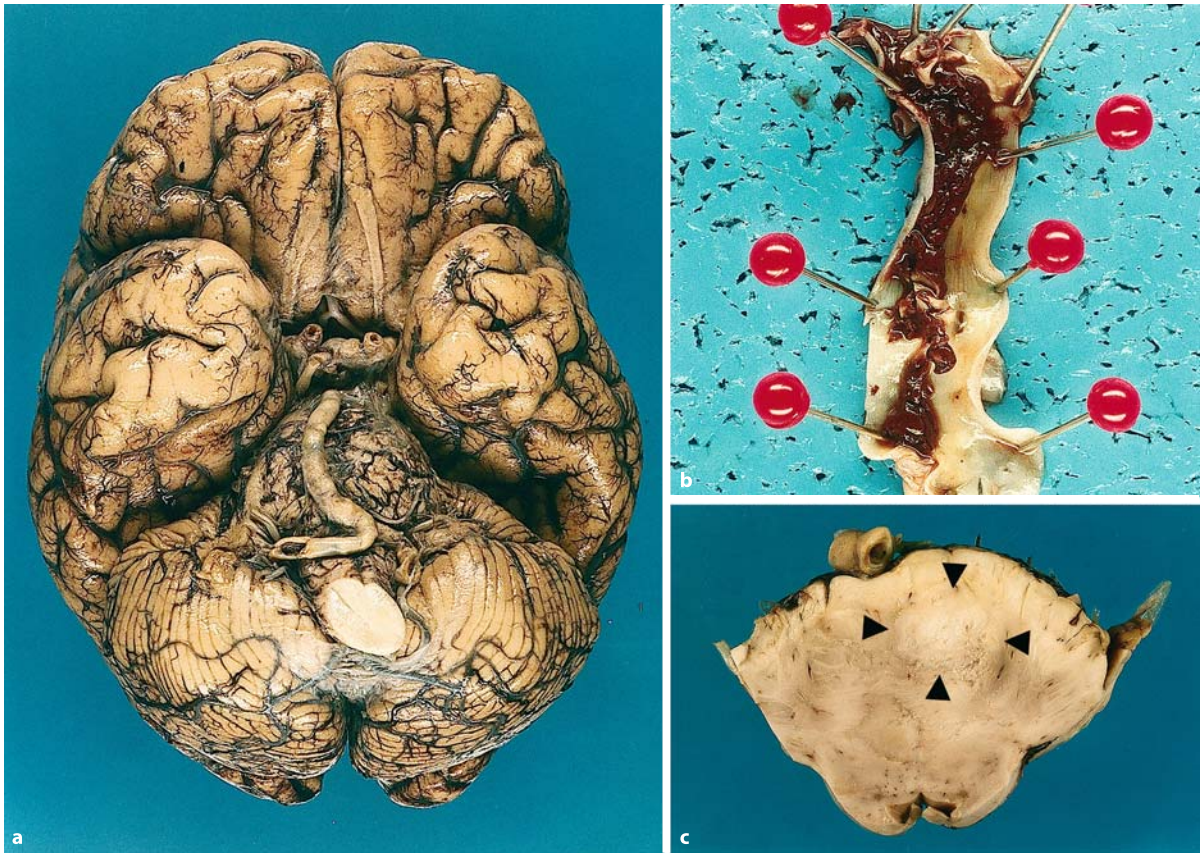

Fig. 28.3a–c. Thrombosis of the basilar artery. **a** Arteriosclerosis of basilar artery; **b** thrombus in the lumen of the basilar artery; **c** necrosis of the central parts of the pons (*arrowheads*) as sequelae of the arterial occlusion

Calcinosis affects 1–2% of the population (Goldschneider et al. 1980; Forstl et al. 1992; Fenelon et al. 1993). Lowenthal (1986) has reviewed the variety of conditions associated with brain calcinosis; it is however a sporadic process unassociated with neurologic deficits.

28.3.3 Cerebral Thromboembolism

Intracerebral arterial vessels may become occluded by *thromboemboli* arising in the heart, i.e., from a fibrillating atrial or ventricular wall adjoining an infarct or damaged valve, or they may derive from the aorta, carotid arteries or pulmonary veins. The most common cause of carotid occlusion is atherosclerotic thrombosis. Cardiac surgery entails a high rate (up to 70%) of fat and fibrin platelet embolism. In rare cases, paradoxical emboli may enter the systemic circulation by passing from leg veins through a patent foramen ovale. The consequence beeing single or multiple infarcts in gray and white matter.

Fat emboli mostly lodge in vessels of the white matter, where they cause multifocal perivascular punctate or ring hemorrhages (Fig. 9.29). In most cases it is not possible to demonstrate embolic material proximal to the infarct. Fisher and Adams (1951) showed that embolism-induced strokes are far more common than is generally assumed, the embolic particles elude detection by drifting to more distant sites or vanishing entirely.

If an embolus vanishes after irreversible infarct, the infarct becomes *hemorrhagic* when exposed to the full force of arterial blood pressure. The majority of hemorrhagic arterial infarcts can be traced to embolism. Pale infarcts, by contrast, are attributable to atherosclerotic thrombosis.

28.3.4 Hypertensive Angiopathy

Acute hypertensive events must be distinguished from the neuropathological and neurological sequelae of chronic hypertension. *Acute hypertensive encephalopathy* is characterized by a sudden and severe rise in blood pressure (malignant hypertension) with the clinical signs of elevated intracranial pressure, e.g., headache, nausea, vomiting, etc. *Chronic*

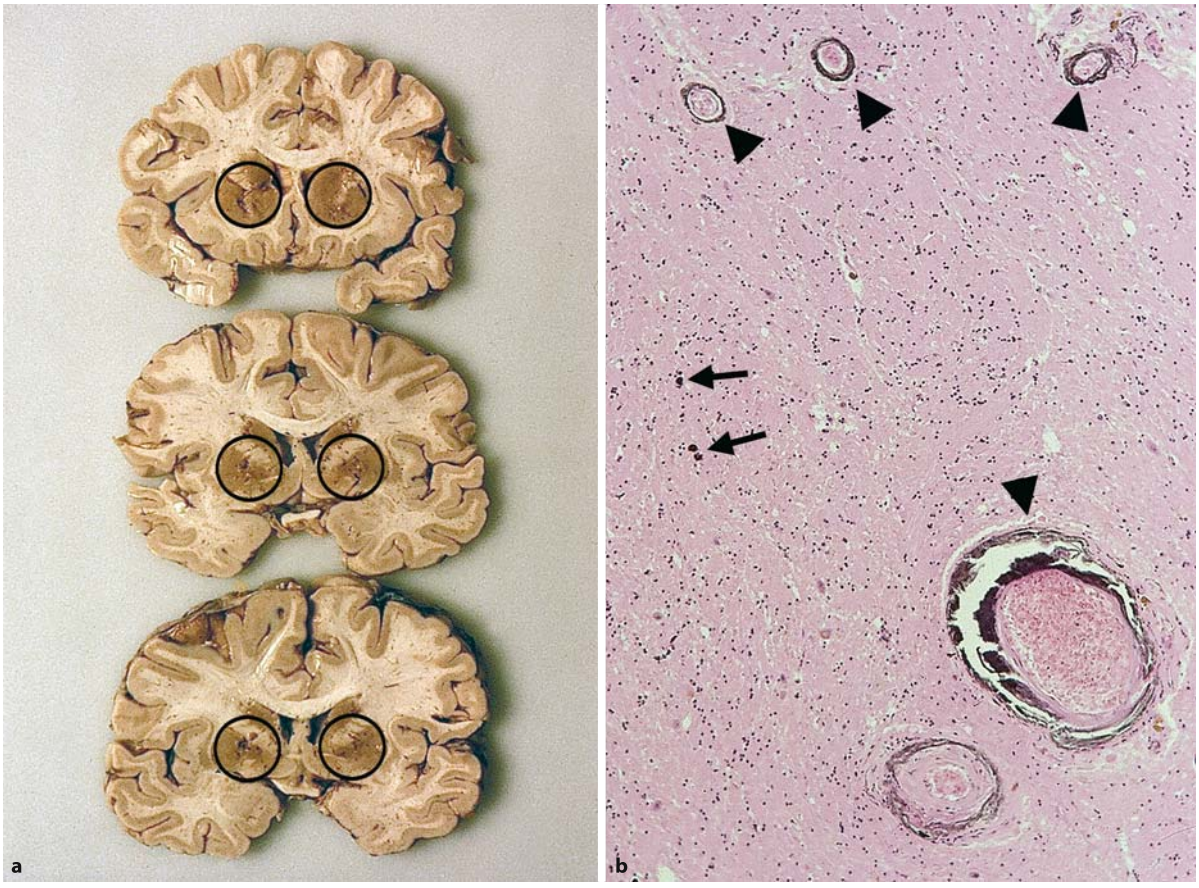

Fig. 28.4a, b. Brain calcinosis. **a** Macroscopically, calcification of the basal ganglia is visible and characterizes so-called Fahr's disease (*circles*). **b** Microscopically, the calcinosis is marked by extracellular globular, basophilic material (*arrows*) as well as calcium deposits in the lamina media (*arrowheads*) of arteries, and in the perivascular tissue of arterioles and capillaries (**b** H&E; magnification ×100)

hypertension (>180 mmHg systolic) gives rise to a specific angiopathy (Fig. 28.5) attributable to forced vessel dilatation secondary to high blood pressure (MacKenzie et al. 1976) or to repeated and prolonged vasoconstriction of arterioles (Toole 1990). Chronic hypertension leads to the development of (non-specific) atherosclerosis of intracerebral vessels combined with the (specific) alterations of small vessels termed "small artery disease" or "small vessel disease." The energy stores for contractile elements are depleted by prolonged vasospasm, resulting in angionecrosis. After many years of hypertension, small arteries (100–200 µm in diameter) and arterioles (100 µm or less) will exhibit fibrinoid necrosis and hyalinosis (Roggendorf et al. 1978). The vessel walls thicken and the lumens narrow, the wall-to-lumen ratio falling progressively from 1:4 to 1:1 or less.

The angionecrosis features an acellular thickening of the intima and media that produces a marked reduction in luminal diameter (Frederiksson et al. 1988). This may result in obscuring of the lumen by arteriolar necrosis, causing *microinfarction* with petechial hemorrhage. The basal lamina becomes thickened and the endothelial layer is damaged. The "fibrinoid" material contains a homogenized mixture of various plasma proteins that are eosinophilic. Necrosis induces the *fibrinoid change*. Another phenomenon is *hyalinosis*, which is a collagenous fibrosis that replaces the fibrinoid material over time. Hypertensive angiopathy is also associated with development of *microaneurysms* secondary to weakening of blood vessel walls. Should a microaneurysm rupture, the consequence is a globular hemorrhage (Fisher 1972).

Hypertensive hemorrhage in the white matter of the frontal lobe as well as of the parietal and temporal lobes may be the sequelae of chronic hypertension and secondary to small vessel disease (Fig. 28.6). A sudden unexpected death as a consequence of the chronic hypertension may occur as a result of the acute increase of intracranial pressure and secondary herniation. The neuropathologist must search for markers of vascular disease, i.e., markers of chronic hypertension. He regularly will find pathologic ves-

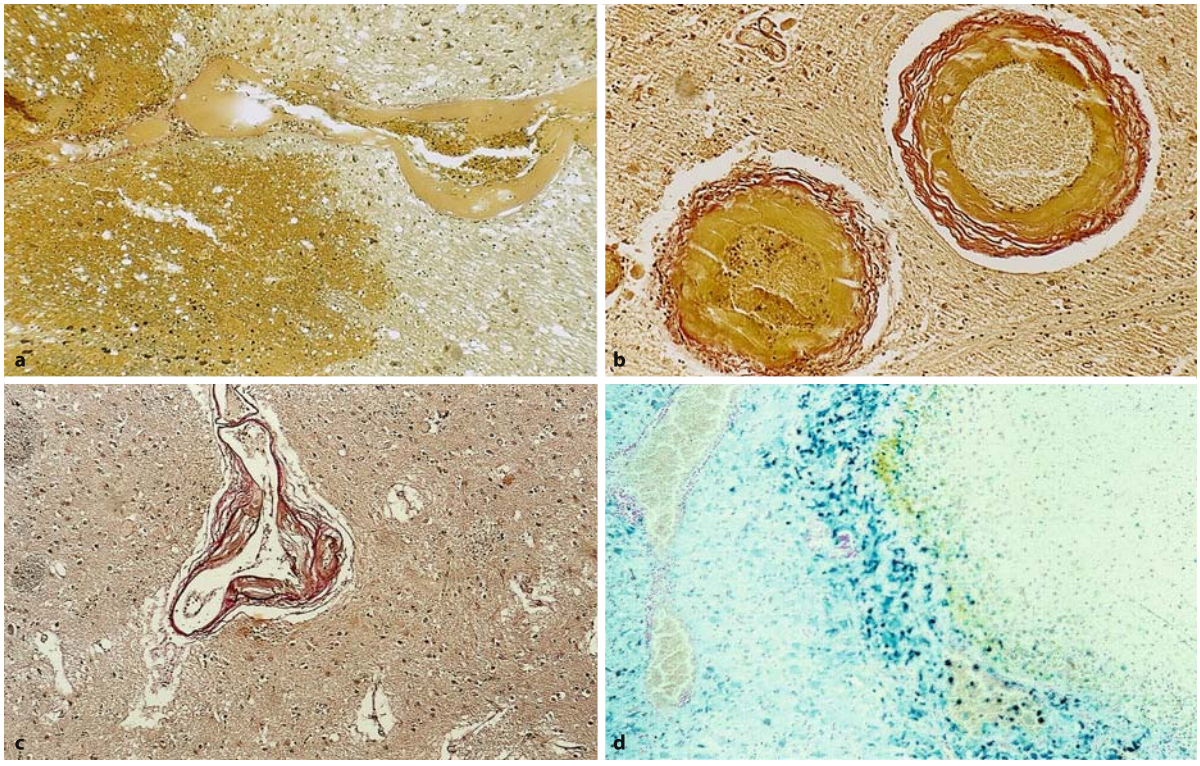

Fig. 28.5a–d. Hypertensive angiopathy and small vessel disease. **a** Fibrinoid necrosis and aneurysmal dilatation; **b** hyalinosis, **c** aneurysmal dilatation and medial coat splitting. **d** Hemosiderin-containing macrophages at the border zone of a hemorrhage give evidence of a relapsing bleeding process (**a–c** van Gieson stain; **d** Prussian blue; magnification **a** ×100; **b, c** ×300; **d** ×500)

sels in the contralateral hemisphere of the hemorrhages, as it will be impossible to find the ruptured vessel within the hemorrhage. Sometimes he will succeed in getting information on old hemorrhages (relapsing bleeding) which will be characterized by cystic scars and/or hemosiderin-containing macrophages (Fig. 28.5d, 28.23a, b).

Intracerebral hemorrhage is also observed in individuals after prolonged exposure to cold (Caplan et al. 1984) (p. 247), which can trigger increased catecholamine release and a consequent major rise in blood pressure (cf. Ramirez-Lassepas et al. 1980; Habermann et al. 1981; Schütz 1988). Moreover, otherwise-caused elevated blood pressure can, of course, also lead to vessel wall damage (see also Sect. 28.7.4).

28.3.5 Lacunar Infarcts

The elderly commonly exhibit small *perivascular cavities* in the basal ganglia (Fig. 28.7a). The existence of multiple small cavities in the gray matter is termed *état lacunaire*; in the white matter, *état criblé* (Blackwood 1958). The cavities may be caused by hypertension-induced spiraling elongation of small intracerebral arteries (Pullicino 1993; Kalimo et al. 2002). Large cavities 5–20 mm in diameter, known as *lacunar infarcts*, are thought to result from occlusion of perforating arteries 100–200 µm in diameter (Fisher 1991). The size of the infarct depends on the site of obstruction (Fig. 28.7b, c). An infarct leads ultimately to lacunae, so called due to their appearance in the cavitated state. Multiple lacunae in the thalamus, lenticular nucleus, and cerebral white matter are often associated with chronic hypertension. Recent studies show that lacunae are probably the result of small artery occlusion secondary to hypertension-induced lipohyalinosis (Fisher 1991) (see also Chap. 31).

28.3.6 Amyloid Angiopathy

Amyloid angiopathies comprise a group of systemic vessel diseases that may also be organ specific, e.g., to the cerebrum. The vessel walls possess extracellular deposition of amyloid, which can be demonstrated histologically by its binding affinity to Congo Red (polarized light: green birefringence), to thioflavine S or T, and to periodic acid Schiff (PAS). Deposition of amorphous material leads to thickening of the vessel walls, which become increasingly more rigid

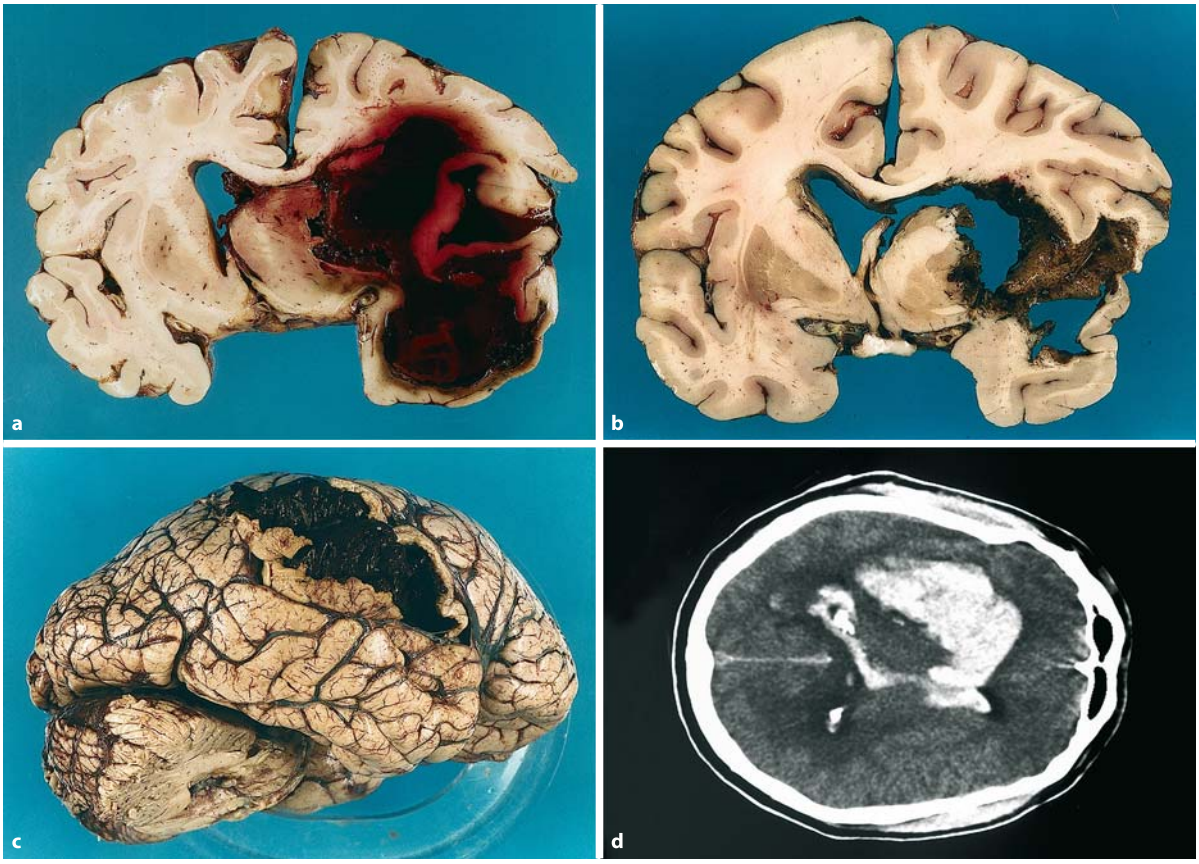

Fig. 28.6a–d. Hypertensive intracerebral hemorrhage. The bleeding commonly occurs within the white matter of the (**a**) frontal and/or parietal and/or temporal lobes partly involving the cerebral deep gray nuclei (**b, d**), often bursting through the ventricular wall and/or (**c**) the hemispheric surfaces. MR-imaging of hypertensive intracerebral hemorrhage associated with secondary ventricular hemorrhage (kindly provided by Professor Dr. H.B. Gehl, Lübeck)

and fragile. The vessels are also conspicuous in H&E stain as being abnormally round and thick-walled, especially in the cortex.

The most common type of amyloid angiopathy is recognizable by deposition of β-amyloid peptide (βA4) affecting medium-sized and small arteries and arterioles (see Fig. 31.4d). Topographically, the sites most often affected are the cerebral cortex and meninges of the parietal and occipital lobes. Bleeding due to vessel rupture occurs in the frontal or frontoparietal regions. Amyloid angiopathy is the cause of 5–12% of all primary intracerebral hemorrhages that are not mechanically induced (Gilbert and Vinters 1983).

28.3.7 Cystic Medial Necrosis

This is a systemic disease featuring extensive deposits between elastic laminae, some foci coalescing to form cysts at the expense of surrounding smooth muscle and elastic fibers. The deposits are reactive with Alcian blue and PAS. Most often affected are larger vessels such as the carotid arteries. The alterations of the lamina media entail an enhanced risk of dissecting aneurysm with consequent arterial occlusion and cerebral infarct. Arterial dissection leads to intramural hematoma due to extravasation of blood into the arterial wall, usually between the intima and media. In intracranial arteries such dissections are very rare events.

28.3.8 Aneurysms

Aneurysms are characterized by focal dilatation of an arterial wall. Four types of intracranial aneurysm can be distinguished morphologically and etiologically. None of the types gives rise to primary symptoms, but each is capable of sudden rupture that leads to possibly lethal subarachnoid hemorrhage (SAH). Aneurysms are one of the most common causes of sudden unexpected death.

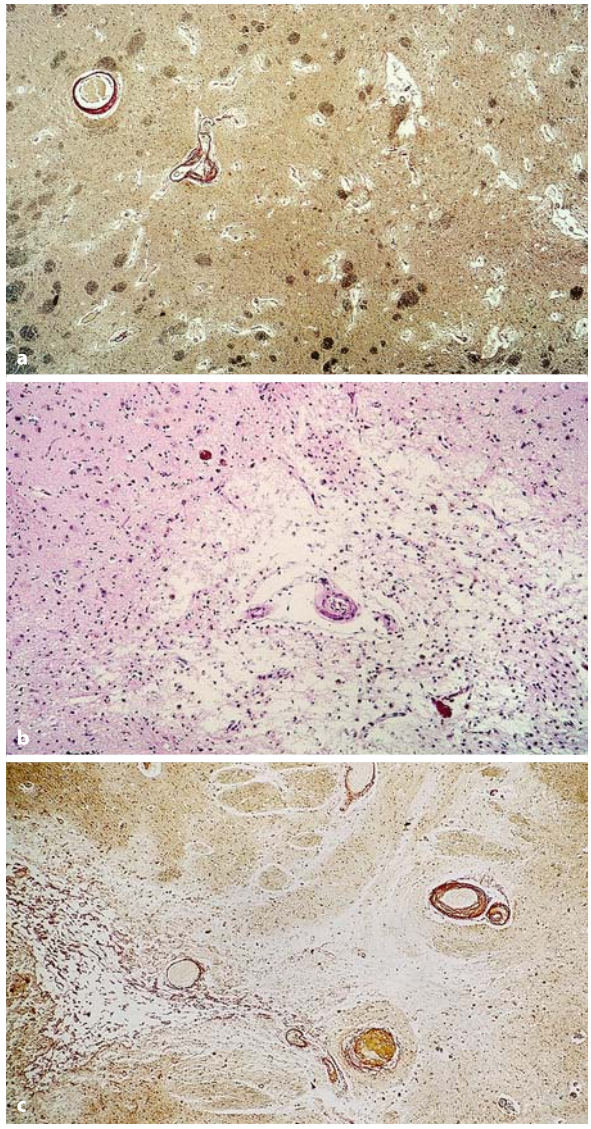

Fig. 28.7a–c. Lacunar infarcts. Sequelae of chronic hypertension may also include the phenomenon of enlargement of the perivascular spaces in central parts of the cerebral white matter and the basal ganglia (**a**), which regularly is accompanied by cystic necroses of different extent (**b, c**) as well as by small vessel disease (**b** H&E; **a, c** van Gieson stain; magnification **a** ×300; **b, c** ×100)

28.3.8.1 Saccular (Fusiform) Aneurysm

Morphology. The sequela of the rupture of an aneurysm of the large basal cerebral arteries is marked by an extensive basal subarachnoid hemorrhage including the cistern of the chiasma, and, rarely, associated with an intracerebral (intraparenchymal) hemorrhage (see p. 573). Saccular aneurysms are spherical, often berry-shaped (Fig. 28.8), but they can also assume a variety of other shapes. The diameter ranges 1–25 mm. For pathologists it is important to note that aneurysms tend to shrink post mortem (McCormick and Acosta-Rua 1970).

An aneurysm can be extraordinarily difficult to find at autopsy. At autopsy and prior to fixation, the clotted blood should be removed with water before excision of the vessel ring. Despite these measures, the aneurysm cannot always be found. Microscopically (Fig. 28.8d), saccular aneurysms lack both the internal elastic lamina and the muscular tunica media. The wall of the aneurysm is composed of endothelial cells and fibrous connective tissue of varying thickness.

Etiology. Saccular aneurysms are noted for the thinness of the vessel wall, the lack of an external elastic lamina, and the absence of perivascular support. Once it was assumed that aneurysms are congenital, caused by an inborn gap in the muscular layer. Today it is thought that aneurysms are acquired degenerative lesions that are aggravated by hemodynamic stress (Stehbens 1989): constant overstretching due to hemodynamic stress at the apical angle of the branching sites of major cerebral arteries cause the elastic and muscular layers to degenerate.

Incidence. Primary non-mechanical SAH account for 5–9% of all strokes, while about 80% of strokes involve mechanically induced SAH, and arteriovenous malformations are responsible for 5–10% of all strokes (Kalimo et al. 2002). The main cause of spontaneous SAH is saccular aneurysm rupture. Such aneurysms are disclosed in approximately 2–5% of autopsies (Weir 1987), the incidence increasing with age. Sixty percent of ruptured aneurysms occur at the age of 40–60 years. Saccular aneurysms are more common in women than in men (ratio: 3:2). The majority of aneurysms (85–90%) occur in the rostral portion of the circle of Willis (A. cerebri anterior, A. cerebri media), 5–10% in the posterior portion (Fig. 28.1). Aneurysms that rupture are almost always more than 10 mm in diameter (Wiebers et al. 1987). Aneurysms increase in size over time gradually attaining the critical diameter of 10 mm. Moreover, a large study (n=100 patients) evaluated the relationship between aneurysm size and the volume of SAH (Russell et al. 2003). The authors stated that the smaller cerebral aneurysm size is associated with a large volume of SAH.

Their findings were confirmed by another group (Day et al. 2003) who noted that the incidence of bleeding progressively diminished with larger lesions; patients with stenosis or occluded vessels most often presented with ischemic symptoms, and occasionally with hemorrhage. Giant focal dilatations or serpentine aneurysms are rarely associated with acute bleeding (see also Fig. 28.9); clinical presentation is most often prompted by mass effect or throm-

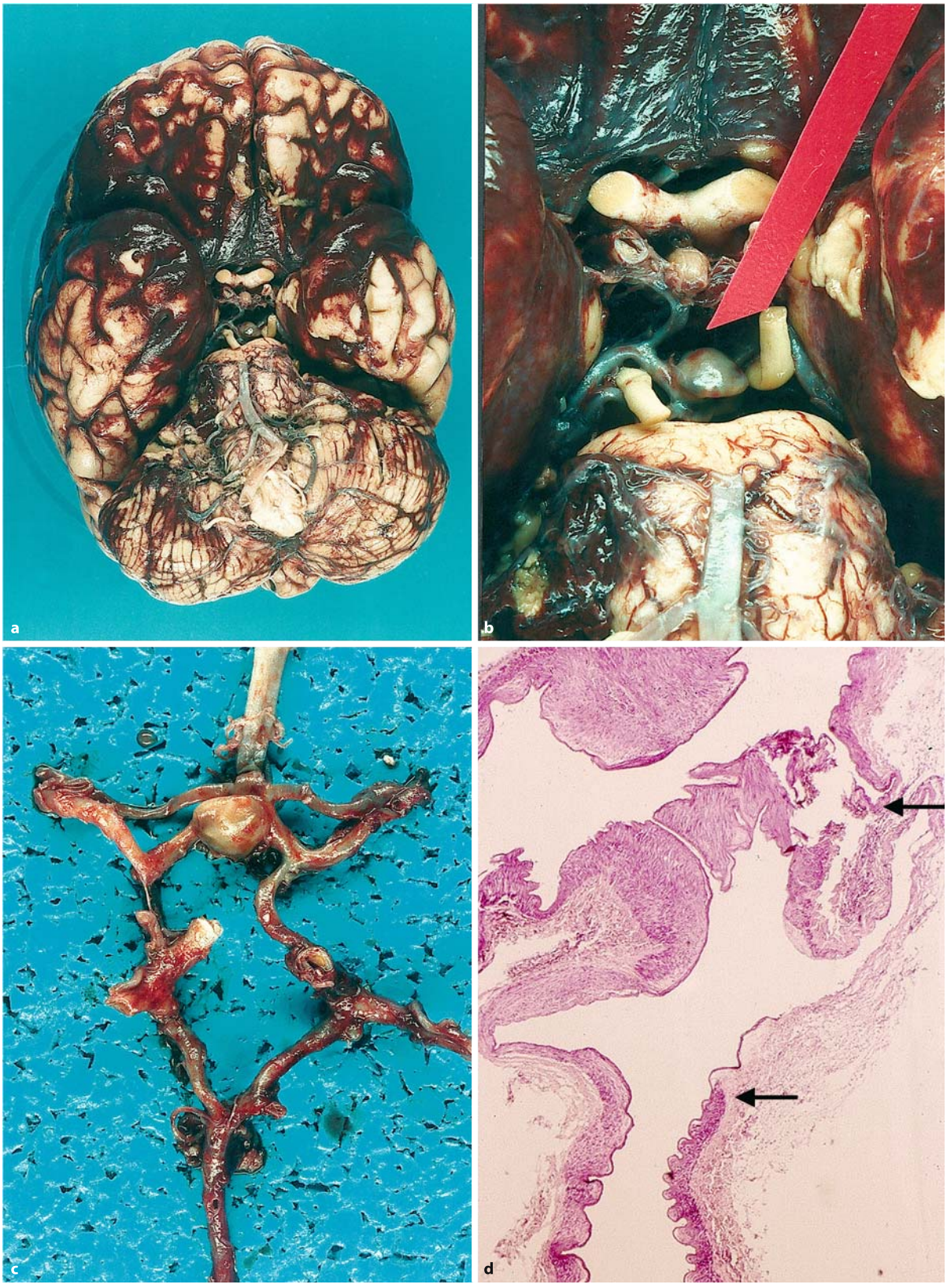

Fig. 28.8a–d. Rupture of a saccular aneurysm. **a** Basal subarachnoid hemorrhage; **b** visible aneurysm in situ; **c** circle of Willis demonstrating the (unusual localization of the) aneurysm at the bifurcation of the basilar artery / Aa. cerebri posterior; **d** histology of the aneurysm; *arrows* demonstrate the edges of the ruptured vessel's wall (H&E, magnification ×50)

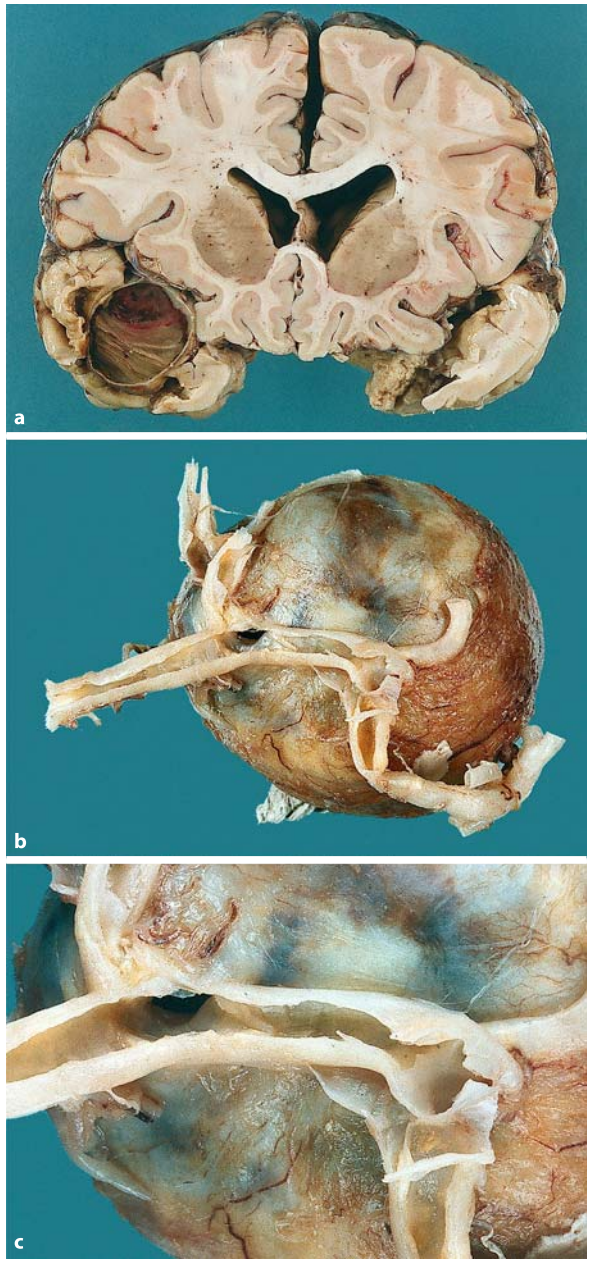

Fig. 28.9a–c. Unruptured giant, fusiform aneurysm of the middle cerebral artery within the white matter of the left temporal lobe (in situ) (**a**), and after isolation (**b**) demonstrating the open communication with the artery (**c**)

boembolic stroke. In contrast to this statement are the results of a review of the literature given by Horie et al. (2003).

Clinical symptoms arising 1–3 weeks prior to rupture of an aneurysm are often of cerebral nature, e.g., headache, nausea, visual defects, etc. The rupture itself is often associated with a rapid rise in blood pressure during physical stress. Clinical diagnosis of saccular aneurysms is made by arteriography, CT, and/or MRI. The therapeutic intervention usually involves cross-clamping the aneurysmal sac. This type of intervention sometimes is accompanied by ischemic stroke of the cortical area supplied by the anterior cerebral artery (Fig. 28.10).

Saccular aneurysms have a high mortality rate: they comprise 16–24% of all cerebrovascular disease-related deaths. The initial hemorrhage is fatal in about 40% of all patients; 30% of patients die within the first 24 h. The overall fatality of saccular aneurysms is approximately 40–50% (Fogelholm et al. 1993; Broderick et al. 1994). If there is no surgical intervention, one-third of the patients will die within 6 months of recurrent bleeding (Rosenørn et al. 1987), 10–20% will remain severely disabled. Only about 40% of patients recover to full self-sufficiency after SAH (Juvela 2000).

If an unruptured intracranial aneurysm is diagnosed (Fig. 28.10), the question arises as to whether surgical measures should be taken or not. While Juvela et al. (2000) think such aneurysms require surgical intervention regardless of size, especially in the young and in adults of middle-age, Raabe et al. (2003) put forth criteria incorporating the data of other authors for deciding whether or not surgical treatment is warranted in the individual case (see also: *Acta Neurochir Suppl*; 2002, 82).

The *neuropathology* is characterized by the demonstration of the ruptured aneurysm and its topographic localization. Moreover, the gross phenomena are a pronounced basal subarachnoid hemorrhage filling out the cisterna interpeducularis and in single cases associated with an intracerebral hemorrhage as a result of a ruptured aneurysm of the middle cerebral artery.

As mentioned previously (Chap. 7, pp. 139 ff), the risk of external violence and aneurysm rupture is discussed. According to the most recent investigations we must accept that there is no association between external violence and rupture of a preexisting aneurysm (Rinkel et al. 1998; Cummings et al. 2000; Juvela et al. 2000).

28.3.8.2 Dissecting Aneurysm

Intracranial dissecting aneurysms are rare compared to extracranial aneurysms of common carotid and vertebral arteries. In the extracerebral carotid, dissecting aneurysms are also often the result of iatrogenic measures, such as puncture of the common carotid artery or iatrogenic-related trauma. Intracranially the supraclinoid segment of the internal carotid artery (Little et al. 1981) and the basilar artery (Steel et al. 1982) are commonly involved. Arteriosclerosis is the underlying cause in the majority of cases, sometimes in combination with hypertension and diabetes mellitus.

Fig. 28.10a, b. The sequelae of **a** cross-clamping the aneurysmal sac of the anterior cerebral arteries: **b** ischemic necroses (*arrowheads*) of the territories supplied by the anterior cerebral arteries

Dissection of intracranial arteries is usually caused by some sort of blunt impact to the head or neck, or by hyperextension of the vertebral arteries. Imaging techniques have shown that such dissections are associated with atherosclerosis, arteritis, hypertension, etc. (O'Connell et al. 1985; Pozzati et al. 1991; Sasaki et al. 1991). The clinical picture features ischemic stroke (stenosis or occlusion) or rupture-induced SAH.

28.3.8.3 Infectious (Mycotic) Aneurysm

Endocarditis may lead to bacterial aneurysms arising from microbe-bearing emboli. The first manifestation involves a local pyogenic infection of the arterial wall, from which the aneurysm develops (Hart et al. 1987). The vessel wall loses its elasticity and stability and is liable to rupture at the site of infection.

28.3.8.4 Mechanically Induced Aneurysm

Rupture of the wall of large vessels at the base of the brain (circle of Willis) is described elsewhere and is mentioned here only for the sake of completeness (see Chap. 7, p. 143).

28.3.9 Inflammatory Vessel Disease (Vasculitis)

An artery is liable to injury from bacterial toxins, direct bacterial invasion, or from chemical and other toxins. In most cases, however, the underlying cause of injury remains unknown. A differentiation must be made between infectious and non-infectious vasculitis on the one hand, and systemic vasculitis and primary CNS vasculitis on the other. The diagnosis of systemic vasculitis (polyarteritis nodosa, thromboangiitis obliterans, systemic lupus erythematosus, Wegner's granulomatosis) is usually facilitated by the presence of extracranial manifestations (for review see Meister 2003). Clinical diagnosis of the early manifestations of systemic vascular disease of the brain or of primary CNS vasculitis is much more difficult. Definitive diagnosis is often only possible by brain biopsy or by autopsy.

In the following only the primary CNS forms of vasculitis will be discussed.

28.3.9.1 Non-Infectious Primary CNS Vasculitis

The causes of these types of vasculitis are not known, although autoimmune processes are thought to play a role. The clinical picture is generally non-specific.

Polyarteritis (Nodosa). Polyarteritis (or periarteritis or panarteritis) is a disseminated disease of unknown origin. It features focal inflammatory lesions affecting various tissues and organs, usually associated with small and medium-sized arteries and arterioles. All coats of the artery are involved in the inflammatory process, as is the perivascular tissue. The processes include swelling, destruction of the internal elastic membrane, necrosis and fibrillation of the media, infiltration of the adventitia by polymorphonuclear leukocytes and, sometimes, by

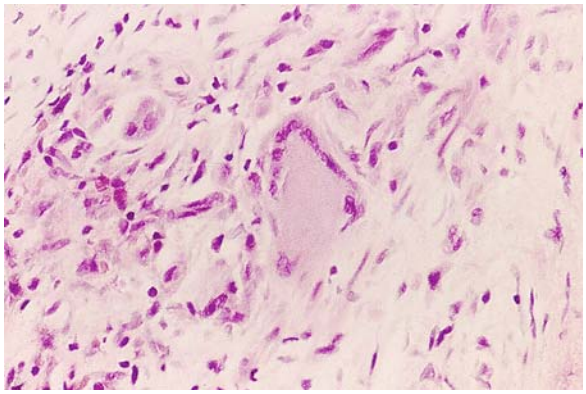

Fig. 28.11. Giant cell arteritis (Horton) which is characterized by multinuclear giant cells of the Langhans' type (H&E; magnification ×500)

eosinophils. The main pathologic change involves focal necrosis of the medial coat, which may lead to formation of an aneurysm and thrombosis. Small aneurysms occasionally rupture, causing frank hemorrhage or hemorrhagic extravasation.

Giant Cell Arteritis (Temporal Arteritis-Horton). In most cases, extracranial arteries of the head are first affected, the temporal artery in particular, but also the carotid, ophthalmic or vertebral arteries. The salient clinical features are loss of vision and headache. Macroscopically the morphology is characterized by thickening and hardening of the temporal artery. Microscopy reveals lymphoplasmacytic infiltrates in the intima and media, with giant cells of both the foreign body and Langhans' types (Fig. 28.11). The lumen usually exhibits narrowing or complete occlusion caused by severe proliferation of the intima, a fibrotic process that involves some smooth muscle cells and is often associated with thrombosis at the site of occlusion. The presence of conspicuous but localized periarteritis and mesarteritis lends the appearance of focal granuloma. Most cases also feature focal necrosis of the media and internal elastic membrane. All cell layers undergo secondary fibrosis causing thickening and functional insufficiency.

Takayasu's Syndrome (Aortic Arch Syndrome). This disease has an etiology similar to that of giant cell arteritis with the difference that it mainly affects the aortic arch and its major branches, especially the left subclavian artery. Thickening of vessel walls can lead to thrombosis, occlusion, and the loss of radial pulse.

Primary Angitis of the CNS (PACNS; Granulomatous Angitis of the CNS). PACNS is a disease not only of arteries, but of veins as well. It affects middle-aged and older persons. Intraparenchymal vessels are mainly involved, as well as various caliber meningeal vessels (Cravioto and Feigin 1959; Aita 1972). The vascular lesions feature proliferation of connective fibers and mononuclear cells of various types, including large mononuclear cells, plasma cells, lymphocytes, and multinuclear giant cells of foreign body and Langhans' type (Fig. 28.12a, b). Sometimes the brain parenchyma exhibits a distinct microglial reaction. Granulomatous inflammation occurs in some vessels in the intima, where a thrombus may develop, with consequent *infarct*. The blood vessels of various viscera may also be affected, but CNS symptoms predominate. The clinical features are non-specific: multifocal neurological deficits, recurring headaches, and diffuse encephalopathy with memory impairment and confusion (Sigal 1987; Moore 1989; Calabrese et al. 1992). CT or MRI reveal irregularly distributed foci of demyelination which sometimes merge with white matter in cortical regions (Fig. 28.12c, d).

Moya–Moya Disease. This disease affects both children and adults and is most prevalent in Japan (Coakham et al. 1979). It usually involves the internal carotid arteries. The clinical picture is initially characterized by repeated transient ischemia followed by hemiparesis, often in combination with subdural hemorrhages. The hemorrhages often result from extreme collateralization of vessels with consequent changes in regional cerebral blood supply (Dietrichs et al. 1992).

Microscopically, signs of arteriosclerosis and arteritis are lacking. The arterial lumina are occluded by a loose meshwork of hypocellular connective tissue. The lamina elastica interna is clearly dilated, a phenomenon often associated with recent clot formation in the engorged leptomeningeal veins (Ikeda and Hosoda 1993), which can lead to bleeding (Kono et al. 1990).

Drug-Induced Vasculitis. Vasculitis is relatively common in drug abusers, caused apparently by an allergic-hyperergic reaction (Krendel et al. 1990; Fredericks et al. 1991). Drug-related vasculitis can lead to intracerebral hemorrhage, often seen in association with cocaine and amphetamine use (Sloan 1993) (see pp. 398 ff).

28.3.9.2 Infectious Vascular Diseases

Many types of *bacterial infection*, especially meningitis, also involve the vessels, but usually not primarily. A special type of vasculitis is *spirochaetal vasculitis*, which is caused by an invasion of arterial walls by *Treponema pallidum spirochaetes* in patients with syphilis. Among the complications associated with mycotic vasculitis, a clinical feature especially common in patients undergoing immunosuppression after organ transplantation, is a so-called mycotic aneurysm, which is liable to rupture.

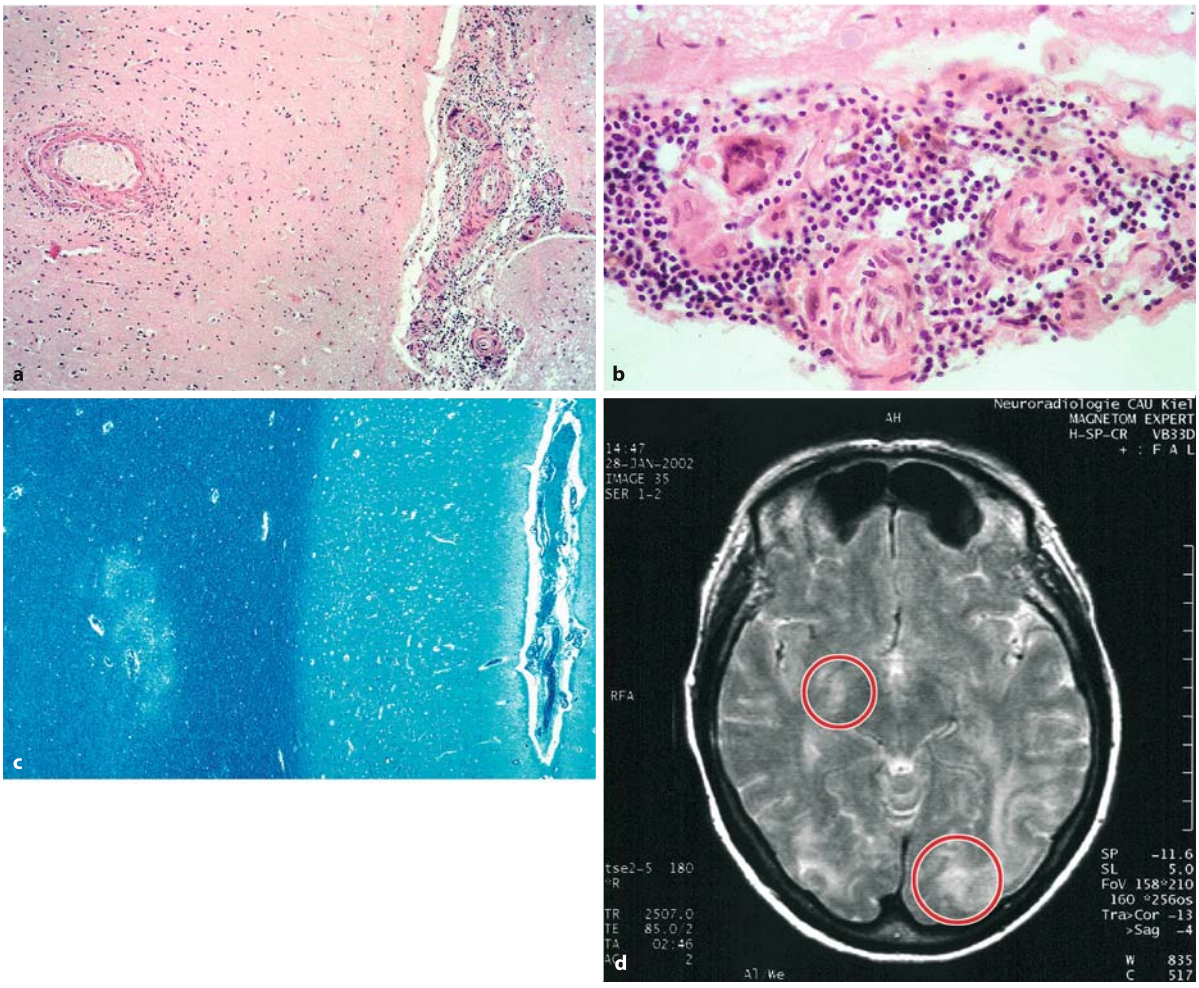

Fig. 28.12a–d. Granulomatous angitis (*PACNS*). Morphologically this type of disease is characterized by perivascular and leptomeningeal infiltration (**a**) with inflammatory cells (lymphocytes, macrophages) as well as giant cells of the Langhans' type (**b**). This inflammation is associated with a characteristic multifocal demyelination as demonstrated by myelin stain (**c**) or by MRI (**d**) (**a, b** H&E; **c** Luxol fast blue stain; magnification **a, c** ×300; **b** ×500)

Lymphocytic granulomatous or necrotizing vessel changes are associated with *viral infections* (Somer and Finegold 1995), herpes virus infections (chiefly herpes zoster-varicella virus) in particular (MacKenzie et al. 1986). Arteritides are known to be associated with human immunodeficiency virus (HIV) infections (Budka 1991). Lastly, fungal vasculitis affects immunocompromised patients in the form of opportunistic infections.

28.4 Pathology of Cerebral Veins

In addition to the vascular malformations discussed below are diseases of the veins, almost exclusively cerebral venous thromboses. About 70% of all intracranial blood is venous blood, located chiefly in the cerebral sinuses.

28.4.1 Cerebral Venous Thrombosis

The incidence of cerebral venous thrombosis (CVT) is unknown. Since numerous venous anastomoses exist, intracranial vein thromboses often remain bland and without appreciable clinical symptoms. Even if clinical symptoms do become manifest, diagnosis is complicated by the wide spectrum of clinical features and highly variable mode of onset (Ameri and Bousser 1992). Because impaired drainage of the vein of Galen is often fatal, from the clinical standpoint case reports continue to be warranted (cf. Funabiki et al. 2002).

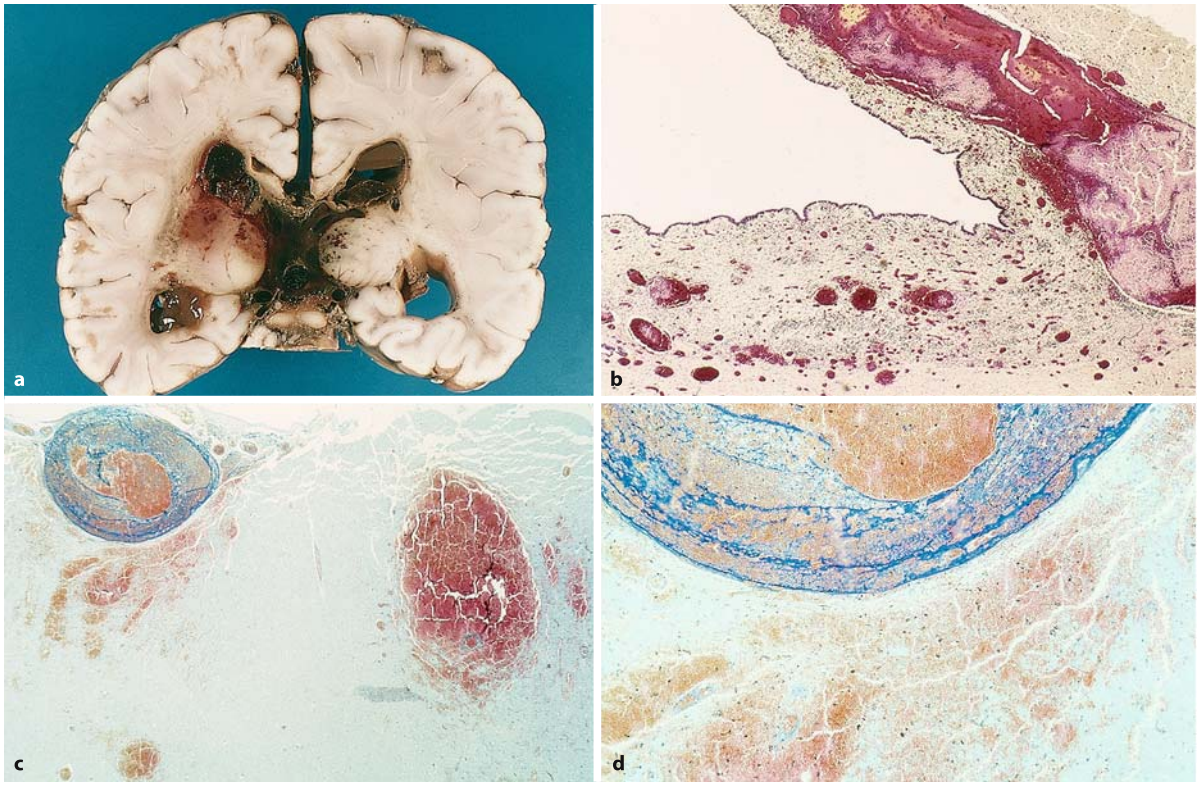

Fig. 28.13a–d. Cerebral venous thrombosis. **a** Thrombosis of the inferior sagittal sinus associated with a periventricular hemorrhage in a newborn child; **b, c, d** fibrin precipitation within the lumen of periventricular vessels (**b** PAS; **c, d** Azan stain; magnification **b, c** ×100; **d** ×300)

Clinical Features. CVT occurs in the perinatal period (see Chap. 22, pp. 436 ff), in middle age, and in advanced age. Women are affected slightly more often than men (Einhäupl et al. 1990; Ameri and Bousser 1992). The clinical picture is characterized by non-specific symptoms of elevated intracranial pressure: headache, impaired vigilance, meningism, focal deficits, seizures, coma. The diagnosis can only be made by radiology (Thron et al. 1986), three-dimensional MR flow imaging in particular (Dormont et al. 1994). The mortality rate of CVT ranges 5–33% (Thron et al. 1986; Ameri and Bousser 1992). The ability to make early diagnosis and the advent of heparin therapy have lowered the mortality of CVT. A review of the clinical outcome in 55 consecutive CVT patients treated over a 4-year period (Breteau et al. 2003) revealed the following: 48 out of the 55 survived; 29 of the survivors experienced headaches, 7 seizures, 6 motor deficits, and 5 visual field defects. In the absence of cancer and focal deficits, the mortality rates of CVT are low, more than 80% of survivors regaining independence after 3 years. Nevertheless, the discussion continues regarding whether thrombolysis therapy is indicated, and under which circumstances (Perkin 2000; Renowden 2000). One therapeutic measure of proven worth is the prophylactic application of thrombolytic drugs (Hamilton et al. 1994). As recently evaluated, a study of 34 cases demonstrated a good neurological and cognitive long-term outcome in patients with cerebral venous sinus thrombosis (Buccino et al. 2003).

Pathogenesis. CVT may occur spontaneously. In women of childbearing age this can result from altered hormonal status due to pregnancy, puerperium or oral contraceptives (Vandenbroucke et al. 2001). Diminished blood flow can be caused by congestive heart disease, heat stroke, polycythemias, dehydration, or by tumor, hematological disorders, or trauma (disseminated intravascular coagulation). CVT is also associated with infectious disease due to chronic mastoiditis, otitis media, and with sinusitis or sepsis (Ebright et al. 2001) chiefly affecting the cavernous sinus due to local invasion of *Staphylococcus aureus* (for review see Ameri and Bousser 1992; van Gijn 2000).

Neuropathology. Stagnated blood flow gives rise to ischemic changes and vasogenic edema. The morphological result is a hemorrhagic infarct (Fig. 28.13). The superior sagittal sinus is most often affected (2/3

of all cases), sometimes in combination with the lateral sinus. The straight sinus is less often affected (Ameri and Bousser 1992). A thrombosis of the deep internal veins and great vein of Galen can trigger an infarct of the basal ganglia and brain stem (Rahman and al Tahan 1993). Whereas the morphological picture in the absence of a demonstrable thrombosis is hard to classify (differential diagnosis: *hemorrhagic infarct* secondary to arterial thrombosis), the neuropathological changes associated with a thrombosis of the superior sagittal sinus are characteristic: symmetric parasagittal hemorrhagic *infarcts* of the white and gray matter. Moreover, an obstruction of venous drainage is another cause of *non-hemorrhagic infarct*. The consequent elevation of venous pressure diminishes the perfusion pressure, with resulting tissue ischemia.

28.5 Vascular Malformations

Lack of normal maturation of embryonic vascular networks leads to vascular malformations. Although some of the names would suggest otherwise, they are not neoplastic (McCormick 1984), but – obviously – can exhibit clearly expansive growth (Siddiqui and Jooma 2001). Because the present terminology is often confusing, a simplified classification is warranted. Roizin (1958) differentiated three types of congenital vascular malformation: aneurysms, hemangioblastomas, and angiomas. But hemangioblastomas are not properly considered under the rubric of vascular malformation.

During embryogenesis diverse malformations can arise if the brain's mesenchymal tissue does not develop properly. Hemangioblastomas, e.g., *von Hippel–Lindau disease* of the retina and cerebellum, appear to originate during vascular plexus formation due to vasoformative cells growing into the neural tube. Facioencephalic malformation of the *Sturge–Weber–Dimitri neuroangiomatosis* type results from arrested growth during differentiation of the vascular plexus into arteries and veins. *Angiomas* of the CNS apparently arise during differentiation of the adult pattern of cerebral and spinal arteries and veins. *Saccular aneurysms*, by contrast, are associated with improper differentiation of vessel wall layers.

Such deformities are sometimes termed "malformation," sometimes "benign neoplasms" due to the space-occupying masses they produce. Bleeding is a common trait of such malformations and is occasionally accompanied by headache or even coma and death. However, sometimes vascular malformations are accidentally found at autopsy without clinical relevance.

Another criterion for classification is the localization of vascular malformations, i.e., whether they are located supratentorially or infratentorially. Malformations of the posterior fossa are more prone to hemorrhage and are more often associated with neurologic deficits than their counterparts superior to the tentorium (Gamache and Patterson 1984).

28.5.1 Cavernous Angioma

Cavernous angiomas (Fig. 28.14) feature large, thin-walled, and sinusoidal vascular channels. Their total mass may be small, but they usually exceed 2 cm in diameter and tend to be encapsulated. The vessels are clustered close together, not being separated by normal neural tissue. They often possess hyalinized or calcified vascular walls. Cavernous angiomas usually occur in the cerebral hemispheres, the subcortical region in particular, but are also found in the pons, internal capsule region (Challa et al. 1995), and in the ventricular system (Reyns et al. 1999). A recent review (Bertalanffy et al. 2002) showed that out of 72 patients with cavernous angioma, the lesion was located within the brain stem in 24, in the deep white matter of the hemispheres in 18, in the basal ganglia or thalamus in 12, in superficial areas of the hemispheres in 11, and in the cerebellum in 7.

28.5.2 Capillary Angioma

Capillary angiomas are composed of clusters of dilated thin-walled capillaries without elastic lamina or smooth muscle. Neural parenchyma is usually found between and around the capillaries.

28.5.3 Venous Angioma

Venous angiomas feature a network of small medullary veins and tend to affect the spinal cord with involvement of the meninges. Although they are a common incidental finding at autopsy, clinically venous angiomas of the brain are thought to represent rare vascular malformations (Handa and Moritake 1984). The vessels of which venous angiomas are composed contain ample elastic tissue and smooth muscle. Thickening of the walls and hyalinization are common features (Wolf et al. 1967).

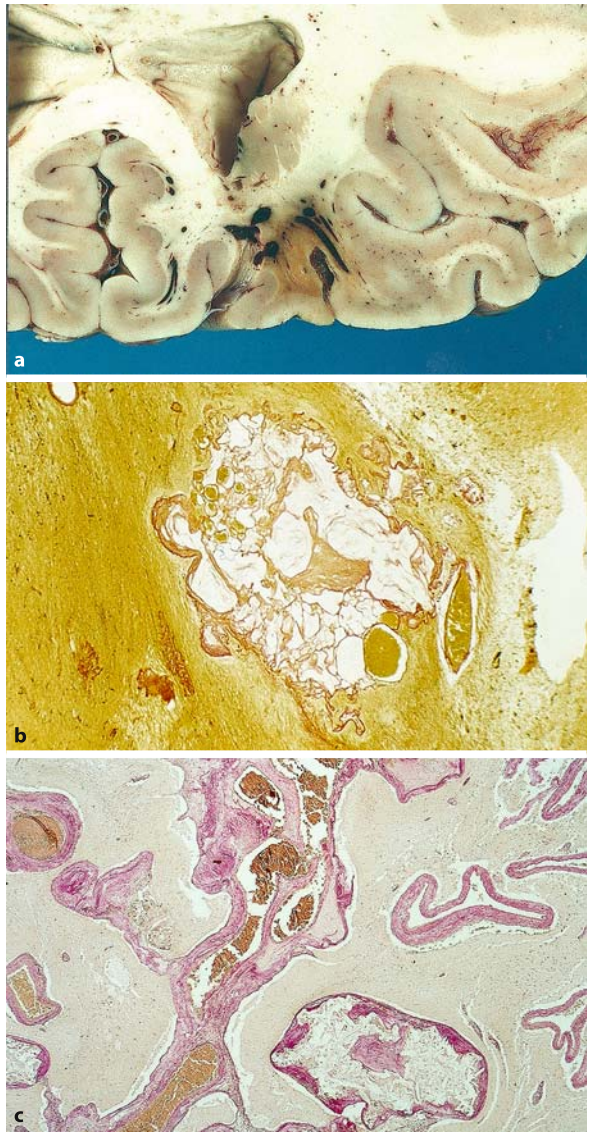

Fig. 28.14a–c. Angioma which is characterized by focal abnormal vessels of arterial and/or venous type with the risk of a spontaneous rupture. **a** Macroscopic and **b, c** microscopic findings of an angioma (**b, c** van Gieson stain; magnification ×100)

28.5.4 Arteriovenous Malformation

Deformities of this type are usually found in the region supplied by the middle cerebral artery involving the vein of Galen. They consist of direct anastomoses between the vein of Galen and the posterior cerebral artery or another branch of the internal carotid. Arteriovenous malformations are uncommon, comprising only one-tenth of all intracranial arterial aneurysms. Each year approximately 2,500 new cases are diagnosed in the United States (Stein 1984).

28.5.5 Von Hippel–Lindau Hemangioblastoma

Hemangioblastomas of this type are found in the retina and cerebellum; they usually occur in isolation (90%), occasionally in combination, and are predominantly cystic with a single large cavity and tumor cells clustering in a small mural nodule (Palmer 1972). In most cases the tumor lies near the surface of the cerebellar hemispheres and is detected by tracing hypertrophied vessels to their site of origin. The large numbers of thin-walled, closely packed capillaries are conspicuous, are lined by plump endothelial cells and are separated by larger oval or polygonal cells with central or eccentric nuclei often containing prominent nucleoli. The cytoplasm exhibits abundant sudanophilic lipids.

28.6 Tumor-Induced Stroke

A study of the incidence of acute unexpected death in tumor patients showed that out of 117 patients with glioblastoma (Silbergeld et al. 1991), 20 (17%) had died suddenly and unexpectedly without antemortem diagnosis. The likely cause of death was identified in 93 out of the 117 patients: in patients with no antemortem diagnosis the tumor was likely to have herniated.

Intracranial tumor-related sudden unexpected death is associated with various types of tumor, including astrocytoma, ganglioglioma, oligodendroglioma, neurocytoma, ependymoma, and rarely subependymoma, but most frequently with metastases. In all such cases, death results from herniation of the tumor located in a vital site, or from fulminating hydrocephalus secondary to ventricular obstruction and necrosis and/or hemorrhage (for review see Ortiz-Reyes et al. 2002).

The actual incidence of stroke involving necrosis or hemorrhage in tumor patients is unknown. By contrast, the regressive processes in primary and secondary CNS tumors are as well known as in their extracerebral counterparts (Zülch 1986). Cerebrovascular necroses and hemorrhage are associated with a variety of tumor-related conditions, among them coagulation disorders, direct invasion, side-effects of chemotherapy, non-bacterial thrombotic endocarditis (Newton 1999), and abnormalities in the structure of vessel walls.

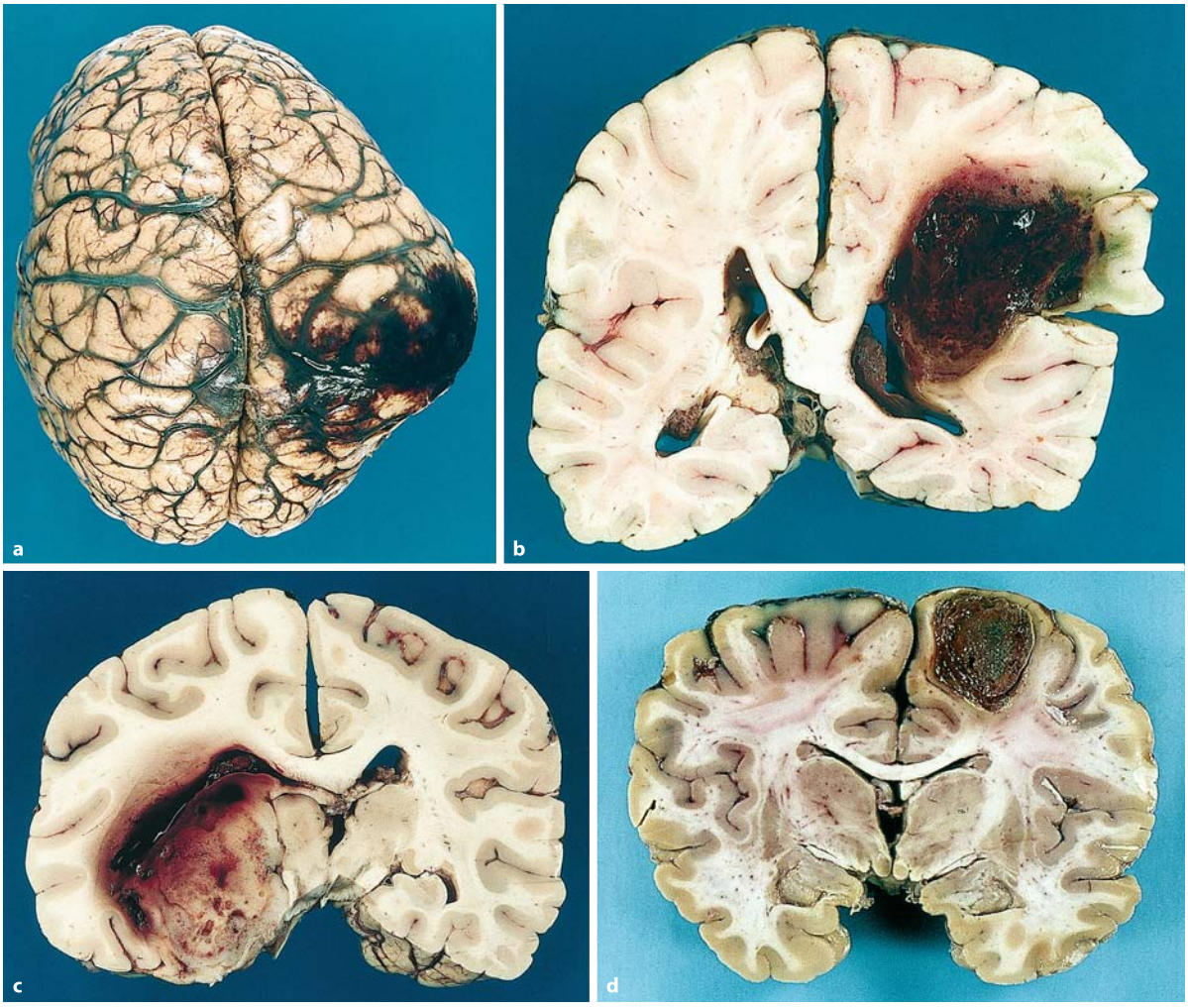

Fig. 28.15a–d. Tumor-induced stroke. Acute hemorrhages in **a, b** an anaplastic oligodendroglioma, in **c** a malignant glioblastoma, and **d** a metastatic tumor of unknown origin

28.6.1 Thrombosis and Embolism

Venous thromboembolism generally affects patients undergoing therapy for primary and secondary cerebral tumors (Walsh and Kakkar 2001). The underlying molecular mechanism may involve a hypercoagulable state that produces the regressive changes described by Zülch (1986). The necrosis is most often found in secondary tumors of small cell carcinomas of the bronchus and in glioblastomas and malignant retinoblastomas, which often exhibit endothelial proliferation and thrombosis. In malignant tumors necrosis is a sudden occurrence. Leukocytes are sometimes noted around the border of necrosis. If the necrosis is survived for long, a zone of macrophages forms near the necrosis. This zone is often made up of rod cells that quickly accumulate fat and frequently transform into round, compound granular corpuscles (fat-containing macrophages).

28.6.2 Tumor Vessels and Hemorrhage

In approximately half out of all cases, intracerebral hemorrhage (ICH) is the first tumor manifestation (Little et al. 1979). Massive hemorrhaging occurs in up to 10% of intracerebral tumors (Zuccarello et al. 1981; Albert 1982), including primary CNS tumors such as gliomas, glioblastomas, oligodendrogliomas, and metastases of hemangiopericytomas, melanomas (Feldman et al. 1991), as well as fibrous histiocytomas (Pimentel et al. 2001), pituitary adenomas, Schwannomas (Asari et al. 1992), subependymomas (Ortiz-Reyes et al. 2002), and primitive neuroectodermal tumors (Aoki et al. 1992). Massive hemorrhages (Fig. 28.15) are attributed to the tumor's rich vascularity, with thin-walled, dilated vessels, and to the rapid growth and hyalinization of the vessel walls.

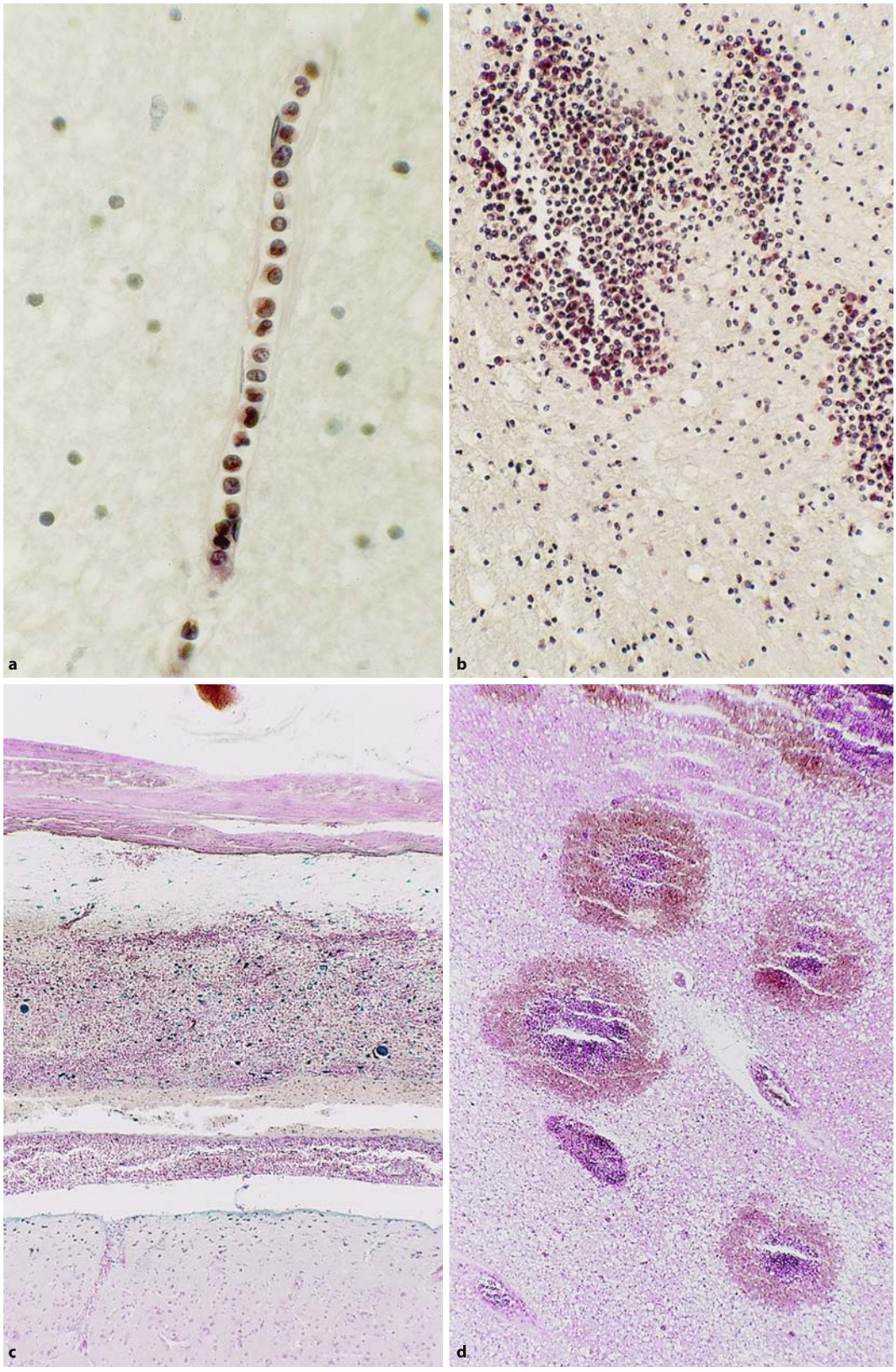

Fig. 28.16a–d. Coagulopathy associated with leukemic CNS infiltration. **a** A capillary filled with a row of (atypical) mononuclear leukocytes; **b** massive brain tissue infiltration by leukemic cells; **c** hemorrhage with siderophages in the subdural and subarachnoid space, and **d** multiple hemorrhages within the brain parenchyma (**a, b** N-AS-DCIAE, **c** Prussian blue stain, **d** PAS; magnification **a** ×1,000; **b** ×500; **c, d** ×100)

The sequelae of intraoperative hemorrhage can also prove fatal, sometimes on account of the rich intratumoral vascularization, sometimes due to necessary interventions on the preformed intracerebral vessels (Silbergeld et al. 1991; Fukai et al. 2002). Zülch (1986) points out that the pressure differences following pneumoencephalography, ventriculography or arteriography as well as the operative draining of high-pressure hydrocephalus have been associated with fatal hemorrhaging.

28.7 Extracerebral Causes of Stroke

Apart from diseases located primarily in the brain, extracranial diseases and effects can lead to cerebral ischemia and hemorrhage. These extracranial disorders are a (general) disturbance of blood coagulation with hemophilia (coagulopathy); alternatively, regional (embolism) or total cerebral blood flow is slowed or arrested due to cardiac arrest or a drop in blood pressure (circulatory disturbance or arrest).

28.7.1 Coagulopathy, Hemostatic Disorder, Cerebral Thrombosis

Cerebral hemorrhages usually result from anticoagulation treatment, e.g., warfarin treatment or the use of thrombolytic agents. Of patients treated with anticoagulants, almost 1% suffer from ICH during therapy. They have a three times greater risk of ICH than controls (Albers et al. 1991). About 10% of ICH are induced by anticoagulants.

Intracerebral bleeding secondary to leukemia is a relatively rare phenomenon (Pedal and Oehmichen 1982). Infiltration of vessel walls can lead to rupture, or a thrombocytopenia can result from suppression of normal bone marrow hematopoiesis (Fig. 29.16). The result can be massive bleeding as well as smaller, multifocal, sometimes confluent hemorrhages, possibly of different ages (Almaani and Awidi 1982).

Primary *platelet diseases* can also cause hemorrhages and/or ischemia. These include hemolytic–uremic syndrome, thrombotic thrombocytopenic purpura, and thrombotic microangiopathy.

Anemias are not a risk factor for stroke, but *polycythemias* (Chievitz and Thiede 1962; Millikan et al. 1987) and *dehydration* (Niaza et al. 1994) leading to elevated hemoglobin levels and hematocrit raise the risk of stroke due to thrombosis (Kannel et al. 1972). Diseases accompanied by aggregation of platelets and activation of the coagulation cascade can lead to intravascular thrombosis, and thus to regional ischemia. Hypercoagulopathy and thrombotic occlusion can be caused by defects of antithrombotic mechanisms, often related to cancer.

28.7.2 Cerebral Embolism

Cerebral vessel occlusions usually result from emboli originating in a fibrillating atrium or a ventricular wall near an infarct or damaged valve of the heart. Cerebral embolism may also arise from the ascending aorta, carotid artery or pulmonary veins. Paradoxical emboli are known to enter the systemic circulation by passing from leg veins through a patent foramen ovale. Trauma-induced fat emboli and bone marrow emboli can also be paradoxical emboli. Tumor cells, infected thrombus as well as amniotic fluid or air are known as emboli.

Although only 20% of the entire circulating blood is contained in the cerebral vessels, 50% of all symptomatic arterial embolisms occur in the brain, where they account for 5–15% of all strokes (Toole 1990). Possible causes include:

1. The brain‘s sensitivity to obstruction of the blood flow.
2. Flow–dynamic processes lead to movement of solid material from the left ventricle via the aorta directly into the truncus brachiocephalicus and into the left common carotid artery.

Emboli may cause infarcts of the cerebral cortex and white matter. In most cases embolic material cannot be demonstrated proximal to an infarct. If this occurs, the differential diagnosis must include vasospasm, cardiac failure or hypotension. In questionable cases “an infarct without demonstrable vascular origin” must be assumed. From the neuropathological standpoint, most hemorrhagic arterial infarcts result from embolism, pale infarcts from atherosclerotic thrombosis (Dudley 1982).

28.7.3 Circulatory Disturbance

Although anemias alone rarely lead to stroke, if they are associated with a *reduction of the local blood flow* they can. While blood flow is normally 50 ml/100 g per min, the critical cerebral blood flow required to maintain a normal electroencephalogram has been calculated to be only 15 ml/100 g per min, or approximately 30% of normal (see pp. 542 ff). The most common sources of neurologic complications are intraoperative embolization and postoperative hyperperfusion syndromes involving an increase of cerebral blood flow to more than 200% of baseline flow, the former being the main cause of ischemic

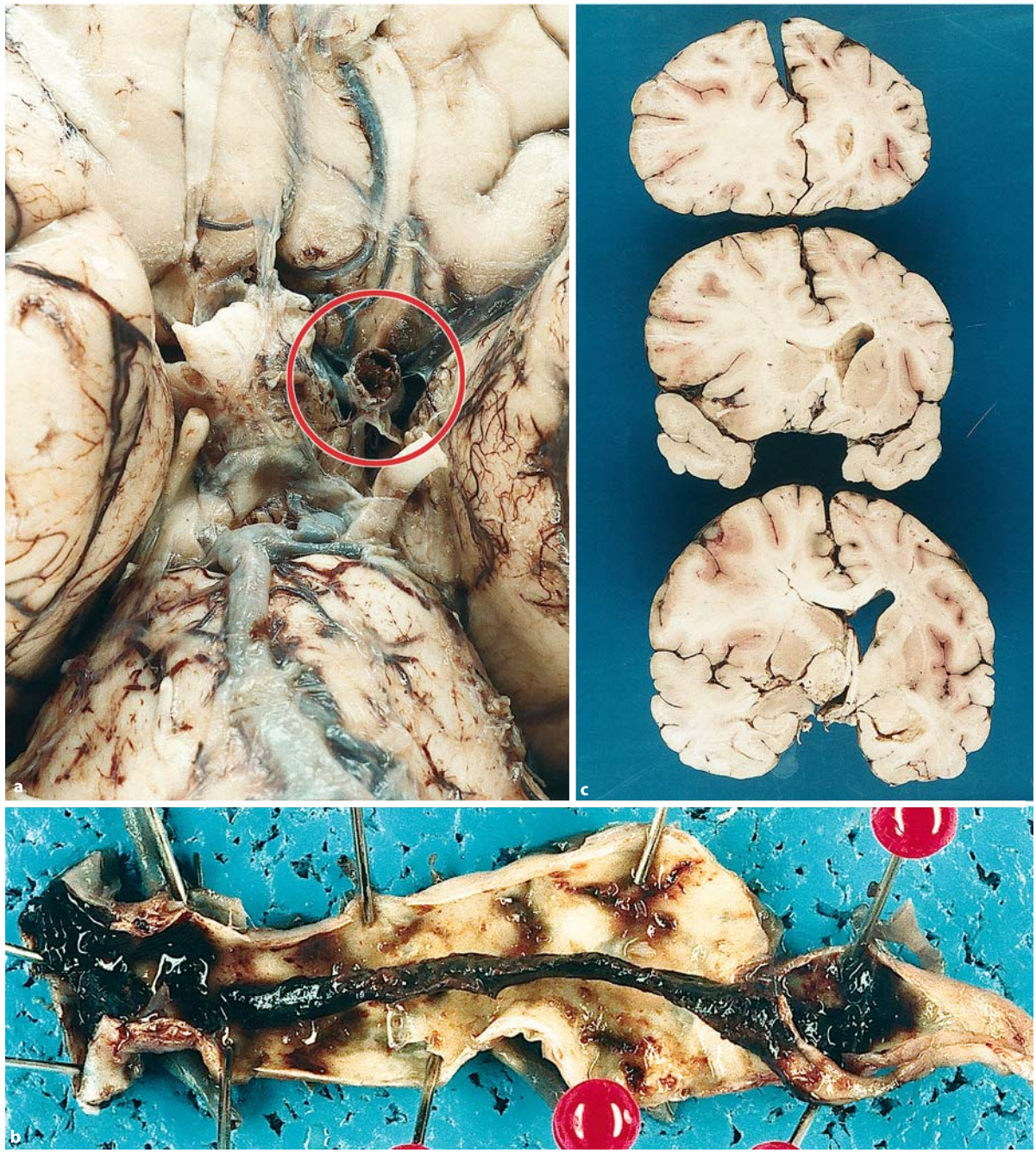

Fig. 28.17a–c. Intracranial thrombosis (*circle*) (**a**) and extracranial thrombosis (**b**) of one carotid artery, associated with unilateral lethal edema causing a massive shift from left to right (**c**)

infarct, and the latter of intracerebral hemorrhages, transient seizures, and migraine variants (Sundt et al. 1981).

A temporary, but long-lasting drop in blood pressure alone can be the cause of local or generalized cerebral ischemia especially of (hypotensive) brain stem necrosis. Finally depending on the duration of cardiac arrest, local necrosis of oxygen-sensitive regions of the brain can develop. Sometimes cardiac arrest leads to generalized ischemia of the brain, with subsequent brain edema and ensuing intracerebral circulatory arrest in the form of respirator brain (brain death syndrome).

The sequelae of *stenosis* or of total *obstruction of the large arteries supplying the brain*, the carotid arteries and the vertebral arteries include focal or generalized necrosis of the brain. In some instances, acute occlusion of the carotid arteries (Fig. 28.17)

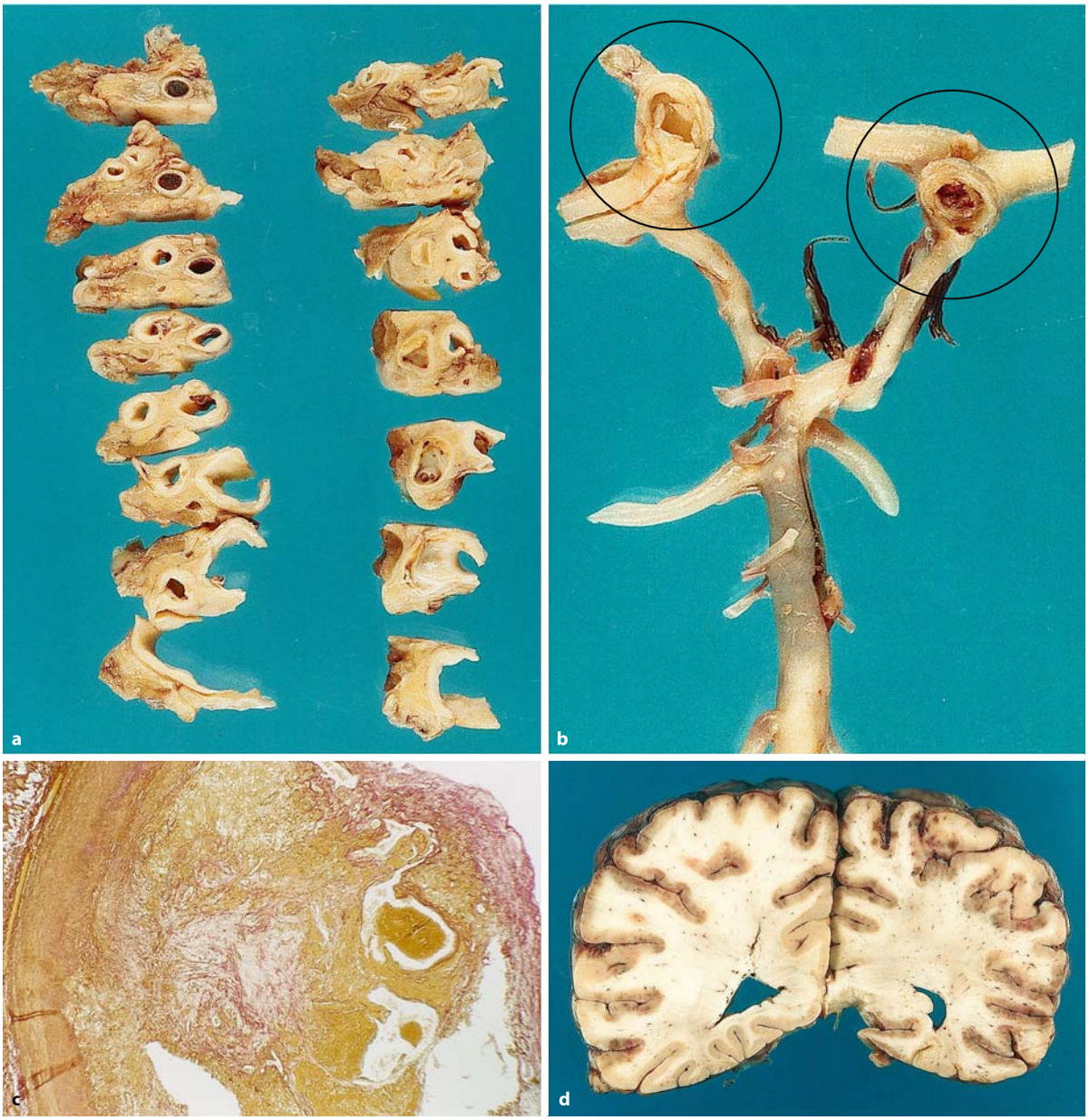

Fig. 28.18a–d. Extracranial arteriosclerosis of the common external carotid arteries. The stenosis, obliteration and occlusion of the external carotid arteries is demonstrable outside (**a**) and within (**b**) the cranial cavity on the stumps of the internal carotid arteries (*circles*); microscopically the occlusion could be affirmed (**c**); obviously an acute bilateral occlusion by a thrombosis which was not demonstrable on autopsy caused the global hemorrhagic infarction **d** of the cerebral cortex (**c** van Gieson stain; magnification ×100)

can impair blood flow to the brain through the medial cerebral artery. Chronic occlusions or stenoses, by contrast, are usually survived without neurologic deficits by virtue of anastomoses forming a collateral circuit. An exception may be the *subclavian steal syndrome* (Toole 1990): complete occlusion of the subclavian artery at its origin leads to a drop in pressure within the ipsilateral vertebral and distal subclavian arteries. As a consequence, blood from the contralateral vertebral and basilar arteries does not flow against the slight resistance within the basilar artery, but down the ischemic vertebral artery and into the arm. There follows a circulatory disturbance of the upper brain stem and pons. We observed a case of chronic stenosis/occlusion of both carotid arteries (Fig. 28.18) demonstrating global cortical hemorrhagic infarction of the brain.

Certain *sites have a predilection for arterial stenosis* or obstruction. The most common such sites in the carotid circulation are within the first few cen-

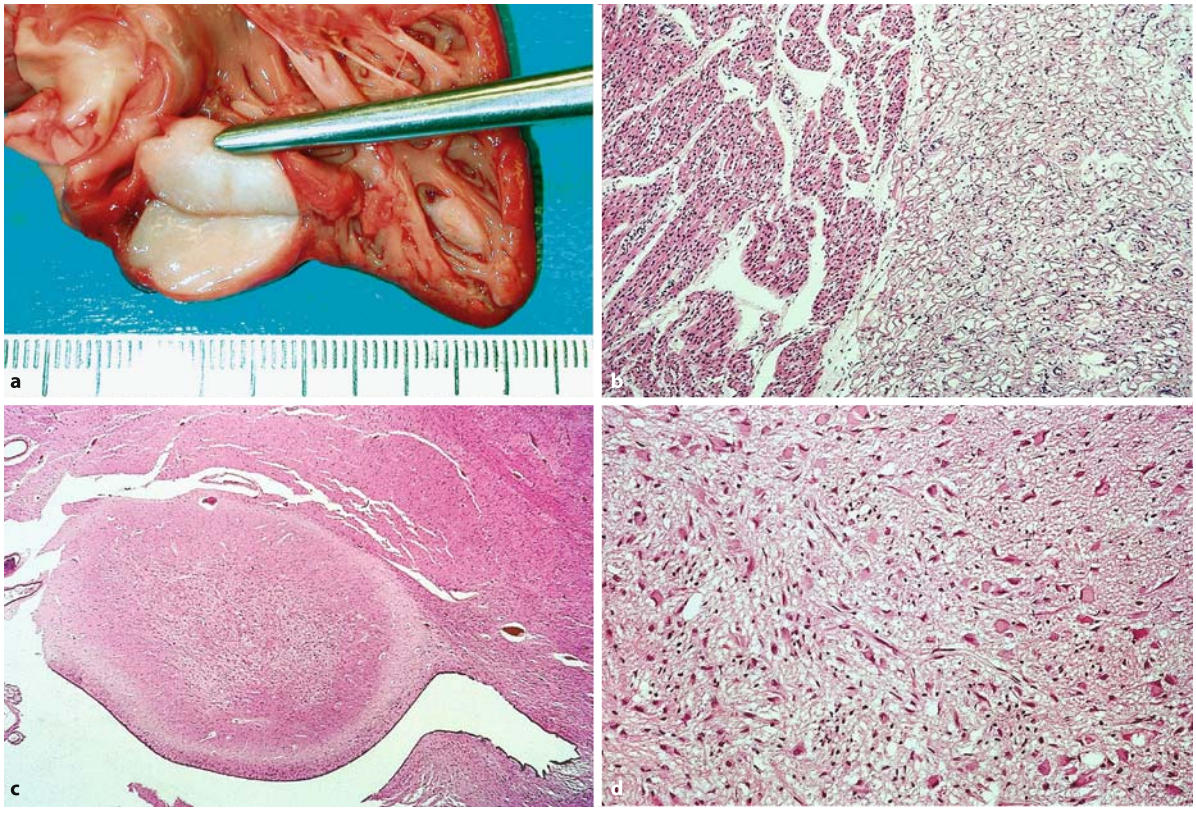

Fig. 28.19a–d. Extracranially caused acute stroke in a child younger than 1 year characterized by symptoms of tuberous sclerosis. **a** Cardiac tumor with the histological features of a rhabdomyoma (**b**) which was associated with small glial tumors in the periventricular cerebral tissue and within the ventricle (**c, d**) (H&E; magnification **b, c** ×100; **d** ×300)

timeters of the internal carotid artery in the neck, followed by the carotid siphon. In the vertebrobasilar circulation, atherosclerosis is most often seen at the origin of the vertebral arteries in the neck, in the basilar artery, and in the intracranial distal portion of the vertebral arteries.

In this respect it will be of (forensic) interest to see whether there is an indication for endarterectomy for asymptomatic carotid artery stenosis. According to the Executive Committee for the Asymptomatic Carotid Atherosclerosis Study (1995), patients with carotid stenosis of 60% or more reduction in diameter whose general health makes them good candidates for elective surgery will have a reduced 5-year risk of ipsilateral stroke if carotid endarterectomy is performed.

Another type of extracerebral circulatory disturbance was observed in a child <1 year old (Fig. 28.19). At autopsy a rhabdomyoma of the heart was found to be the cause of the sudden, unexpected death, which was associated with patches of depigmentation in the skin and small intraventricular tumors. These symptoms are characteristic of tuberous sclerosis (Fig. 28.18d).

28.7.4 Illegal Drugs

ICH is also associated with *illegal drug abuse*, especially involving cocaine, heroin and sympathomimetics such as phenylpropanolamine, phencyclidine, and amphetamines (Levine et al. 1991; Sloan 1993). The cause of the hemorrhages is sometimes elevated arterial pressure, and sometimes pathological changes of the vessel's wall, i.e., arteritis (see also Chap. 19, p. 399). *Alcohol* also increases the risk of ICH, in a manner strictly dependent on the amount consumed (Gill et al. 1991), as well as on the coagulopathy caused by any accompanying liver disease.

28.8 Ischemic Stroke: Infarction

As already mentioned, cerebral blood flow disturbances, e.g., cerebral infarction or intracerebral hemorrhage, can lead to stroke. A number of diseases and conditions are risk factors for hemorrhagic versus ischemic stroke (Table 28.1). Moreover,

Table 28.1. Risk factors associated with cerebral hemorrhagic and ischemic stroke. Source: Walter et al. 2001

Risk factor	Hemorrhagic stroke	Ischemic stroke
Age	+	+
Hypertension	+	+
Smoking	+	+
Alcohol consumption	+	+
Diabetis mellitus	–	+
Atrial fibrillation	–	+
Thrombophilia	–	+
Anticoagulants	+	–

we have to state that 20–40% of ischemic infarcts lead to hemorrhagic transformation (Alexandrov et al. 1997; Nighoghossian et al. 2002 – for review see Ferro 2004).

28.8.1 Classification of Cerebral Ischemia

Two forms of cerebral ischemia must be differentiated: global ischemia with a reduction of O_2 metabolism extending to the entire brain, and focal ischemia with diminished blood flow to a specific area of the brain.

Global ischemia is caused by a disease-induced drop in systemic blood pressure, due to lowered cardiac output (cardiac arrest, hypovolemic shock), decreased pO_2 (respiratory insufficiency), or reduced systemic vascular resistance (vasovagal syncope or septic shock). The sequelae of permanent global ischemia (respirator brain) are described in Chap. 15 (pp. 319 ff). In this part of the present chapter the sequelae of focal ischemia are described.

In *focal ischemia* a circumscribed portion of the brain receives a deficient amount of blood. Focal arterial ischemia is usually caused by atherosclerosis (60–70% of cases) and by the aforementioned vascular diseases, including obstructed cerebral venous drainage and embolic processes.

28.8.2 Clinical Features of Transient and Permanent Focal Ischemia

Focal arterial ischemia is characterized clinically by transient ischemic attacks (TIA) or by permanent neurological deficits due to infarction or long-lasting systemic ischemia.

TIA and stroke are both included among the serious conditions caused by brain ischemia (Albers et al. 2002). Each is a marker of current or impending disability bearing a risk of death (Wilterdink and Easton 1992). TIA, however, is more amenable to treatment forestalling the onset of brain infarction. After the first TIA, 10–20% of patients suffer a stroke within the next 90 days, 50% of these patients suffering the stroke 24–48 h post-TIA (Johnston et al. 2000).

TIA is typically associated with transient episodes of neurological dysfunction attributable to a temporarily insufficient supply of blood to a region of the brain (Siekert et al. 1980). The patient's condition returns to normal between attacks. Therapy corresponds to the data of Johnston (2002). In its final phase, TIA can lead to potentially fatal infarction. Acute occlusion of a large vessel can also cause sudden unexpected death due to edema-induced herniation.

Permanent focal cerebral ischemia is caused by a long-term drop in blood flow to parts of the brain. The sequelae depend on the duration of the obstruction, the area of the brain where supply is cut off, and on the neuronal sensitivity to ischemic stress.

Compared to global cerebral ischemia, focal cerebral ischemia is less severe and irreversible injury takes longer to develop. Clinically, focal ischemia is characterized by neurological deficits, the nature of which depends on the affected region and which may persist for hours or days. Neurological deficit lasting for several days is an indication that infarction has occurred. If the infarction is extensive enough, the patient can die. Death in many cases is caused

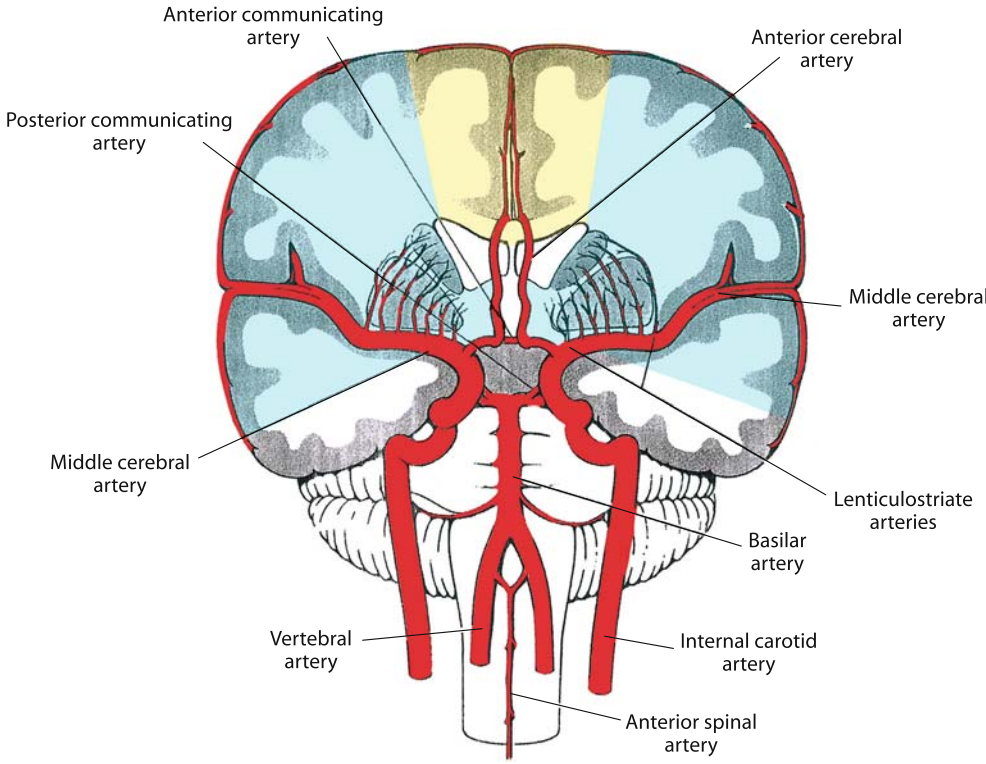

Fig. 28.20. The territories supplied by the different large basal arteries

by the associated brain edema producing herniation through the tentorium cerebelli.

The neurological deficits produced by focal ischemia can be assigned to distinct neurological syndromes, depending on the territory damaged. Lateral medullary syndrome is generally differentiated from medial medullary vertebral artery syndrome (Siekert et al. 1980).

Clinically, global cerebral ischemia features brief or prolonged loss of consciousness, with persistent global cerebral damage or focal neurological deficits depending on the cause and duration of the ischemia. A warm ischemia lasting for more than 5 min can cause generalized brain damage entailing a risk of death. The stroke symptoms were summed up by Rathore et al. (2002): headache 27%, gait disturbance 11%, convulsions 4%, vertigo 2%, speech deficits 24%, diplopia 6%, hemanopia 14%, motor deficits 82%, and sensory deficits 45%.

28.8.3 Neuropathology

The neuropathology of the *infarct* corresponds closely to that of "*necrosis*" described elsewhere (Chap. 4, pp. 56 ff). The infarct can have a *central necrotic core* surrounded by a zone of tissue receiving more than 30–45% of normal perfusion and thus is able to recover if adequate perfusion is restored. This zone has been termed the *penumbra* (pp. 63 f). The late deterioration of the penumbra zone may be reversed by early reperfusion of these regions stimulated by thrombolytic therapy or Ca^{2+} channel blockers.

Stroke is characterized by regressive changes, but it can also be compromised by an inflammatory process (Danton and Dietrich 2003): inflammation is promoted by the vascular endothelium through upregulation of adhesion molecules such as P-selectin, E-selectin, and intercellular adhesion molecules (ICAM), the binding of which to circulating leukocytes facilitates their migration into the CNS. Their production of cytotoxic molecules, once in the CNS, appears to promote cell death. We must therefore assume that complement components in reperfused ischemia injure tissue (Riedemann and Ward 2003). The response of macrophages and microglia to injury can be detrimental by facilitating cell death in neurons that may otherwise have recovered or be beneficial in the scavenging of necrotic debris.

Depending on the occluded cerebral artery, different parts of the cortical and subcortical structures are injured – the territories that are normally supplied by the occluded artery (Fig. 28.20). According to Ferro (2004) these include infarcts in the territory of: (1) the deep perforators of the middle cerebral artery, anterior cerebral artery, and posterior cerebral artery as well as the posterior communicating ar-

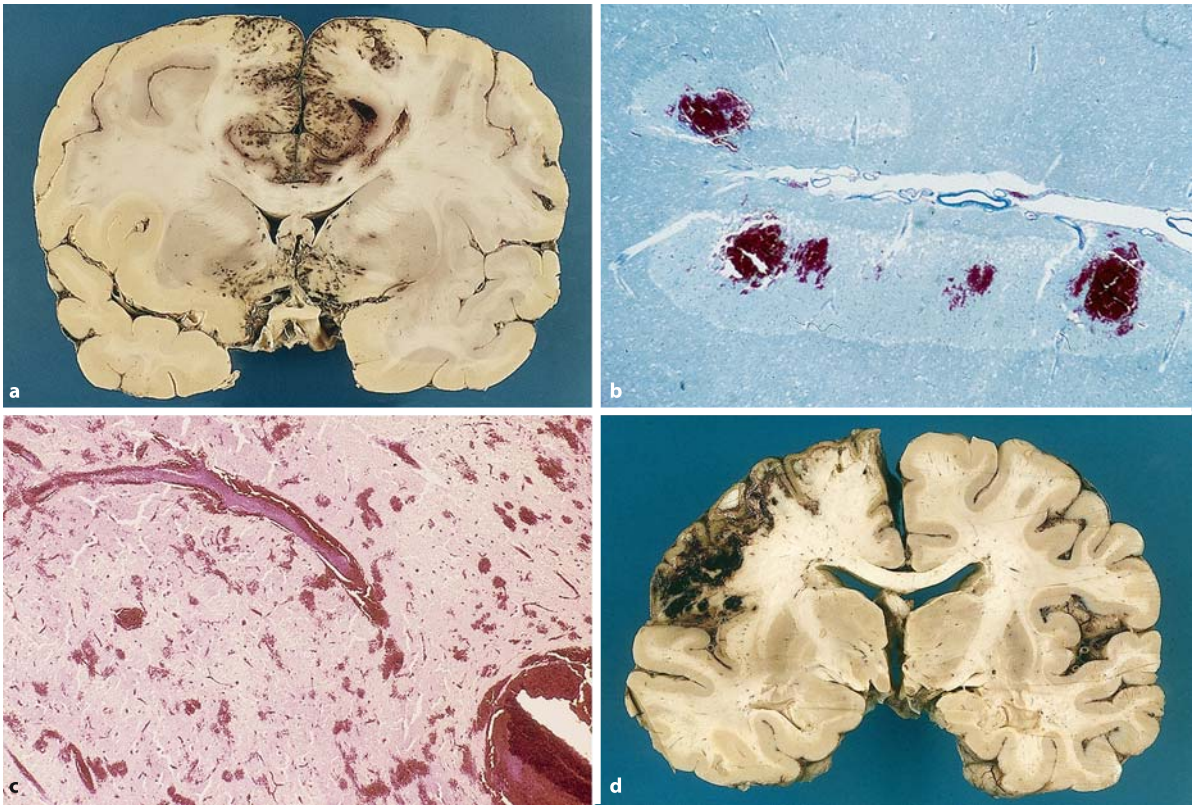

Fig. 28.21a–d. Acute hemorrhagic infarct. **a** A bilateral hemorrhagic infarct resulting from a thrombotic occlusion of both the anterior cerebral arteries associated with **b** cortical edema and multiple cortical hemorrhages; **c** the phenomenon of congestion and perivascular hemorrhage which is characteristic of an acute hemorrhagic infarct; **d** late phase of a hemorrhagic infarct as a result of the unilateral occlusion of the anterior and middle cerebral arteries (**b** trichrome stain; **c** H&E; magnification **b** ×50; **c** ×200)

tery, lenticulostriate arteries, and anterior choroidal artery; (2) the superficial perforators (white matter medullary branches) of the superficial pial arteries; (3) border zone or junctional infarcts between (1) and (2); and (4) combined infarcts (Bogousslavsky 1993). Small (<1.5 mm infarct-lacunas) are usually caused by single perforator disease while larger infarcts have a more diverse pathophysiology including embolism. Infarction of border zone and white matter medullary branches is usually caused by hypoperfusion due to large vessel occlusion or stenosis (Ferro 2004).

The necrosis may involve all the nerve cells (infarction) or only some of them (selective neuronal necrosis); depending on the possibility of recirculation, the necrosis becomes hemorrhagic (Fig. 28.21) or pale (Fig. 28.22). The common scavenger process of necrotic areas will take place and the final phase of hemorrhagic and/or pale infarct will be a necrotic cyst as can be demonstrated by means of microscopy (Fig. 28.23) and/or by macroscopic examination (Fig. 28.24). The time-dependent histological alterations are summed up in Table 28.3 on p. 572 (Schröder 1983).

Reperfusion following focal cerebral ischemia can lead to a *restitutio ad integrum*. A number of non-reflow factors can hamper reperfusion: perivascular edema, endothelial swelling, increased blood viscosity, or intravascular clotting and inflammatory factors, especially release of adhesion molecules (p-selection, ICAM-1), which can trigger occlusion of the lumen of microvessels. Even successful reperfusion does not guarantee full restitution: an increase in oxygen levels in excess of consumption might promote the formation of highly reactive oxygen free radicals, lipid peroxidation, and protein oxidation, with consequent damage to neuronal DNA (Chan 1994).

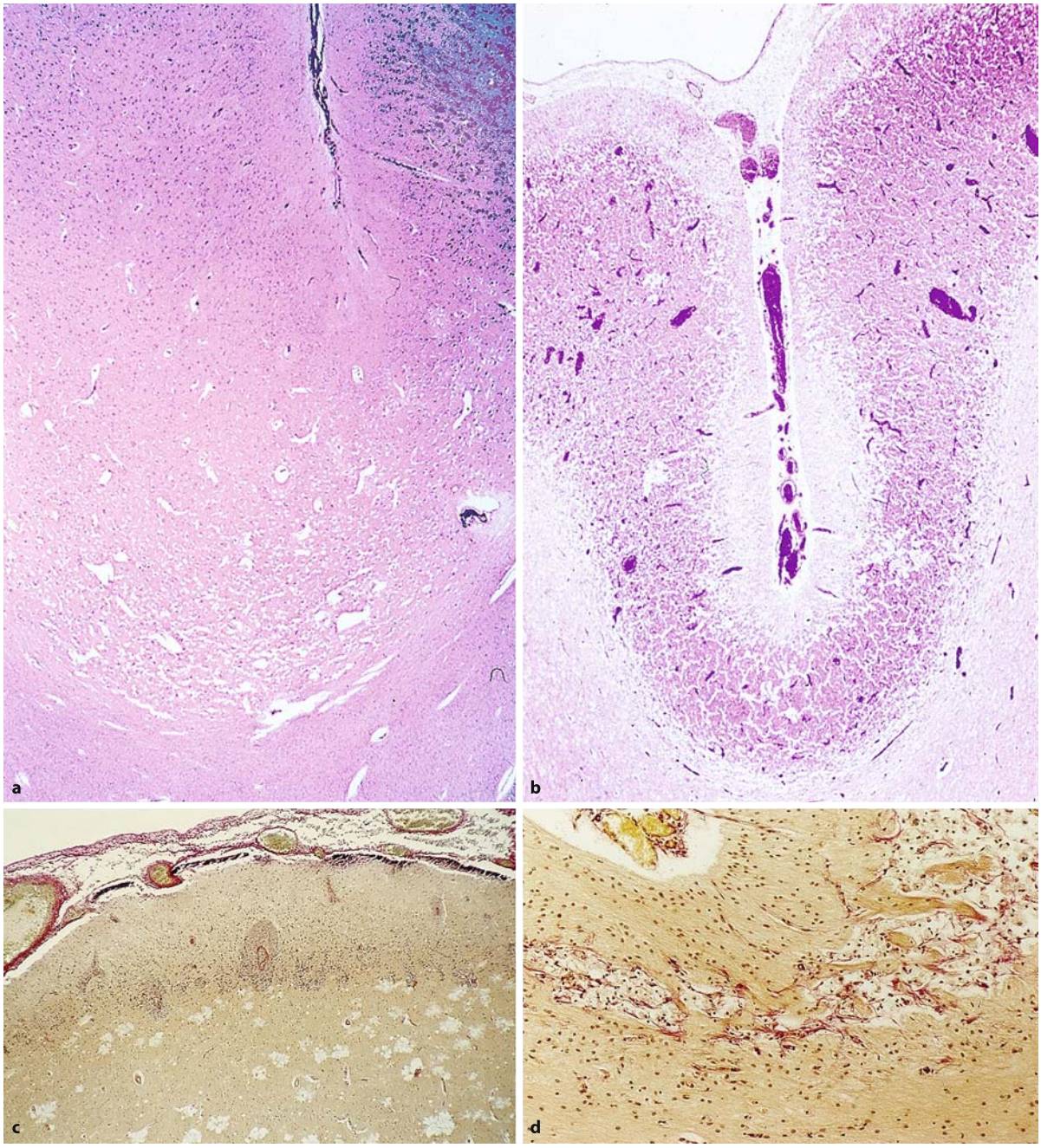

Fig. 28.22a–d. Pale (ischemic) infarct. **a** The first phase is marked by edema preponderantly in the depth of the sulcus between the 1st and 2nd frontal gyrns (watershed); **b** the second phase shows a demarcated cortex as an indication of necrosis, dilatation of vessels and edema; **c** the sequelae of endothelial reactivity will be an increase in capillaries which may result in **d** a lamellated cortical structure associated with cystic alterations and neuronal loss (**a, b** H&E; **c, d** van Gieson stain; magnification **a** ×200; **b, c** ×50; **d** ×500)

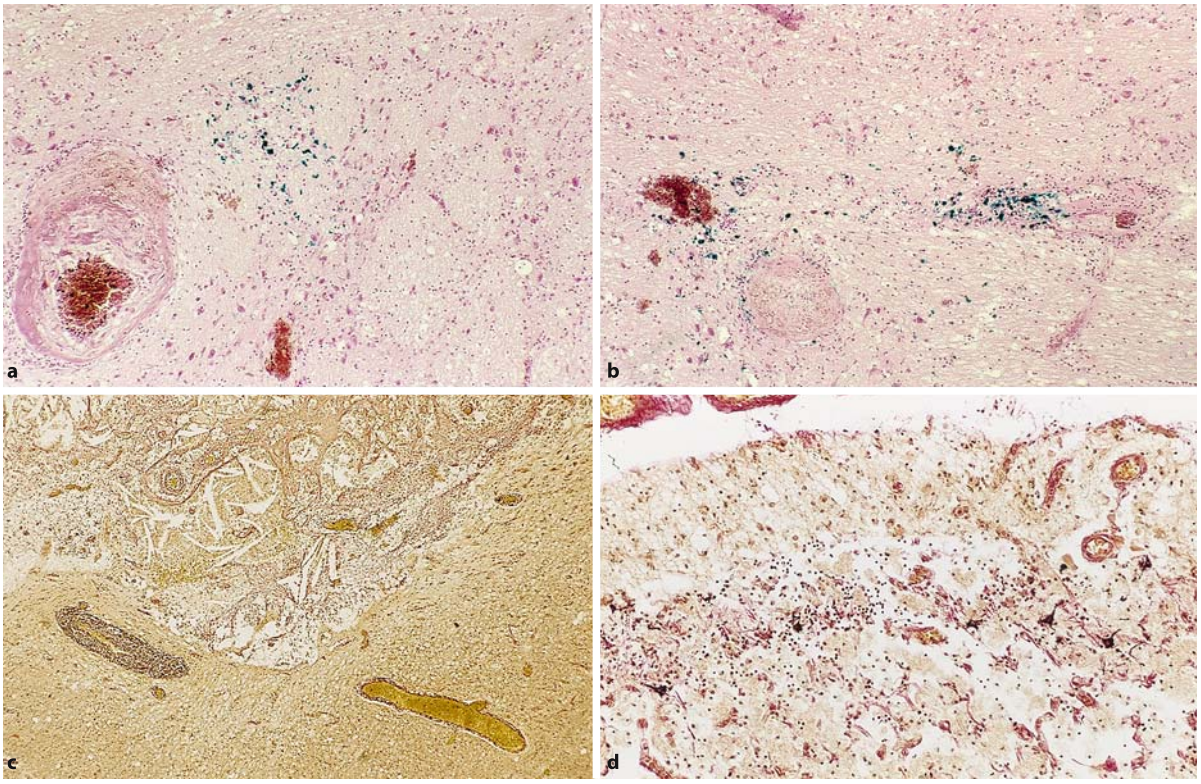

Fig. 28.23a–d. Cystic scars as a result of hemorrhagic and pale infarcts. The last stage of necrosis is marked by a glial–mesenchymal structure with islands of hemosiderin containing macrophages (hemosiderophages) in cases of hemorrhagic infarct (**a, b**), while ischemic infarcts usually are characterized by a lack of hemosiderin containing macrophages but an increase of macrophages (**c, d**) (**a, b** H&E; **c, d** van Gieson; magnification **a–d** ×100)

28.9 Spontaneous Intracerebral Hemorrhage

28.9.1 Incidence

Worldwide the incidence of spontaneous intracerebral hemorrhage (SICH) ranges from 10 to 20 per 100,000 population, the incidence increasing with age (Broderick et al. 1992). In the USA about 37,000 to 52,400 people suffer SICH annually (Broderick et al. 1999). SICH accounts for 10–15% of all cases of stroke and is associated with a high mortality rate, with only 38% of affected patients surviving the first year (Dennis et al. 1993). The various possible causes of SICH are listed in Table 28.2. Two groups can be differentiated:

- Primary SICH accounts for 78–88% of all cases of ICH and is caused by the spontaneous rupture of small vessels that have suffered prior damage from chronic hypertension or amyloid angiopathy.
- Secondary SICH occurs in patients with vascular abnormalities such as aneurysms, malformations, tumors or in patients who have impaired coagulation.

The most important risk factor for SICH is hypertension, which is defined as a systolic blood pressure of at least 160 mmHg and a diastolic blood pressure of at least 95 mmHg. Cerebral amyloid angiopathy is another risk factor for SICH, especially in the elderly. Another factor predisposing to SICH is excessive alcohol consumption, which impairs coagulation and thus directly affects the integrity of cerebral vessels (Gorelick 1987; Klatsky et al. 1987). Feldman (1994) summed up the frequency of some well-defined causes of SICH as follows: hypertension (50%), cerebral amyloid angiopathy (12%), anticoagulants (10%), tumors (8%), illicit and licit drugs (6%).

28.9.2 Clinical Features

The symptoms of SICH usually appear suddenly and unexpectedly and can lead to neurologic deficits

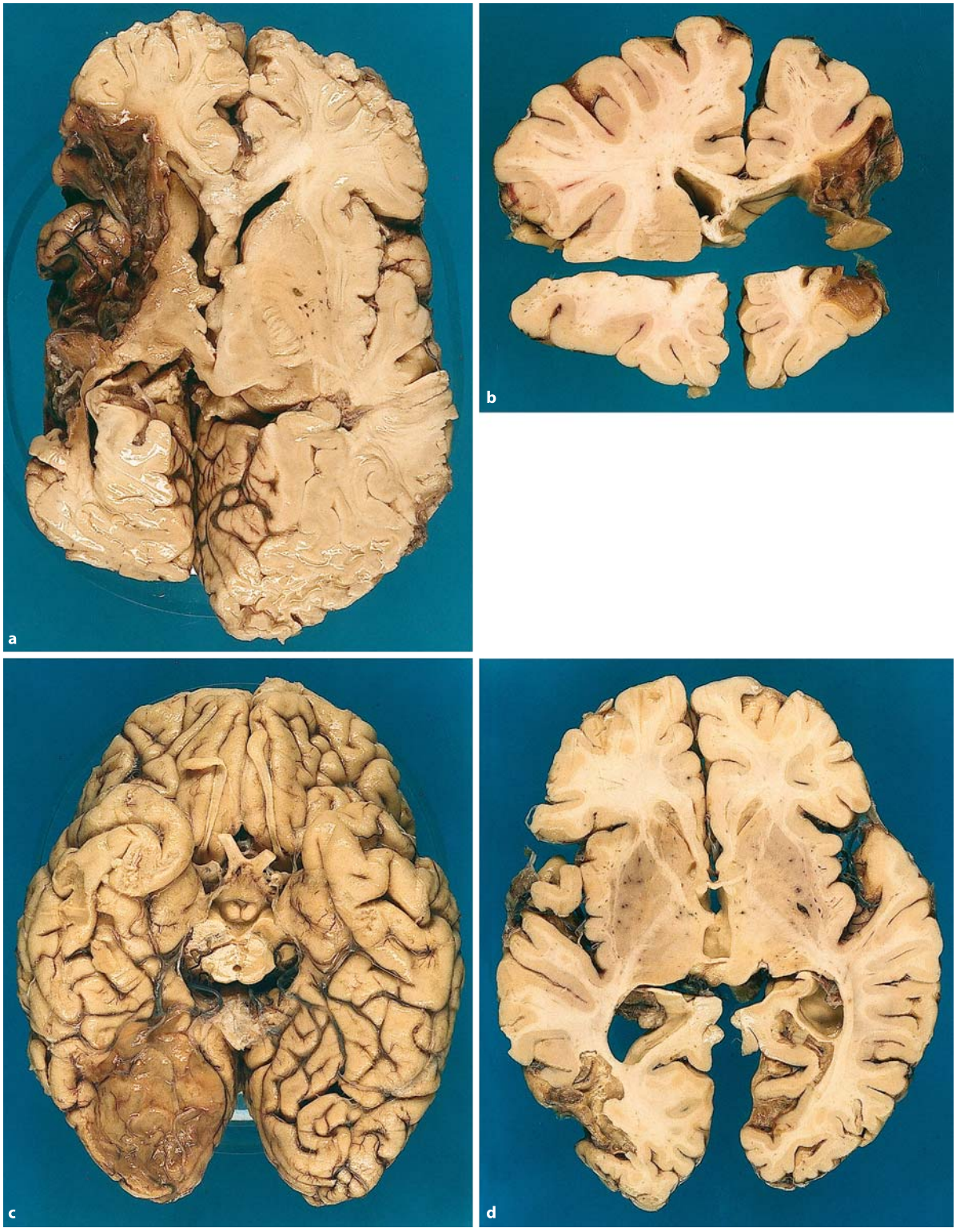

Fig. 28.24a–d. Final stage of a stroke by occlusion of large arteries. The sequelae of occlusion of the anterior cerebral arteries are seen in Fig. 28.9b. The sequelae of occlusion of the middle cerebral artery are demonstrated, in **a, b,** while the occlusion of the posterior cerebral artery is visible in **c, d**

Table 28.2. Causes and characteristics of intracerebral hemorrhages. Source: Qureshi et al. 2001

Causes	Characteristics
Hypertension	Rupture of small arterioles related to degenerative changes
Amyloid angiopathy	Rupture of small and medium-sized arteries with deposition of β-amyloid protein
Arteriovenous malformation	Rupture of abnormal small vessels connecting arteries and veins
Intracranial aneurysm	Rupture of saccular dilatation from a medium-sized artery that is usually associated with subarachnoid hemorrhage
Cavernous angioma	Rupture of abnormal capillary-like vessels with intermingled connective tissue
Venous angioma	Rupture of abnormal dilatation of venules
Dural venous sinus thrombosis	Result of hemorrhagic venous infarction
Intracranial neoplasm	Results of necrosis and bleeding within hypervascular neoplasms
Coagulopathy	Most commonly associated with use of anticoagulants or thrombolytic agents
Vasculitis	Rupture of small and medium-sized arteries with inflammation and degeneration
Cocaine or alcohol use	Underlying vascular abnormalities; vasculitis may be present
Hemorrhagic ischemic stroke	Hemorrhage in region of cerebral infarction as a result of ischemic damage to blood–brain barrier

or acute death depending on the severity, i.e., the extension, of the bleeding. The clinical picture depends on the localization and size of the hematoma. Due to the elevated intracranial pressure and direct compression or distortion of cerebral nuclei such as the basal ganglia, thalamus, and brain stem reticular activating system, individuals suffering massive SICH generally experience sudden headache, vomiting and meningismus as well as a decreased level of consciousness or coma (Andrews et al. 1988).

Deep supratentorial SICHs of the thalamic nuclei and basal ganglia entail contralateral sensory-motor deficits variable in severity due to internal capsule involvement. The occurrence of visual deficits is an indication of deep hemorrhages (Massaro et al. 1991). *Infratentorial SICHs* typically exhibit signs of brain stem dysfunction including cranial nerve abnormalities, abnormalities of gaze, and contralateral motor deficits. Hematoma expansion is the principal cause of underlying neurologic deterioration during the first 3 h after hemorrhage onset. Cerebral edema increases the symptoms in the first 24–48 h. The 6-month mortality rate of SICH ranges 23–58% (Lisk et al. 1994; Tuhrim et al. 1995).

The *prognosis* of deep supratentorial SICH as well as infratentorial SICH depends on its location, size, and the age of the patient. If alcohol is implicated, then the amount of alcohol consumed during the prior week also affects prognosis (Juvela 1995). According to Fogelholm et al. (1992), the 30-day mortality rate is 25–72% with a weighted mean of 48%, while Juvela (1995) sets the 1-year mortality at 37%. Only about 5% of patients with unilateral segmental hemorrhages succumb, versus more than 80% of patients with large pontine hemorrhages (Chung and Park 1992).

To *distinguish between SICH and cerebral infarction* a CT scan must be done. Angiography should be performed in patients in whom secondary causes of SICH such as aneurysm, arteriovenous malformation, or vasculitis are suspected. This includes all patients without a clear cause of hemorrhage and who are candidates for surgery, especially young patients whose condition is clinically stable and who do not have hypertension. Management regimens tailored to the needs of individual patients are described by Qureshi et al. (2001).

28.9.3 Neuropathology

As a clinical condition in neuropathology, SICH is *classified* as either supratentorial and infratentorial hemorrhage, and as lobar hemorrhage and deep hemorrhage involving the central regions of the brain, i.e., the basal ganglia and thalamic nuclei. Among the common causes of lobar hemorrhages are arteriove-

Table 28.3. Time-dependent cytological alterations of spontaneous brain hemorrhages

Reactive phases	Cytological reactivity	Time course
1	Intact red blood cells, leukocyte emigration but no macrophages	30 min–5 days
2	Isolated foci of macrophages	10 h–12 days
3	Isolated macrophages containing siderin	>4 days
4	Red blood cell ghosts, iron staining in astrocytes	>5 days
5	Macrophages containing hemosiderin predominate	>10 days
6	Hemosiderin	>11 days
7	Cyst with a few iron-positive macrophages within the cyst wall as well as in the cyst's cavity	>114 days

nous malformations and leukemia, whereas hypertension is the chief cause of deep hemorrhages (Massaro et al. 1991; Heiskanen 1993). SICHs are supratentorial in most cases (about 80%), deep hemorrhages being more common than lobar hemorrhages (ratio: 2:1 – Massaro et al. 1991). Infratentorial hemorrhages are seen in 20% of cases and are localized in the cerebellum (70%) or pons (30%) (Massaro et al. 1991).

Determining the *cause of bleeding* poses a special problem because the bleeding nearly always destroys the source of bleeding, rendering detection impossible. Subarachnoid bleeding that is localized predominantly basally therefore should raise suspicion of a saccular aneurysm. In cases of primary intracerebral bleeding, the cause can often only be speculated upon based on its localization and on the patient's medical history and age because the ruptured vessel is not visible. If generalized vascular disease is present, vessel disease must also be sought in brain sections where bleeding has not occurred, possibly by staining serial sections of the paraffin block with the phosphotungstic-acid hematoxylin method of Mallory (Fisher 2003).

It must always be considered that a *hematoma* will *expand over time* (Kazui et al. 1996; Brott et al. 1997), mainly due to continued bleeding from the primary source and disruption of surrounding vessels. Other potential contributors to the expansion include acute hypertension, a local coagulation deficit, or both (Olson 1993; Kazui et al. 1997).

The hematoma initiates an *edema* that can persist for 5 days (Yang et al. 1994) or up to 2 weeks following stroke (Zazulia et al. 1999). Early edema in the region surrounding the hematoma is caused by the accumulation and release of osmotically active serum proteins from the clot (Wagner et al. 1996). Cytotoxic and vasogenic edema follow disruption of the blood–brain barrier, sodium pump failure, and neuronal death. The *death of neurons* in the area around the hematoma is mainly necrotic, with signs of programmed cell death of neurons and astrocytes within 24 h after hemorrhage (apoptosis – Hickenbottom et al. 1999; Gong et al. 2001).

Irrespective of its cause, the *morphology* of a hemorrhage is always the same, the centrally located bleeding being sharply demarcated from the structurally intact neuropil. An edema forms around the bleeding. The edematous parenchyma adjacent to the clot is often discolored by degradation products of hemoglobin. Histological sections from the region surrounding the hematoma exhibit evidence of edema, neuronal damage, macrophages, and neutrophils. The hemorrhage expands between planes of white-matter cleavage, leaving nests of intact neural tissue within the surrounding hematoma (Morris 1999). The time course of cytological reactivity is reviewed in Table 28.3.

Direct distortion and injury of axons and dendrites cause only comparatively slight destruction of the surrounding parenchyma (Kalimo et al. 2002). For the outcome of ischemia, whether global or perifocal and global, damage to the surrounding area plays a major role. Thus the intracranial space-occupying mass created by the hematoma causes a reduction in local blood flow, while substances derived from the clot can induce arterial spasms, for example, which give rise in turn to ischemia.

28.9.3.1 Causes of Spontaneous Intracerebral Hemorrhage

Hypertensive SICH most often occurs in the thalamus and putamen (see pp. 546 f). Besides the hypertensive SICH, the cerebral *amyloid angiopathy* is the most common cause of lobar SICH, which is observed in elderly normotensive patients. Hemor-

rhage of this type may occur in multiple sites over time and is sometimes associated with subarachnoid hemorrhage. It is assumed today that *microaneurysms* are the cause of arterial rupture (Wakai et al. 1992). In most cases, the ruptured arteries are small, and the size of the hematoma also depends in part on blood pressure.

Hemorrhages caused by *anticoagulants* or *thrombolytic drugs* often prove fatal, in most cases because the hemorrhages are multiple (Boysen 1993). There is a greater risk of SICH during thrombolytic therapy for acute cerebral ischemia (Hacke et al. 1995). SICH patients taking anticoagulants have a mortality twofold greater than overall mortality (Rådberg et al. 1991).

Arteriovenous malformations (see pp. 557 ff) can lead to bleeding, the type of which depends on whether the localization is subarachnoid (about 10% of cases; Brown and Wiebers 1993), parenchymal or intraventricular SICH. The hemorrhage commonly destroys small malformations, rendering them undetectable.

Illegal drugs generally induce hemorrhage within 4–6 h of application. The bleeding usually occurs in the white matter and may be fatal (Delaney and Estes 1980). At autopsy, changes in the vessel walls are often seen in the form of "toxic speed vasculitis," which is characterized by fibrinoid necrosis of the media and intima as well as by perivascular cell infiltrates (Harrington et al. 1983).

Saccular aneurysms (comp. pp. 550 ff) occurring in the middle cerebral artery or in the internal carotid or anterior communicating artery lead not only to subarachnoid hemorrhages, but also to SICH. Hemorrhages due to rupture of an aneurysm in the middle cerebral artery tend to cause asymmetrically distributed bleeding that involves the brain parenchyma in the form of an intracerebral or intraventricular hemorrhage. Subarachnoid hemorrhage sometimes extends into the subdural space. Ruptures are often associated with vasospasm and delayed ischemic infarction (Adams et al. 1987), as well as with hydrocephalus and increased intracranial pressure. No aneurysm can be found by either neuropathology or by angiography (Rinkel et al. 1991) in approximately 15% (range 5–28%) of patients with confirmed subarachnoid hemorrhage. In some patients, the locus of bleeding is perimesencephalic, the ruptured vessels thus being veins or capillaries around the midbrain.

28.10 Vascular Diseases of the Spinal Cord

In the most recent review (Spetzler et al. 2002), vascular lesions of the spinal cord must be divided into three categories: neoplasms, aneurysms, and arteriovenous lesions. Sudden unexpected death due to spinal vessel diseases is extremely rare.

28.10.1 Anatomy of the Spinal Vessels

There are three vascular areas of the spinal cord, each representing both an anatomical unit and a functional unit (for details, see Lazorthes 1978). A perimedullary arterial network supplies the spinal cord via the posterior spinal arteries, the anterior spinal artery, and the central arteries.

The anterior spinal artery coming from the vertebral arteries supplies the upper cervical segments (C1–C4). The cervicothoracal region (C5–T2) has an independent blood supply that originates in the vertebral arteries and the deep and ascending cervical arteries. A single artery branching off the dorsal spinal artery supplies the midthoracic segments (T3–T8). A single artery, the large anterior radicular artery of Adamkiewicz, provides for the thoracolumbosacral region.

28.10.2 Pathology of the Spinal Vessels

The pathology of spinal vessels resembles that of the brain: vessel lesions lead to strokes secondary to ischemia or hemorrhage. The clinical features reflect disturbances of the segmental arterial supply and segmental lesions of the spinal cord.

The main supplying arteries (aorta, vertebral, intercostal, lumbar arteries) are subject to lesion-related occlusion. A unilateral thrombosis can be compensated by the collateral or anastomotic supply. Lesions of the intramedullary and juxtamedullary arteries may be caused by external compression or arteritis. Multisegmental softening of variable extent is a result of anterior spinal artery obstruction.

The obstruction of the anterior artery leads to a soft ischemic lesion which is centrally located, while the peripheral area is protected from ischemia by the peripheral network. Obstruction of a single central artery generally produces unilateral softening of a central segment.

For further information on the pathogenesis and sequelae of rare spontaneous vascular lesions of the spinal cord the reader is referred to the relevant primary literature on spinal vascular malformations

and neoplasms (see Jellinger 1978; other types of vascular lesions – see Spetzler et al. 2002).

28.11 Forensic Aspects of Stroke

The question often arises as to whether ICH really arises spontaneously (SICH) or has been caused by a fall or blow, especially as the victim of a SICH can fall induced by an acute loss of consciousness resulting in an impact and a galeal hematoma. Since the vessels in the area of intracerebral bleeding can no longer be found, the intact vessels on the contralateral side must be examined microscopically. To exclude a cause by mechanical violence signs of cortical contusion and bruising of the scalp must be sought. The patient's medical history can reveal whether they had hypertension, diabetes mellitus, coagulopathy, etc.

As already stated, SICH can also be caused by acute stress, especially in individuals with hypertensive angiopathy (cf. Tsementzis et al. 1985). According to Schütz (1988) the sources of such stress include: lifting of a big mass, overeating, working in a stooped position, bicycle riding, passing stool, etc. None of these circumstances, however, represents an extreme or extraordinary cause of stress and all are merely everyday sources of stress.

Acute hypertensive stress or even a blow can also lead to the rupture of a saccular aneurysm. This fact is of particular relevance if a rupture has occurred during a physical conflict or in immediate association with an impact. First it must be determined whether the stress or force was sufficient to cause a rupture. If the temporal association between the physical altercation and the rupture is close, the question arises as to whether a spontaneous rupture unassociated with the altercation or forces could also have led to the victim's collapse.

The forensic pathologist is often asked to estimate for how long a victim survived pale or hemorrhagic insult. The time-dependent histological features of pale impacts are summed up in Table 28.3. For hemorrhagic stroke it is extremely difficult to answer especially since hemorrhaging is a progressive process. At best, the longest possible survival time is to be estimated based on evidence of the cytological reaction (see criteria on timing of blood breakdown, pp. 190 ff). Moreover, special investigations for determining the time course of SICH (and ICH) have been provided by, among others, Takasugi et al. (1985) and Jenkins et al. (1989).

Initially, necrosis of neurons and glial cells in the adjacent parenchyma are observed. The first cytological reaction is an infiltration of leukocytes. The next phase of the reaction features the breakdown of erythrocytic hemoglobin to hemosiderin by macrophages, later by astrocytes as well. Between 0.65 and 0.7 ml of a clot will be reabsorbed per day (Takasugi et al. 1985).

Use of anticoagulants or thrombolytic therapy in cases of thrombosis or thromboemboli is a matter of medical discussion. Application of thrombolytic drugs to treat myocardial infarction reduces the mortality from myocardial infarction but raises the risk of SICH. The risk is especially high for thrombolytic therapy of acute cerebral ischemia, where thrombolytically treated patients had a three times higher incidence of SICH than placebo patients. The number of patients recovering, however, was significantly higher among patients receiving thrombolytic therapy than among placebo patients (Hacke et al. 1995).

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Inflammatory Diseases 29

Because infectious diseases of the nervous system are generally accompanied by a conspicuous clinical picture, they are rarely associated with "sudden" unexpected deaths. Isolated cases do occur, however, usually due to fulminant processes such as acute generalized bacteremia, septicemia, or viremia. Sometimes, too, an infectious disease will follow a slow, latent course that eludes detection by the attending physician. Failure to make a timely diagnosis can also be due to the patient's poor insight into the nature of their illness, poor compliance, or unwillingness to undergo the indicated diagnostic procedures and therapy.

The essential clinical and neuropathological findings of selected bacterial and viral diseases as well as of prionic diseases (transmissible spongiform encephalopathy) will be presented here. For more detailed information the reader is referred to the relevant clinical-neuropathological textbooks. Moreover, our short remarks should mention the group of non-infectious inflammatory diseases, especially multiple sclerosis and allied diseases.

The CNS is normally well protected against microorganisms by structures of the surrounding covering and by the blood–brain barrier (BBB). Once these defenses are breached, however, the CNS is more vulnerable to infection than most other body organs. Pathogenic organisms may reach the CNS via four different routes (Chason 1977):

1. The most common route of spread are the blood vessels, mainly the arteries, after the organisms have first infected the lungs or cardiac valves. Microorganisms also invade the CNS through diploic or emissary veins in the context of a retrograde thrombophlebitis or an embolus draining neighboring infections, or from distant structures. The paravertebral venous system is rarely implicated.
2. The brain or spinal cord or their coverings may be involved in the spread of infections from the mastoid sinuses, middle ears, paranasal sinuses, skull, and vertebrae.
3. Mechanical violence, gunshot wounds, or medical procedures, including surgery and lumbar puncture, can cause microorganisms, chemical toxins, or even particulate materials to be im-

planted directly upon the coverings or within the CNS.
4. By centripetal movement within the cellular cytoplasm and perhaps through the neurotubules, certain viruses – including rabies, herpes simplex and herpes zoster, once implanted within the axoplasm of a peripheral nerve – are able to reach the perikaryon within the spinal ganglia, spinal cord, or brain.

After the organism has invaded the CNS, an infection can spread by direct continuity or by following the usual direction of fluid flow (anterograde), retrograde, or in both directions within the ventricular, subarachnoid, or Virchow–Robin spaces.

The basic principles of CNS immunology are described elsewhere in this volume (p. 67). Inflammation of the CNS is as difficult as that of other organ systems (Bauer et al. 2001). T-lymphocytes play a key role in immune surveillance and in the regulation of the inflammatory response (as seen especially in multiple sclerosis, see Lassmann 1998). Major contributions are also made by B-lymphocytes and activated macrophages and/or microglia (Gay et al. 1997), by cytokines (Cannella and Raine 1995) and chemokines, especially by adhesion molecules (Sobel et al. 1990), as well as by their receptors (Simpson et al. 1998). The roles of these players are complemented by local expression and/or upregulation of class I and class II histocompatibility antigens (Traugott 1987), markers of T-lymphocyte and macrophage activation (Brueck et al. 1995). Finally, apoptosis of T-lymphocytes also occurs (Bauer et al. 1999).

29.1 Bacterial CNS Diseases

The mortality rate of bacterial CNS diseases in adults is about 25%. Survivors often experience sequelae such as memory deficits, seizures, hearing loss or vestibulopathies (Smith 1988; Durand et al. 1993). These sequelae are caused not only by the inflammatory process, which is mainly confined to the leptomeninges, but by the associated complications such as brain edema, cerebrovascular insult, hydrocephalus, and/or elevated intracranial pressure (Pfister et al. 1992, 1993). As in patients with bacterial CNS infection, nitrotyrosine (a marker of the formation of reactive nitrogen species, such as peroxynitrite) could be demonstrated immunohistochemically in the cerebrospinal fluid (CSF) (Kastenbauer et al. 2002); this finding indicates that oxidative stress due to reactive nitrogen species and altered antioxidant defenses are additional factors that play important roles, and that in humans these factors are involved in the pathophysiology of bacterial meningitis.

Clinically and morphologically the following forms of bacterial inflammation associated with the CNS can be differentiated:
1. Purulent leptomeningitis
2. Abscess
3. Mycotic aneurysm
4. Septic encephalopathy

29.1.1 Purulent Leptomeningitis

Bacterial dissemination usually occurs secondarily, originating in the blood and spreading within the CNS mesenchyma and/or spaces of the CSF, i.e., within the leptomeninges (subarachnoid space), along the Virchow–Robin spaces, and within the ventricles (Fig. 29.1). Since the arachnoid laminae possess no capillaries, the rate of neutrophil invasion may be insufficient to generate an early cytological reaction. The leptomeninges of the brain and spinal cord (Fig. 29.2) are equally affected.

Bacteria may also invade the CNS primarily by virtue of fractures or surgery, of ventricular drainage or ventricular or lumbar puncture. Recurrent meningitis can arise secondary to a head injury due to a defect created in the dura at the base of the skull.

The most common *microorganism* is *Staphylococcus epidermidis*, which is observed in 50–65% of cases of purulent meningitis. *Staphylococcus aureus* is demonstrated in 15–25% of cases of CNS infection, Gram-negative bacteria in 5–15% (Editorial, *Lancet*, 1989; I:647–648). *Prognosis* depends in large part on the type of microorganism. Although prognosis has improved dramatically in the meantime, the data from 1984 are still able to illustrate how truly dangerous the various microorganisms can be: pneumococcal meningitis was fatal in 95–100% of cases, *Haemophilus influenzae* meningitis in 90%, and meningococcal meningitis in 70–90% (Swartz 1984).

The *clinical picture* is first characterized by nonspecific generalized symptoms: fever, somnolence, nausea, and vomiting. The clinical diagnosis is based on the presence of "meningismus" (neck pain and stiffness) and is confirmed by lumbar puncture (purulent CSF, cytological CSF analysis – see Oehmichen 1976, and positive bacteriological culturing). Cranial computed tomography is normal in most cases. Focal neurological deficits are rarely, if ever, seen. Treatment consists of administration of high-dose antibiotics.

In this regard we have to refer to the alleged risk of cerebral herniation complicating lumbar puncture performed to diagnose acute bacterial meningitis (Oliver et al. 2003). All cases of purulent meningitis are associated with increased intracranial pressure, but herniation is a rare complication (5%). An accurate clinical history combined with recogni-

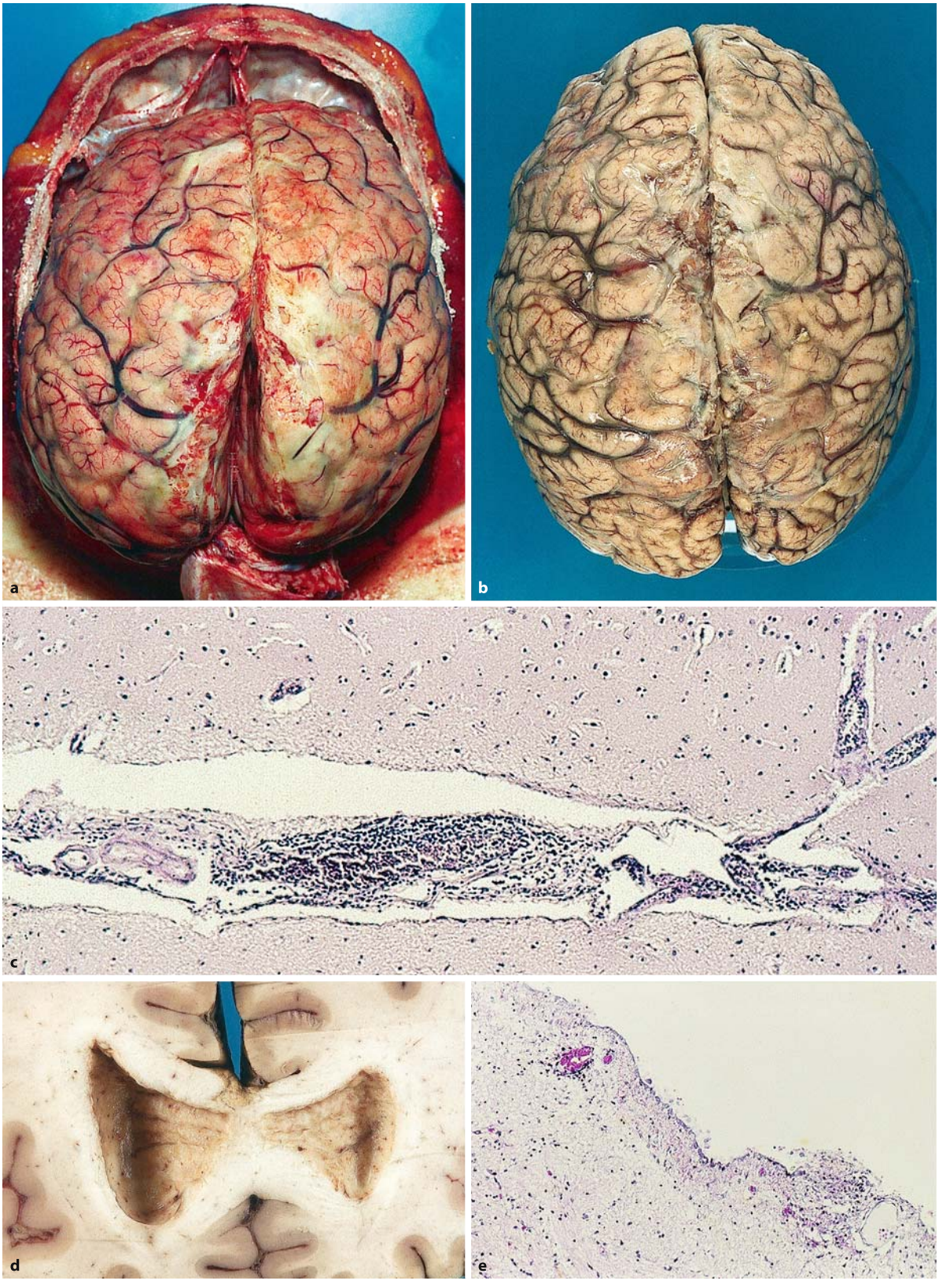

Fig. 29.1a–e. Purulent leptomeningitis. **a** Autopsy findings are characterized by distinct creamy-purulent yellow-to-green deposits in the leptomeninges, **b** while the post-fixation expression often is non-characteristic; **c** leptomeningeal infiltration as well as infiltration of the Virchow–Robin spaces. The inflammation may involve the ventricular system causing an ependymitis (**d**) marked by glial nodules at the ventricular surface (**e**) (**c, e** H&E; magnification ×200)

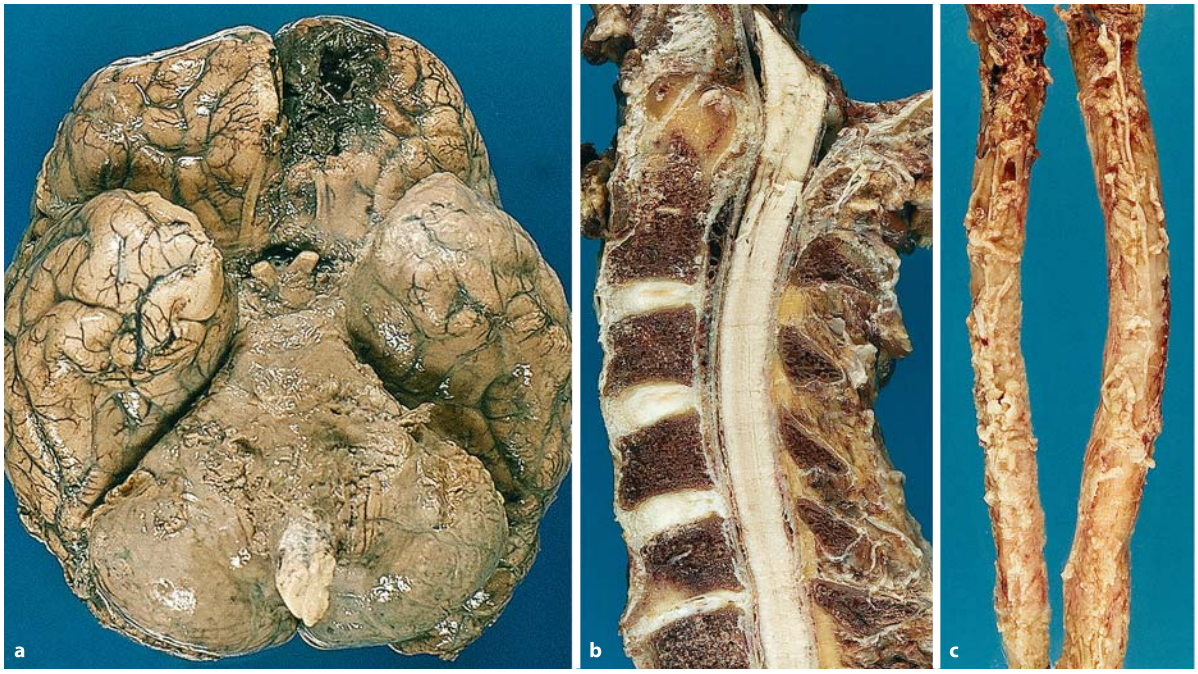

Fig. 29.2a–c. Purulent meningitis. **a** Secondary meningitis after a traumatic event associated with a basal skull fractures, **b, c** with inflammatory invasion of the subarachnoid space along the spinal cord

tion of the early systemic and neurologic findings of bacterial meningitis will indicate a safe setting for performance of a diagnostic lumbar puncture with little likelihood of complicating herniation. However in patients whose disease process has progressed to the neurologic findings associated with impending cerebral herniation, a delay of the diagnostic procedure is indicated (Oliver et al. 2003).

29.1.1.1 Neuropathology

The morphological picture is characterized by purulent infiltration of the leptomeninges. In cases with hematogenous dissemination, the hemispheres are especially likely to be symmetrically affected. Tuberculous or syphilitic infections feature a basal cytological infiltration.

At autopsy, creamy-purulent, yellow or green deposits are macroscopically evident in the leptomeninges (Fig. 29.1a). Formalin fixation reduces this to a grayish cloudiness of the leptomeninges (Fig. 29.1b), rendering macroscopic diagnosis difficult. Acute cases generally exhibit concomitant petechial hemorrhages in the skin and gastrointestinal tract, bilateral adrenal bleeding, plus morphological changes secondary to shock syndrome in the lung, liver, and kidney.

The macroscopic changes are visible at the surfaces of the hemispheres, the base of the brain, and in the basal cisterns. As already stated, diagnosis is confirmed by both bacterial culture and cyto-histomorphology. The histological examination discloses a dense infiltration of the leptomeninges with neutrophils. Bacteria are sometimes visible intracellularly and/or extracellularly. Sometimes there is a concomitant infiltration of the perivascular spaces of the cortical vessels, and – rarer still – a leukocytic infiltration of the cortical neuropil. The cortex is spongiform and edematous, with demonstrable ischemic neuronal alterations.

After antibiotic therapy or in subacute cases a decline in the number of neutrophils is seen with a parallel increase in the number of plasma cells and macrophages. Fibrinoid necrosis and thrombosis of blood vessels may produce small foci of cortical necrosis. A few neutrophils are evident within the subpial neuropil and perivascular spaces. There is also a slight proliferation of microglia and astrocytes, especially in pneumococcal infections.

Bacteria and pus may be found within the ventricular system. The ependymal surface is sometimes covered by flakes and pus. Neutrophils infiltrate the choroid plexus, which sometimes exhibits hemorrhagic inflammation.

Hydrocephalus is an almost invariable feature (Fig. 29.1c, d), sometimes caused by impaired resorption due to extensive inflammatory exudate, sometimes by occlusion of the exit foramina of the fourth ventricle resulting from the presence of thick pus or granulation tissue. If a leptomeningitis is survived, the altered fibrous leptomeninges can remain

visible as a cicatrix even decades after the inflammatory process.

29.1.1.2 Late Complications

Late complications due to *S. pneumoniae* meningitis are especially likely in children, who can suffer neurological damage involving auditory neuritis, sensorineural deafness, labyrinthitis, and injury of central auditory pathways. Children are also liable to further neurologic, intellectual, and behavioral deficits. Three further phenomena are of morphological interest:

1. Purulent meningitis, especially of meningococcal meningitis, often causes meningeal fibrosis featuring thickening of the leptomeninges around the spinal cord.
2. Subdural effusions or hygromas, clear or blood stained, can develop; their cause, however, is not known.
3. A brain abscess with encapsulation may form, even in adults, but this is not the rule. Usually, abscess and meningitis remain distinct types of infection without crossover.

The following diseases constitute special forms of purulent leptomeningitis:

29.1.1.3 Neonatal Meningitis

The pathogen is usually maternal genital *Streptococcus agalactiae* or *Escherichia coli*. Infants of low birth weight and/or requiring resuscitation at birth are most at risk of developing neonatal meningitis. Their host defenses are relatively ineffectual. Neonatal meningitis has a high mortality of up to 60% and morbidity as high as 50% (see Kroll and Moxon 1988).

29.1.1.4 Meningococcal Meningitis

The most common cause of meningitis in infants and children is a Gram-negative bacillus, *Neisseria meningitidis*, which tends to epidemic outbreaks since meningococci are spread in airborne droplets that colonize the throat and nasopharynx. Similar patterns have been attributed to group A meningococci in many parts of the world. Since meningococci are sensitive to penicillin, prompt treatment can reduce mortality to less than 7% (Wylie et al. 1997; Schildkamp et al. 1996), 9% (Thorburn et al. 2001) or 20% (Derkx et al. 1996).

If sepsis complicates a case of meningitis (meningococcal septicemia), however, the mortality increases two- to threefold. Such cases are termed Waterhouse–Friderichsen syndrome and are complicated by all phenomena associated with shock, particularly disseminated intravascular coagulation, which in turn is often associated with dermal petechial and adrenal hemorrhages. The septicemia may precede the meningeal manifestations, thus no signs of a purulent leptomeningitis are found. Such fulminating septic events with high fever generally involve *Neisseria meningitidis*, which in these cases can only be diagnosed in blood via bacteriological culture or polymerase chain reaction (PCR). Death can occur within a matter of hours.

29.1.1.5 *Haemophilus Influenzae* Meningitis

Another major cause of purulent meningitis in children aged 3 years and younger is the small Gram-negative aerobic *Haemophilus influenzae*. It, too, is spread by airborne droplets. Once cellular immunity is acquired, it persists for life.

29.1.1.6 Pneumococcal Meningitis

Although the microorganism *Streptococcus pneumoniae* is sensitive to most strains of penicillin, it is responsible for a 15–20% mortality rate in instances of meningeal manifestation. This pathogen is the most common cause of meningitis in adults. The walls of pneumococcal cells are potent stimulators of inflammation. The inflammatory cascade is accelerated by lysis of bacteria as a result of antibiotic therapy.

Kastenbauer and Pfister (2003) reviewed 87 of their own cases and summarized the complications. A good outcome was observed in 48.3% of the cases. The respective incidences of diffuse brain edema (28.7%), hydrocephalus (16.1%), arterial (21.8%) and venous (9.2%) cerebrovascular complications as well as spontaneous intracranial hemorrhages were very high. The in-hospital mortality was 24.1%.

29.1.2 Epidural Abscess

Within the epidural space, bacterial infections are very rare. They are caused by the spread of microorganisms from the mastoid sinuses, middle ear, and paranasal sinuses due to osteomyelitis – of basal skull fractures – or neurosurgery. In the majority of these cases a focal epidural abscess forms. An associated subdural empyema may arise if microorganisms invade via emissary or diploic veins. Epidural infections affect the spinal cord more often than the cranium because osteomyelitis is more prevalent in the vertebral canal. The dura mater's adhesion to the

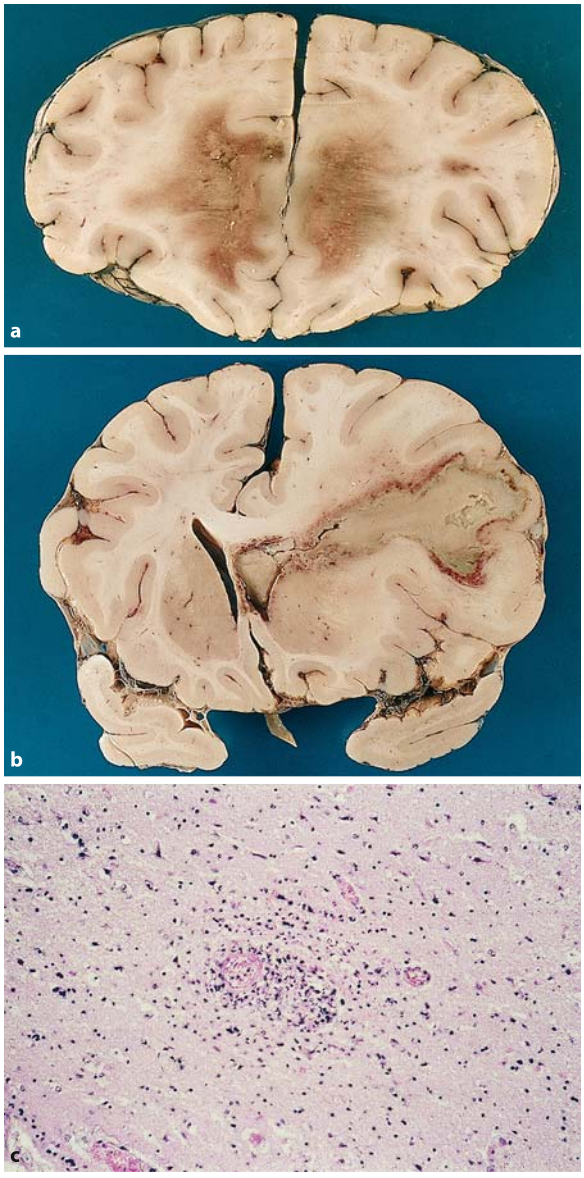

Fig. 29.3a–c. Bacterial brain infection. **a** Early indistinct infiltration of the neuropil (cerebrítis); **b** demarcated abscess; **c** hematogenous origin of multiple microabscesses associated with intense neutrophilic infiltration of the brain parenchyma (H&E, magnification ×200)

inner skull surface usually restricts the infection to a small, flattened space-occupying process. In addition, the dura's resistance to infection confines the inflammatory process in most instances to the epidural space.

29.1.3 Subdural Abscess and/or Empyema

Infection of the subdural space seldom leads to encapsulated purulent inflammation, but rather to inflammation extending along the entire subdural space in the form of an empyema. The sources of inflammation are the same as those listed above for epidural abscesses. "Sympathetic" purulent infections are common within the subarachnoid space due to the numerous capillaries and their absence from the arachnoid. The result is an accompanying purulent meningitis. Only rarely is a pachymeningitis seen, which may then spread to the subdural space.

29.1.4 Brain Abscess

Abscesses of the brain may be blood-borne or local. Hematogenous dissemination often occurs secondary to septic emboli (bronchiectasis, lung abscess, bacterial endocarditis, etc. – Strong and Ingham 1983). Immunodeficient patients with sepsis may develop multiple brain abscesses. Hematogenous dissemination is common in drug addicts with endocarditis or infected injection sites (Karch 1993). A local source of abscess may be pericranial infections (sinusitis, mastoiditis). They may be a severe complication of stab wounds and gunshot injury of the brain via local infection of the brain by microorganisms transmitted by knives or bullets into the brain. The source of infection remains unknown in 10–15% of cases.

Clinical Features. The clinical pictures depend initially on the nature of the primary insult, e.g., on whether it is endocarditis, sepsis, gunshot injury, etc. Solitary metastatic abscesses may be slow in developing, by which time the original infection may have healed, for example *Staphylococcus aureus* from skin sepsis of osteomyelitis. After wounding by gunshot, it may take years before an abscess develops.
The clinical symptoms reflect the presence of infection (fever, etc.) and may include focal neurological deficits depending on the size and localization of the abscess.

Neuropathology. The brain may be characterized by a diffuse leukocytic infiltration of the white matter associated with serodiapedesis and erythrodiapedesis like a phlegmenous inflammation (cerebritis) (Fig. 29.3a); because of the fulminant fatal infectious process no glial reaction occurs. However, abscesses are characterized by a prolonged inflammatory process. Abscesses of local origin are dependent on the location of external infectious lesions (Fig. 29.3b). Abscesses of hematogenous origin (Fig. 29.3c) are usually distributed by the middle vertebral artery, followed in order of frequency by the anterior cerebral artery and posterior circulation. Cytologically the abscess is characterized by a wall-like aggregation of mononuclear cells (lymphocytes, plasma

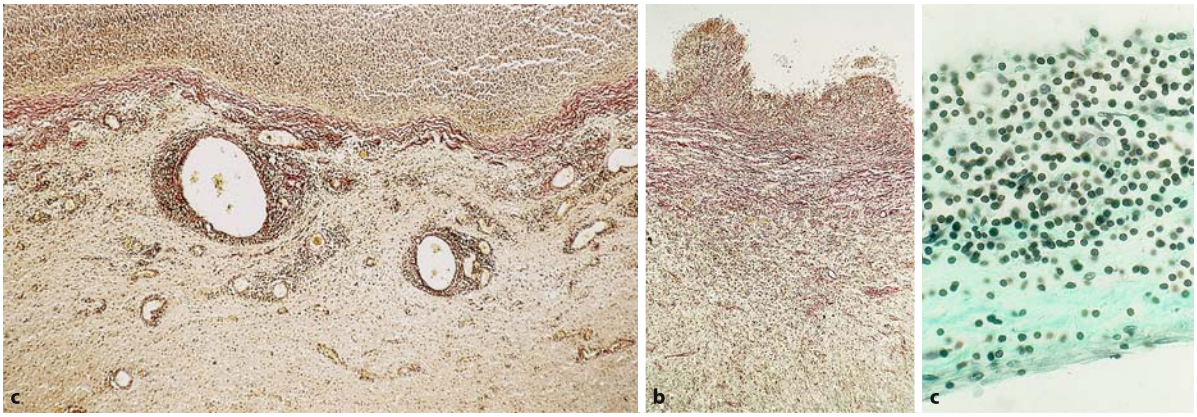

Fig. 29.4a–c. Abscess membrane. Wall-like aggregation of mononuclear cells (macrophages and plasma cells) accompanied by a network of collagenous fibers (**a, b** van Gieson stain; **c** trichrome stain; magnification (**a, b** ×100; **c** ×500)

cells, and macrophages) accompanied by collagenous fibers around a core of neutrophils and neutrophilic debris (Fig. 29.4). Grey and Alonso (2002) describe the stages of abscess development in detail:

- The infection begins with microvascular injury, giving rise to an early cerebritis 1–3 days after inoculation. The lesion features congestion, parenchymal necrosis, microthromboses, petechial hemorrhages, perivascular fibrinoid exudate, and neutrophil infiltration.
- The late cerebritis (4–9 days after inoculation) still exhibits a necrotic purulent center.
- In the next stage (10–13 days) a capsule forms composed of granulation tissue (lymphocytes, macrophages, plasma cells, fibroblasts, capillaries, and collagen fibers).
- The capsule grows firmer (>14 days) due to the production of collagen fibers; invading macrophages are visible.

In all instances, the abscess is surrounded by an extensive edema that sometimes has a light green tinge.

29.1.5 Tuberculous Brain Infection

Infection of the CNS by *Mycobacterium tuberculosis* manifests mainly in the form of a "tuberculous" meningitis, rarely as a tuberculous abscess or tuberculoma.

CNS infection can be fulminant, especially in children: the mycobacterium will spread from a primary tuberculous focus and the fulminant process seems to be a hypersensitivity phenomenon. The cytology in these cases typically features neutrophils in the subarachnoid space.

In most cases the tubercular lesion is caused by bacillemia following a primary infection or may result from late reactivation of a latent infection elsewhere in the body. Commonly, the process of pathogen spread will be subacute. Infection can also occur in connection with a miliary tuberculosis.

Clinical Features. A tuberculous meningitis should always be suspected if there has been prior contact with infected patients or a high-risk group. Diagnosis is made by examining the CSF for cell count, cell picture including lymphocytes, neutrophils, plasma cells, macrophages (Oehmichen 1976), bacterial culture, and PCR (Lin et al. 1995).

Pathology. Macroscopically the basal cisterns contain a gelatinous exudate and there is a slight opacity of the meninges over the convexity. Microscopically the infiltrating cells include lymphocytes, neutrophils, macrophages, and plasma cells which may be accompanied by a dense network of collagenous fibers (Fig. 29.5a, b). Some cases exhibit a vasculitis accompanied by fibrinoid necrosis and/or thrombosis. Sometimes tubercle bacilli are demonstrable (Fig. 29.5c, d). Tuberculomas and tubercular abscesses are rare.

29.1.6 Septic Encephalopathy

Septic encephalopathy is a reversible condition of the CNS that is seen in 9–71% of patients with sepsis (Sprung et al. 1990). More effective management of sepsis has led to an increase in the number of registered encephalopathy cases. Twenty-three percent of the 1333 sepsis patients evaluated by Sprung et al. (1990) had septic encephalopathy. This group had a higher mortality rate (49%) than cases without mental involvement (26%).

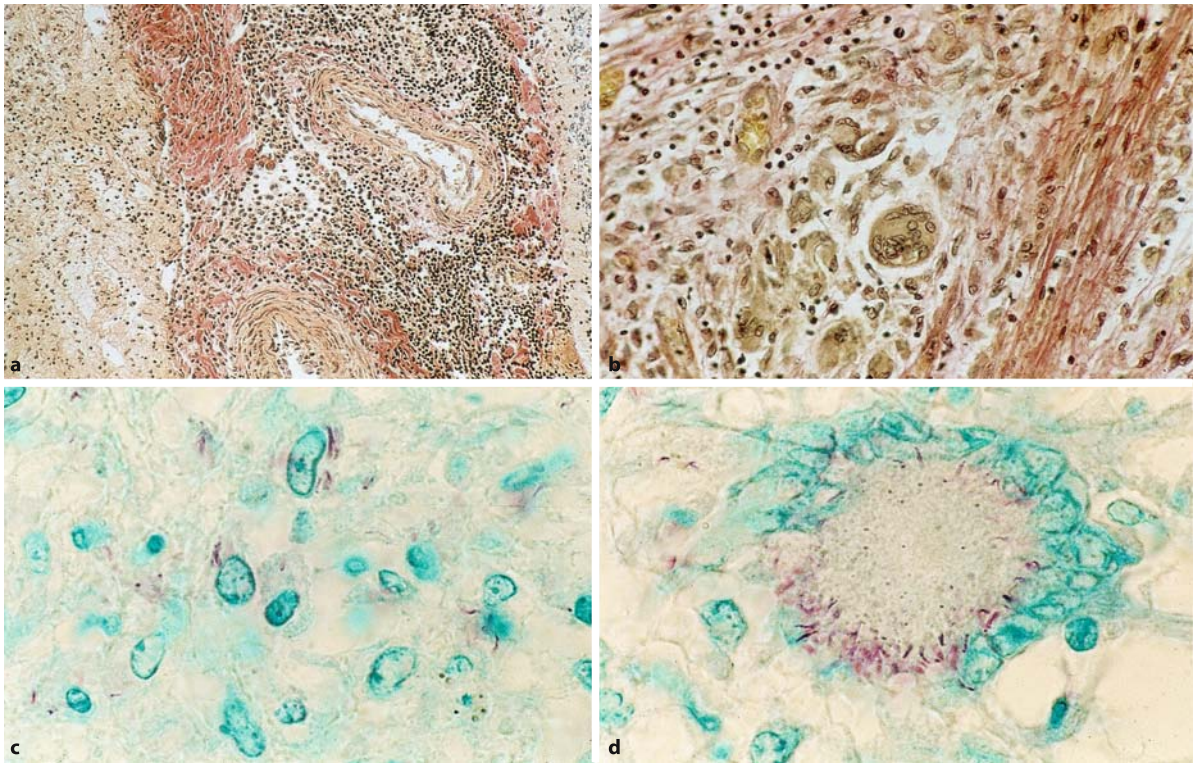

Fig. 29.5a–d. Tuberculous meningitis. **a, b** The typical sign is a granulomatous inflammation consisting of a macrophage-lymphocytic-granulocytic cell mixture associated with collagenous fibers; the cytological marker may be the demonstration of giant cells of the Langhans' type (**b, d**); **c, d** tubercle bacilli may be visualized by specific staining techniques. (**a, b** van Gieson stain; **c, d** Ziehl–Neelsen stain; magnification **a** ×100; **b** ×500; **c, d** ×1,000)

Clinical Features. The clinical diagnosis requires either the exclusion of other causes, or the presence of obvious changes in the level of consciousness and EEG findings, which are a sensitive index of brain function (Young et al. 1990; Bogdanski et al. 1999). Characteristic are cranial nerve dysfunctions, symptoms of diffuse brain dysfunction without focal deficits, paralysis, or decerebrate posturing as well as cardiovascular autonomic failure. Sepsis gives rise not only to CNS symptoms but also to peripheral nervous system involvement known as "*critical illness polyneuropathy*" (Nauwynck and Huyghens 1998), which is mainly a motor axonal dysfunction and affects about 7% of patients (Witt et al. 1991) in a setting of respiratory insufficiency (Nauwynck and Huyghens 1998). Sepsis is also associated with "*critical illness myopathy*" (Latronico et al. 1996), which occurs in 50–80% of the critically ill. There is a correlation between the severity of septic encephalopathy and mortality, bacteremia, and renal and hepatic dysfunction (Eidelman et al. 1996). Septic encephalopathy entails a mortality rate of 50% (Sprung et al. 1990; Young et al. 1990).

Pathogenesis. *Septic* (or "*early*") *encephalopathy* cannot be explained by hepatic or renal dysfunction, hypoxia, or hypotension, whereas "*late*" *encephalopathy* is attended by multiple organ failure, hypotension, and other systemic disorders (Papadopoulos et al. 2000). In early encephalopathy, sepsis leads to a derangement of plasma and brain amino acids: branched chain amino acids decrease, most neutral amino acids increase (Mizock et al. 1990; Basler et al. 2002). Aromatic amino acid levels correlate with mortality. The mortality rate correlates with levels of ammonia and amino acids containing sulfur (Sprung et al. 1990). The definitive cause of septic encephalopathy remains unknown, although it has been related to respiratory insufficiency during systemic inflammatory response syndrome or multiple organ dysfunction syndrome. The systemic inflammatory response to sepsis has been attributed in part to the adrenergic system, which is thought to participate in controlling blood–brain barrier permeability since perimicrovessel edema formation is inhibited by the β_2-adrenoreceptor agonist dopexamine, whereas it is provoked by the α_1-adrenoreceptor agonist methoxamine (Davies 2002). Originally defined as "altered brain function related to the presence of microorganisms or their toxins in the blood" (Bolton and Young 1989), septic encephalopathy is today thought to involve a cytotoxic response by brain cells to in-

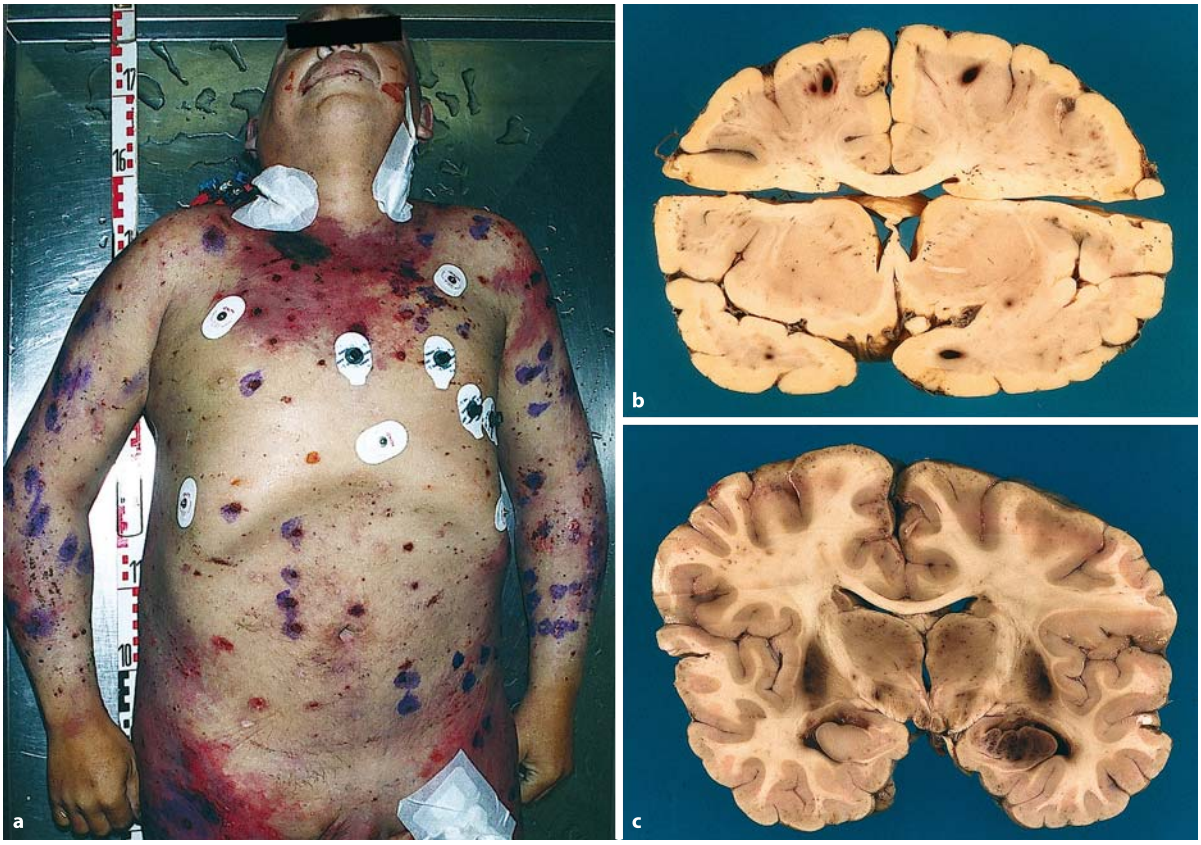

Fig. 29.6a–c. Septic encephalopathy. **a** The external inspection of the corpse demonstrates multiple hemorrhages which give evidence of disseminated intravascular coagulation; **b** this presumptive diagnosis was confirmed by gross inspection of brain sections which also demonstrated multiple hemorrhages; **c** the obviously secondary (ischemic) encephalopathy may also be expressed by isolated hypoxic brain lesions diagnosed by the dark-brown color of the putamen and hippocampus

flammatory mediators (cytokines and others) or the action of these mediators on the brain (Papadopoulos et al. 2000). A more recent study gave evidence of an association of septic shock with neuronal and glial apoptosis within the autonomic centers, which is strongly associated with endothelial expression of inducible nitric oxide synthase (iNOS) (Sharshar et al. 2003).

Neuropathology. The brain morphology features marked edema (Fig. 29.6a, b) secondary to a breakdown of the blood–brain barrier (Papadopoulos et al. 2000). Cytologically there is a disruption of astrocyte end feet in association with perivascular edema (Papadopoulos et al. 1999). Astrocyte damage in turn may hinder the regulation of local blood flow. The injury of astrocyte end feet may impair the transport of energy substrates from microvessels to neurons, thus reducing synaptic activity (Tsacopoulos and Magistretti 1996). Hemodynamically controlled pigs were found to have shrunken, dark, apparently degenerating neurons in the frontal cortex after only 8 h of fecal peritonitis (Papadopoulos et al. 1999). It is not known, however, whether sepsis in humans induces neuronal injury. It is known that septic encephalopathy occurs in sepsis before cerebral hypoperfusion or cerebral hypoxia/ischemia could have caused neuronal death. Nevertheless, in single cases we see intracerebral hemorrhages caused by disseminated intravascular coagulation (Fig. 29.6a, b) as well as hypoxic changes – possibly secondary to the septic disease (Fig. 29.6c). Moreover, in histological sections we have to refer to edema (Fig. 29.7a) as well as to the phenomenon of pyemia, i.e., the embolic transport of bacteria into the brain parenchyma (Fig. 29.7b, c). The latter gives rise to the neuropathologic finding of innumerable microscopic glial nodules (Young et al. 1990; Fig. 29.7d). These microabscesses or glial nodules (Fig. 29.7d) could easily be missed if the brain is only examined and cut in the fresh state, without proper fixation and microscopic examination.

A recent investigation in 23 patients who had died in an intensive care unit from septic shock (Sharshar et al. 2003) gave evidence of hemorrhages in 26%, hyper-coagulability syndrome in 9%, microabscesses

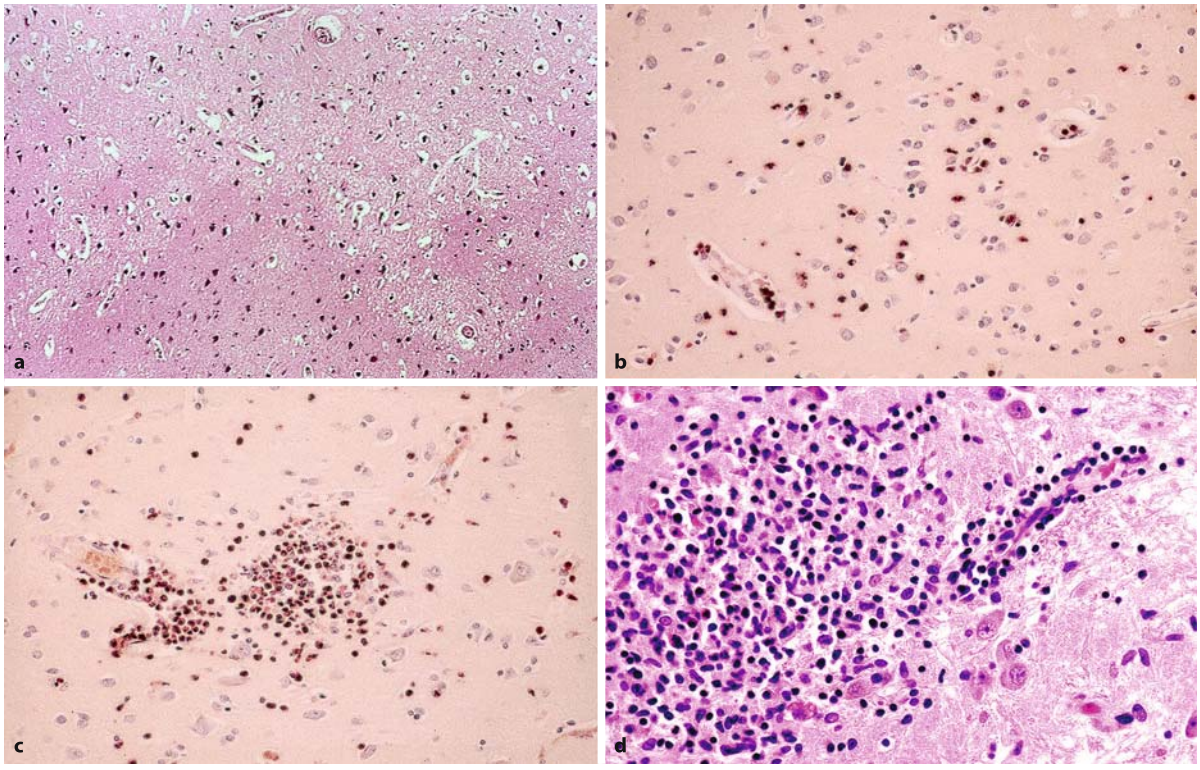

Fig. 29.7a–d. Histological features of septic encephalopathy. **a** Edema; **b** septicopyemia with neutrophilic infiltration; **c** multiple microabscesses as a result of metastatic distribution of bacteria and/or infectious thrombi; **d** innumerable glial nodules (**a, d** H&E, **b, c** NAS-DCIAE; magnification **a** ×200; **b, c** ×300; **d** ×500)

in 9%, multifocal necrotizing leukoencephalopathy in 9%, and ischemia in 100%. Vascular iNOS expression assessed by immunocytochemistry was higher in sepsis and correlated with neuronal apoptosis in the autonomic centers. The authors concluded that septic shock is associated with diffuse cerebral damage and specific autonomic neuronal apoptosis which may be due to circulating factors, particularly iNOS.

29.2 Abacterial CNS Diseases

29.2.1 Classification

There are two types of abacterial meningitides: viral meningitis and non-infectious, abacterial inflammation. The latter has non-viral causes, including non-specific reactions to iatrogenic chemical/mechanical irritation of the leptomeninges and adverse reactions to medications (for review see Love and Wiley 2002; see also Oehmichen 1976; Oehmichen et al. 1977a, b).

Viral infections of the CNS may manifest as viral *meningitis* or as *encephalitis* or *encephalomyelitis*, or even in combined form as *meningoencephalitis*. Viral meningitis is a benign infection that seldom entails sequelae. Encephalitis and encephalomyelitis are accompanied by edema and destruction of neurons and glial cells, as well as proliferation of astrocytes and microglia. The sequelae differ depending on the infecting virus' properties of neurotropism, neuroinvasion, and neurovirulence. Neurotropism refers to the attraction of certain viruses, such as poliomyelitis virus or herpes simplex virus, to neurons in certain CNS locations. Neuroinvasion refers to the non-specific invasive capabilities of the virus in penetrating the nervous system via the blood–brain barrier or via peripheral nerve axons. Neurovirulence refers to the consequences once the virus enters the nervous system, and may range from benign dormancy to causing hemorrhagic necrotizing disease.

Acute post-infectious encephalitis (post-vaccinal encephalitis) is known to follow chickenpox, measles, rubella or mumps, as well as rabies or smallpox vaccination. Some viruses, measles viruses in particular, are capable of causing subacute encephalitides with clinical symptoms that persist for months or years, as a cause of *subacute sclerosing panencephalitis* (SSPE). *Progressive multifocal leukoencephalopathy*

(PML) is caused by an opportunistic viral infection of an immunocompromised host's brain. For more on the immunological background the reader is referred to the reviews by Schneider-Schaulies et al. (1997) or Love and Wiley (2002).

29.2.2 Pathogenesis

The predominant *entry* route of CNS infection is via the mucous membranes of the gastrointestinal or respiratory tracts. If the invading virus is not neutralized by IgA antibody, it infects the cell of first contact and multiplies, spreading to local lymphatic tissue and often to the blood stream. Viral infection of the CNS begins with local virus growth in non-neural tissue and then disseminates via the neural or hematogenous route to the cord or brain. Viruses taking the neural route (herpes virus, rabies, and polio virus) can grow in axon cylinders distant to the perikaryon's metabolic activity – both centripetally and centrifugally. However, access is gained by most viruses via the blood stream.

29.2.3 Clinical Features

In most cases the first manifestations are meningeal symptoms and psychopathological deficits. Neurological deficits may also occur, especially if the parenchyma of the brain (encephalitis) or spinal cord (myelitis) is involved. The diagnosis must be confirmed by virological analysis (PCR or antibody). Examination of the CSF in most cases demonstrates infiltration by plasma cells and lymphocytes and may disclose a slight increase in the cell count (Oehmichen 1976).

29.2.4 Neuropathology

Macroscopically there may be vascular congestion, a slight meningeal opacity, and swelling of the brain (Fig. 29.8). These phenomena however are non-specific. In cases with pronounced edema, symptoms of herniation are found, together with the sequelae of ischemia. In some cases spot-like hemorrhages are found (Fig. 29.8c) as an indication of a hemorrhagic meningoencephalitis. The *microscopic alterations* are diverse and partly specific (Esiri and Kennedy 1997); most cases are characterized by a mononuclear meningitis that is associated with an encephalitis – at least morphologically.

- *Inflammatory cells*: the salient cytological alteration of viral meningitis and encephalitis is a

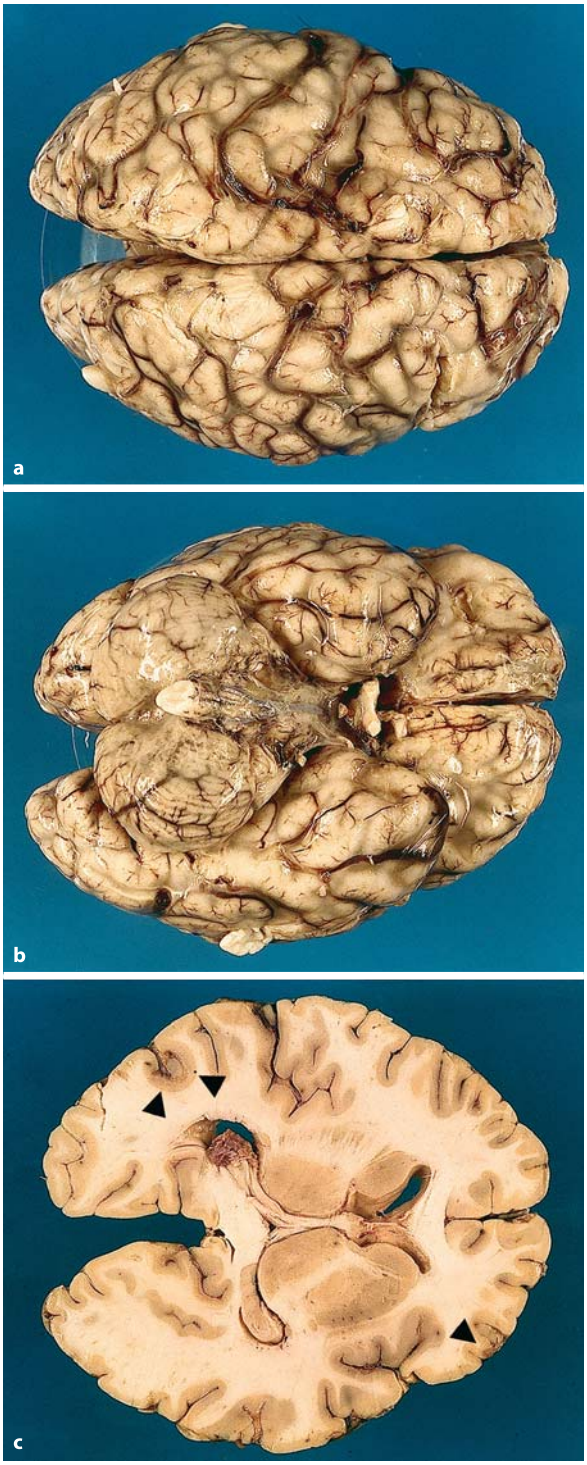

Fig. 29.8a–c. Viral meningoencephalitis. **a, b** A slight opacity of the leptomeninges and – in some cases – **c** a distinct brain swelling may be macroscopic markers of a viral infection; spot-like hemorrhages are partly seen as an indication of a hemorrhagic meningoencephalitis (**c** *arrowheads*)

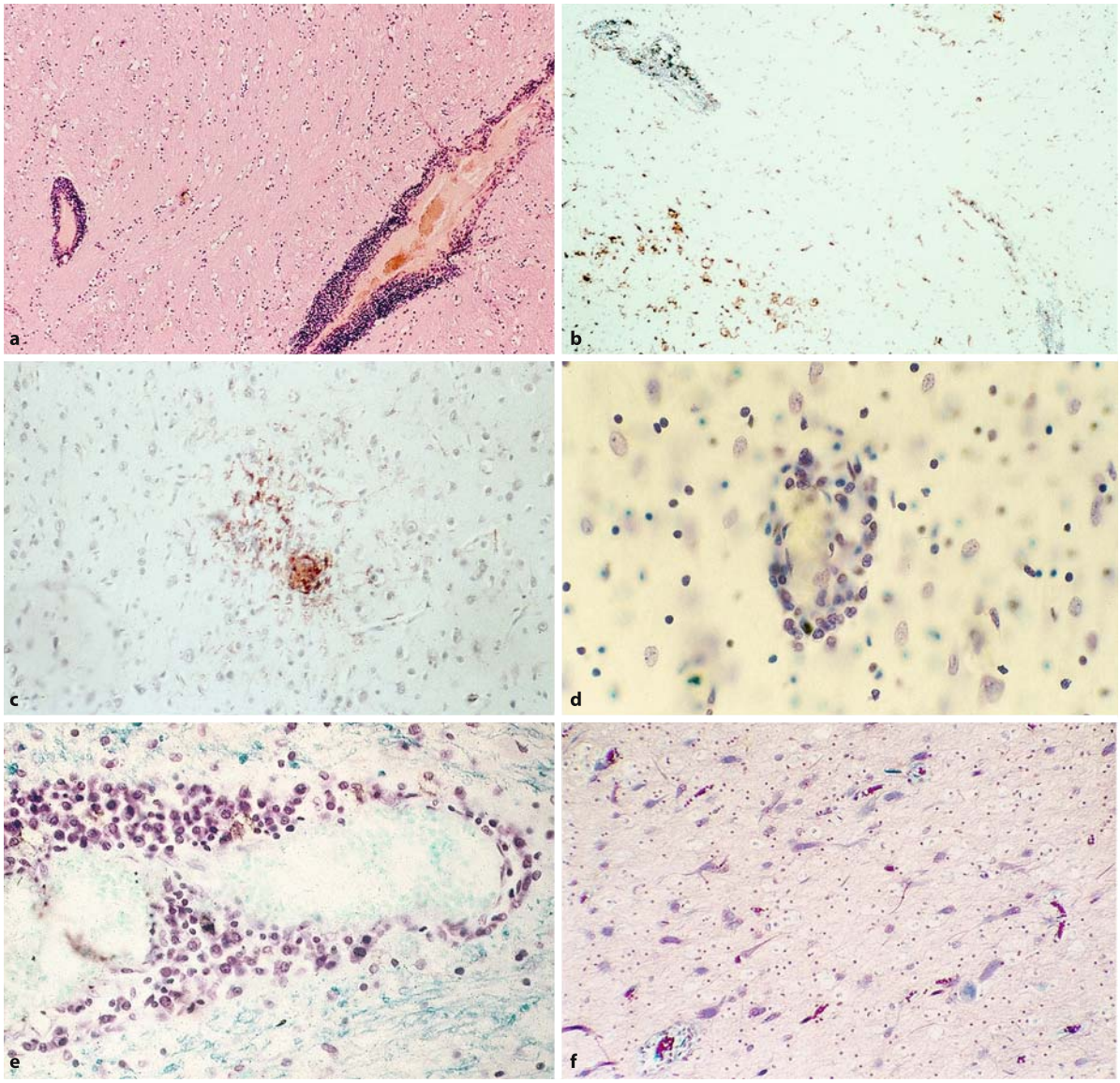

Fig. 29.9a–f. Viral meningoencephalitis. **a** Leptomeningeal and perivascular infiltration by mononuclear cells, mainly by lymphocytes, **b** microglial and plasma cells; **c–f** perivascular cuffing and lymphocytic infiltration of the brain parenchyma with extensive microglial reaction (**a, d, e** H&E; **b, c** CD68 reactivity, **f** trichrome stain; magnification **a–c** ×100; **d–f** ×500)

moderate increase of plasma cells, lymphocytes, macrophages, and neutrophils in the perivascular (perivascular cuffing) and/or subarachnoid spaces (Fig. 29.9a, e). The numerical relationships among the different cell types vary with the stage of inflammation and the nature of the infection. In the early phases, for example, neutrophils predominate over lymphocytes, whereas later plasma cells and finally macrophages predominate.

- *Activation of microglia*: the numbers of microglial cells increase in the encephalitic type and these cells become hypertrophic to form so-called rod cells (Fig. 29.9b–d). A typical feature of viral encephalitis is microglial nodules (Fig. 3.8e), reflecting the neuronophagic process.
- *Astrocytic activation*: the activation of astrocytes (Fig. 29.9f) depends on both tissue destruction and edema in cases of encephalitic participation. Both phenomena are present in encephalitis, together with a proliferation of astrocytes expressing vimentin and/or GFAP as further indications of astrocytic upregulation.
- *Neuronal changes*: the neuronal alterations include loss of Nissl substances, swelling of perikaryon or shrinkage of the cell body, plus eosinophilia of the cytoplasm, all of which are non-specific. In a few cases it cannot be determined with

certainty whether these changes are secondary results of agony or of the edema.

- *Endothelial activation*: this is triggered by up-regulation of the adhesion molecules VCAM-1 and ICAM (Sobel et al. 1990; Raine and Cannella 1992). The morphological alterations of endothelial cells are non-specific and marked by an adhesion and emigration of leukocytes.
- *Inclusion bodies*: inclusion bodies are highly specific for virus-induced inflammation of the brain parenchyma in general and for the type of virus in particular. They occur in astrocytes, neurons, and oligodendrocytes, usually in the form of intranuclear or intracytoplasmic bodies (Negri body of rabies). High-magnification microscopy reveals the majority of inclusion bodies of viral origin to have oval or round eosinophilic bodies, sometimes surrounded by a clear halo.
- *Cell and tissue necrosis*: in viral encephalitis necrosis ranges in extent from selective neuronal necrosis to total eradication of large areas of neural tissue. The pattern of distribution may be non-specific, but can be highly typical as is its occurrence in the temporal lobe in herpes simplex encephalitis, or widespread distribution in the CNS in St. Louis encephalitis.
- *Demyelination*: white matter lesions in post-infectious encephalitis arise after acute exanthematous diseases such as chickenpox, measles, rubella or mumps, or following immunization against rabies. Microscopically the lesions exhibit cuffing of small veins by a mixture of inflammatory cells composed of lymphocytes, polymorphs, and macrophages. Neural tissue destruction is marked by a breakdown of myelin.

The specific morphological changes associated with the various viral infections are described in the relevant textbooks of clinical neuropathology. Only AIDS-related infections of the CNS will be discussed here.

29.3 AIDS and the Nervous System

Acquired immunodeficiency syndrome (AIDS) is caused by a retrovirus, the human immunodeficiency virus (HIV), HIV-infected CD4+ lymphocytes and macrophages. The dramatic drop in the number of T-helper cells compromises the cell-mediated immunity and leads to other abnormalities in the host immune response. Opportunistic infections and neoplasms figure prominently in the neurological manifestation of AIDS. A distinction must be made between:

1. Primary, HIV-associated nervous system infection, and
2. Secondary infections of the nervous system

The following text is based largely on the review by Honig (1997).

29.3.1 Primary HIV-Associated Nervous System Infection

The level at which the nervous system is affected depends on which part of this organ system is infected.

29.3.1.1 HIV Encephalopathy (Subacute Dementia Encephalopathy)

Clinical Features. The most prominent clinical feature is a progressive cognitive decline over a period of months and years exhibiting the hallmarks of "subcortical" dementia. Common manifestations are personality change, apathy, decreased drive, diminished attentiveness, vegetative symptoms, and forgetfulness. Orientation, language, and remote memory functions are comparatively spared. The cumulative prevalence of HIV encephalopathy varies between 30% and 90%.

Neuropathology. The brain exhibits macroscopic pallor of the white matter (Navia et al. 1986; de la Monte et al. 1987). Microscopically, demyelination, gliosis as well as macrophage and multinucleated giant cell infiltration are found. An intense infiltration of the brain parenchyma by activated microglia associated with vasculitis and neuronal loss is demonstrable (Fig. 29.10a, b). Additionally HIV encephalopathy is characterized by intravasal fibrin precipitation and/or secondary recanalization as well as by serodiapedesis (Fig. 29.10c) and astrocytic activation (Fig. 29.10d). The frontal cortex matter is also involved, with substantial loss of neurons (20–40% – Ketzler et al. 1990; Everall et al. 1991) and of synaptic and dendritic complexity (Masliah et al. 1992). Molecular techniques reveal intraparenchymal HIV infection of macrophages, microglia, and multinucleated giant cells.

29.3.1.2 HIV Myelopathy

Clinical Features. About 20% of AIDS patients have spinal cord involvement (Budka 1991) that commonly presents as subacute or chronic progressive thoracic myelopathy with loss of the dorsal column sensory modalities (proprioception and vibration)

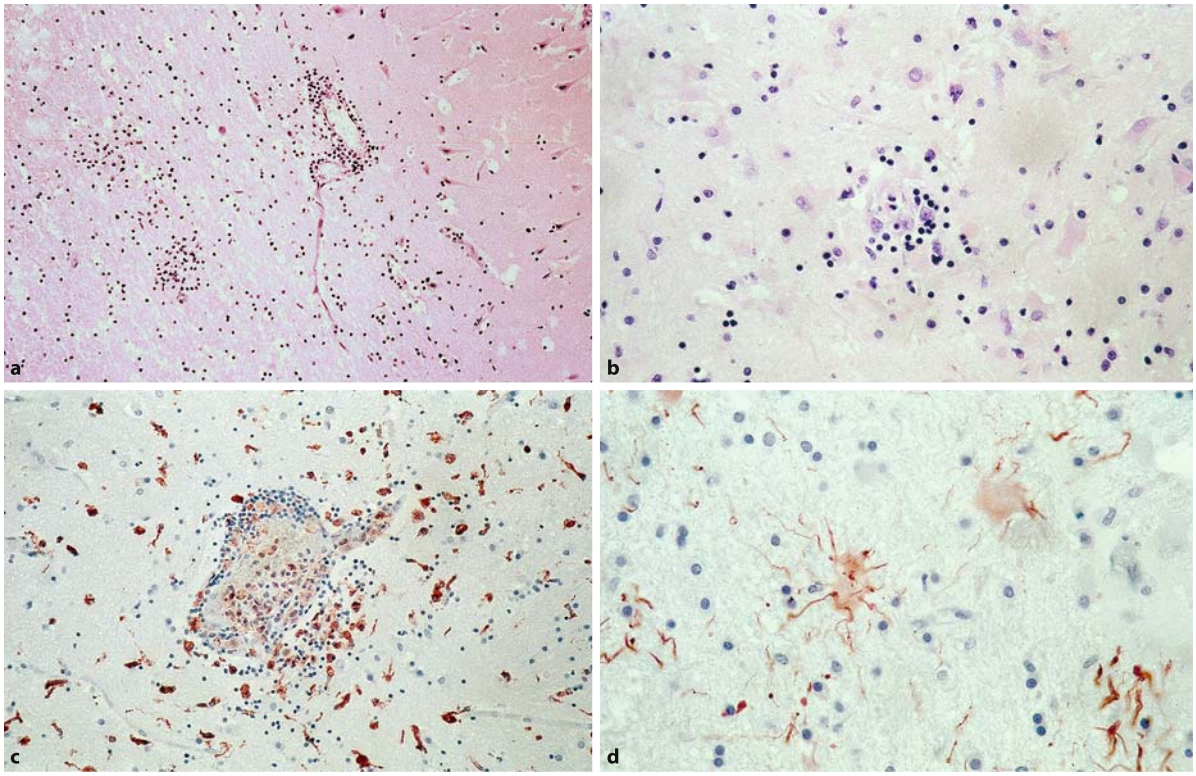

Fig. 29.10a–d. a Intense diffuse and **b** focal microglial infiltration of the brain parenchyma with perivascular clusters of microglia/macrophages; **c** vasculitis and perivascular microglial infiltration; **d** astrocytic activation (**a, b** H&E, **c** CD68 reactivity, **d** GFAP reactivity; magnification **a** ×100; **b–d** ×500)

and spastic weakness of both legs. Cord atrophy may be disclosed by MRI.

Neuropathology. Pallor marks the white matter tracts, especially in the dorsal and lateral funiculi. Microscopy reveals a spongy appearance attributable to vacuolation of variable size and coalescence between the myelin sheath lamellae; the term vacuolar myelopathy derives from these changes. Axons are intact, and the degeneration of myelinated white matter resembles that associated with vitamin B12 deficiency.

29.3.1.3 HIV Neuropathy

HIV-infected individuals are afflicted by various types of neuropathy: acute and chronic inflammatory demyelinating polyneuropathy, distal symmetric polyneuropathy, motor polyradiculopathy, mononeuritis multiplex, and autonomic neuropathy. These disorders derive in part from drug or nutrition toxicity or from opportunistic infections. A number of neuropathies, however, appear to be intrinsic to HIV infection.

29.3.2 Secondary HIV-Associated NS Infection

Because of the profound immunodeficiency state induced by HIV infection, patients are vulnerable to a wide range of historically rare neoplasms and opportunistic infections. T-cell dysfunction is combined with significant B-cell dysfunction and the appearance of leukopenia, which is most often due to bone-marrow suppression induced by medications. Because AIDS usually involves impaired cell-mediated immunity due to CD4+ T-cell depletion, patients are beset by a variety of fungal, parasitic, mycobacterial, eubacterial, and viral infections (Bredesen et al. 1988; Johnson et al. 1988). Among the pathogens are herpes virus (Fig. 29.11), *Mycobacterium tuberculosis* (Fig. 29.5), *Treponema pallidum* (Fig. 29.12a,b), cytomegalovirus, and parasitic infections such as *Cryptococcus neoformans* (Fig. 29.12c, d), *Toxoplasma gondii* (Fig. 29.13a–c), *Taenia solium* (cysticercosis) (Fig. 29.13d), *Candida* (Fig. 29.14) or *Aspergillus*, etc.

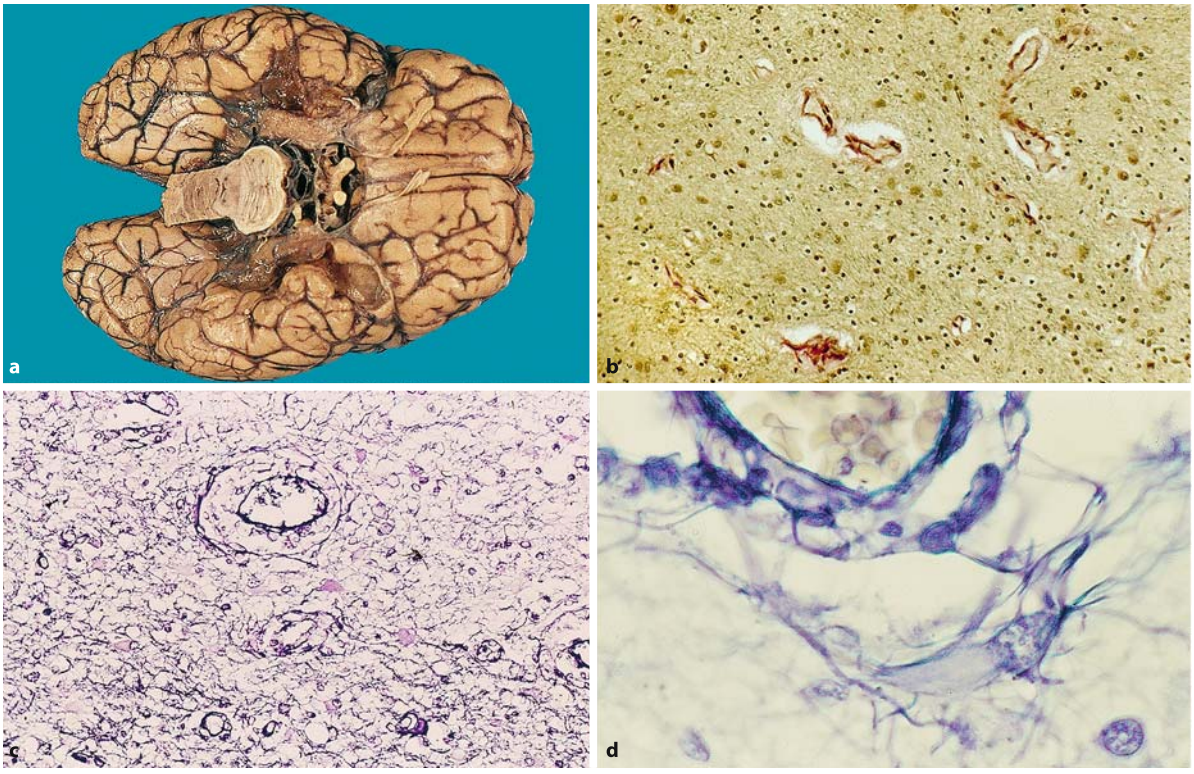

Fig. 29.11a–d. Subacute necrotizing herpes encephalitis (van Bogaert). Bilateral hemorrhagic necrosis and – in the last stage – cystic alteration (**a**) of the temporal lobe is as characteristic as the intense astrocytic reaction which is demonstrated by van Gieson stain (**b**) or by Holzer's glial stain (**c, d**) in the white matter (magnification **b, c** ×300; **d** ×1,000)

29.4 Transmissible Spongiform Encephalopathies

Included under this heading is a group of diseases with similar contagiosity and morphology. They can be transmitted to both humans and animals and are characterized morphologically by vacuolar degeneration of neurons and neuropil. However, they lack a cellular inflammatory response. They include sporadic and dominantly inherited Creutzfeldt–Jakob diseases (CJD) and familial fatal insomnia, dominantly inherited Gerstmann-Sträussler-Schenker syndrome, as well as kuru, iatrogenic CJD, and the new variant CJD (nvCJD), all of which are acquired by prion infection (DeArmond et al. 2002). Prion diseases have been in the spotlight since the advent of a new variant of CJD caused by transmission of the bovine spongiform encephalopathy (BSE) pathogen to humans (Aguzzi 1996; Will et al. 1996).

The etiology and pathogenesis of sporadic, genetic, and infectious (iatrogenic) forms of these diseases are currently attributed to a conformational change in the prion protein (PrP), a normal cell membrane protein expressed in nerve cells at particularly high levels (Kretzschmar et al. 1996). The pathological protease-resistant, scrapie-like isoform of the prion protein (PrP^{Sc}) accumulates in brain gray matter, where it is responsible for converting normal cellular PrP molecules into the pathologic isoform (Aguzzi et al. 1996; Wieland et al. 1996).

Because about 15% of all human prion diseases are dominantly inherited and accompanied by long-lasting neurological deficits, diagnosis is usually made in the living patient; sudden unexpected death is extremely rare. This disease picture is therefore seldom encountered at legal autopsy. One of the present authors has encountered a single case of sporadic CJD, in which death was attributed to chronic heavy metal poisoning (Oehmichen et al. 2001).

Neuropathology. Since prion diseases are highly infectious – even after formalin fixation of tissue – all possible measures must be taken to prevent contamination. Decontamination must be performed with formic acids. Brain tissue blocks also need to be decontaminated with formic acids prior to embedding in paraffin (cf. Schulz-Schaeffer et al. 1998; see also p. 83).

Microscopically the following histomorphological alterations are revealed:

1. In the cerebral cortex a marked astrocytic gliosis, a moderate to severe neuronal loss, and a severe

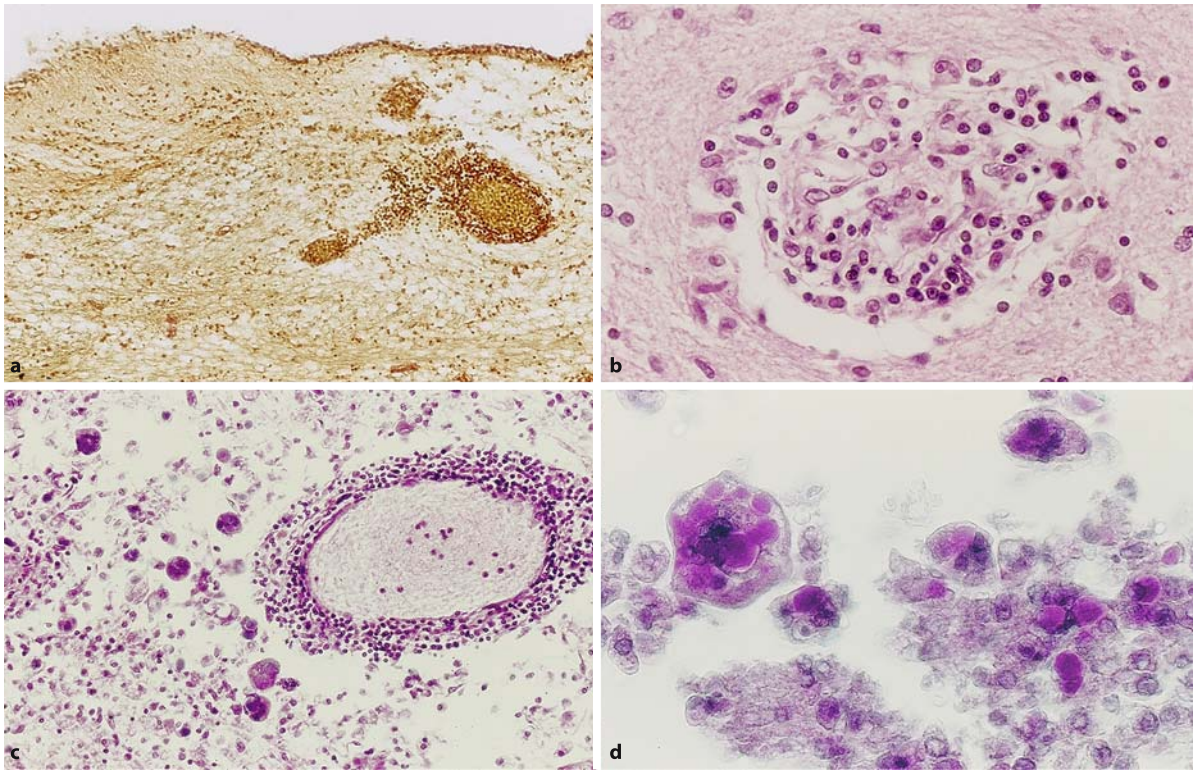

Fig. 29.12a–d. Lues cerebrospinalis (neurosyphilis) and *Cryptococcus neoformans*. **a, b** Lues cerebrospinalis associated with perivasal mononuclear infiltration and vasculitis; **c, d** *Cryptococcus neoformans* characterized by PAS-positive inclusions and giant cells (**a** van Gieson stain, **b** H&E; **c, d** PAS; magnification **a** ×100; **b** ×500, **c** ×300, **d** ×1,000)

spongiform changes with confluent vacuoles are evident (Fig. 29.15a, b).
2. Thalamic nuclei and basal ganglia exhibit the same vacuolation.
3. The white matter features astrocyte activation (Fig. 29.15d) plus marked diffuse axonal injury.
4. Perivacuolar reactivity can be demonstrated in the gray matter using a specific antibody (Gö 138 – Kretzschmar et al. 1996) against amino acids 138–152 of the human prion protein (Fig. 29.15c), while focal granular and plaque-like PrPSc deposits are found in the cerebellum, primarily in the molecular layer.
5. Diagnosis is confirmed by molecular genetic analysis, which is currently possible in specialized laboratories (Nicholl et al. 1995).

29.5 Non-Infectious Inflammatory Diseases

There are three particular types of autoimmune diseases of the CNS that are characterized by demyelination, relative sparing of axon cylinders, periventricular and perivascular inflammation, and macrophage infiltration. The mechanism by which diverse immune stimuli can trigger a similar pattern of tissue injury is unclear (for review see Genain and Hauser 1997).

29.5.1 Acute Hemorrhagic Leukoencephalitis (Hurst's Disease)

Clinical Features. The beginning of the disease is acute or hyperacute and rapidly progressive. The disease may occur without known antecedent or may follow immunization (post-vaccinal encephalomyelitis) or infection (post-infectious encephalomyelitis). The disease is characterized by a monophasic fulminant inflammatory hemorrhagic demyelination of white matter, usually post-infectious, and associated with death or severe morbidity within a few days (Geerts et al. 1991; Rossman et al. 1997). The symptoms are signs of meningitis and neurologic deficits, most commonly hemiparesis, aphasia, brain stem dysfunction, and seizures followed by coma and brain death.

The *pathophysiology* remains unknown. The disease obviously is triggered by infectious respiratory antigens (Geerts et al. 1991; Rossman et al. 1997). The disease seems to be a hyperacute form of the

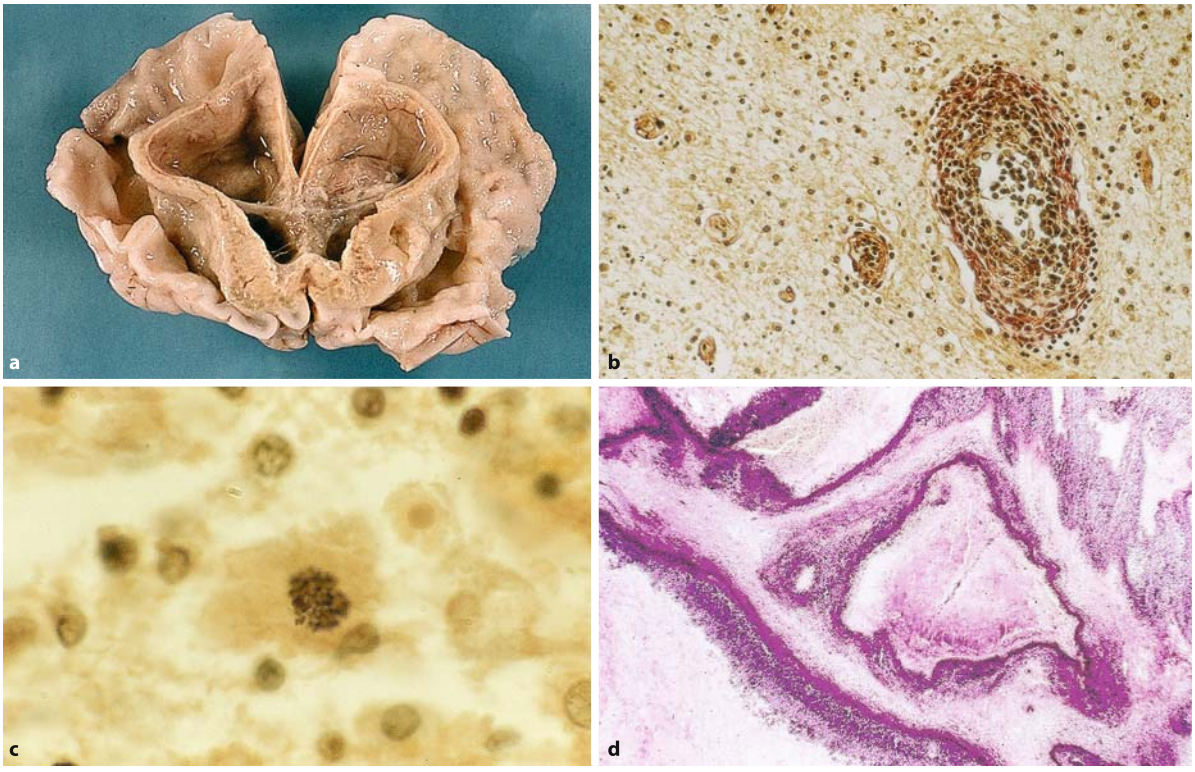

Fig. 29.13a–d. Encephalitis caused by *Toxoplasma gondii*, and cysticercus. **a** Macroscopically an extreme demyelination associated with an internal hydrocephalus caused by *Toxoplasma gondii*; **b, c** a distinct cellular infiltration of Virchow–Robin spaces and brain parenchyma is seen as well as the intracellular tachyzoite form of *Toxoplasma gondii*. **d** The cysticercosis is characterized by multiple cysts within the brain parenchyma (**b, c** van Gieson stain; **d** PAS; magnification **b** ×500; **c** ×1,000; **d** ×100)

more common acute disseminated encephalomyelitis. Both seem to result from an autoimmune process directed against the CNS myelin (Vartanian and Monte 1999).

Neuropathology. The brain is markedly swollen with uncal and tonsillar herniations and loss of gray–white demarcation. The deep white matter has a mottled gray appearance with focal hemorrhages. The microscopy is characterized by edema, leukocytic infiltration, extravasal erythrocytes, and loss of myelin – without evidence of active infection (Kuperan et al. 2003).

29.5.2 Acute Demyelinating Disease

The acute type of multiple sclerosis is characterized by the acute onset and often is associated with a post-vaccinal or post-infectious beginning. With rabies immunization this disease is most likely to occur from vaccines that are prepared by propagation in brains of adult animals (Hemachudha et al. 1987). Post-infectious encephalomyelitis may follow any of the common childhood viral exanthemas, especially a natural infection with measles virus (Johnson et al. 1984).

Clinical Features. The patients complain of acute fever and headache or neck pain accompanied by evolving visual, motor, or sensory symptoms. In severe cases, lethargy may rapidly evolve to somnolence or coma. The multiplicity of neurologic deficits is the most characteristic feature of this disease.

Pathologically the disease is characterized by multiple foci of perivenous inflammation (lymphocytes, macrophages) and demyelination found scattered throughout the cerebral hemispheres, brain stem, and spinal cord (Griffin 1990). All lesions are of the same age. A distinction between the acute and chronic (multiple sclerosis, MS) demyelinating disease may be possible because the acute type has lesions with more irregular edges while the chronic disease (MS) is thought to be created by concentric outward growth, resulting in a smoothly rounded or oval appearance (Genain and Hauser 1997).

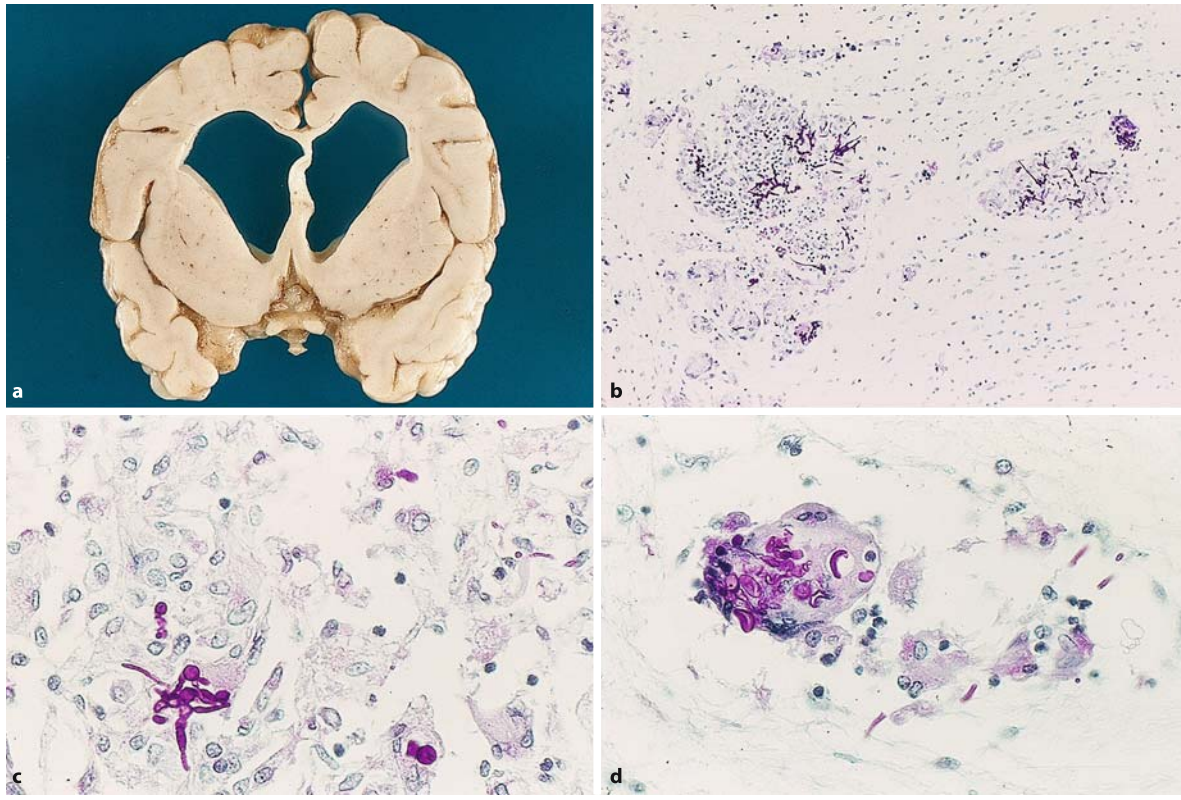

Fig. 29.14a–d. *Candida* encephalitis. **a** The macroscopic feature is characterized by hydrocephalus while the microscopy (**b–d**) reveals PAS-positive fungal filaments and an intense macrophage reaction combined with multinucleated giant cells (magnification **b** ×200; **c, d** ×1,000)

29.5.3 Chronic Demyelinating Disease: Multiple Sclerosis

Multiple sclerosis (MS) or encephalomyelitis disseminatais a chronic disorder characterized in its initial stages by episodes of neurological dysfunction (relapses). These relapses are considered to reflect injury primarily of the central nervous system, myelin or its cell of origin, the oligodendrocyte, mediated by an inflammatory response initiated by autoreactive lymphocytes recognizing neural (myelin) constituents.

Clinical Features. The neurologic deficits are characterized by sensory symptoms, motor weakness, visual blurring due to optic neuritis, diplopia, ataxia, bladder, bowel or sexual dysfunction, and cognitive dysfunction (Goodkin et al. 1991; Matthews 1991). The onset of the disease may be insidious or dramatic. Neurologic examination will reveal signs of pyramidal tract dysfunction, e.g., spasticity, but focal areflexia indicates an interruption of the lower reflex. There are two types of MS:

1. Relapsing–remitting MS, which is characterized by discrete attacks of neurologic dysfunction.
2. Chronic progressive MS, which results in gradually progressive worsening without periods of stabilization or remission.

The gross *pathology* is characterized by multiple sclerotic areas, so-called plaques (Fig. 29.16), which vary in size and localization. Mostly the plaques are centered around small veins and concentrated in the periventricular tissue. Acute lesions consist of periventricular cuffing with mononuclear cells (Fig. 29.17b; see Adams et al. 1989). A demyelination (Fig. 29.17a) occurs with aggregation of macrophages which scavenge myelin debris, and – secondarily – astrocytes proliferate (Fig. 29.17c; see Adams et al. 1989; Prineas et al. 2002). The final stage is characterized by complete demyelination and dense gliosis. Inflammatory cells may be present (chronic active plaque) or absent (chronic inactive plaque).

Epidemiology. MS is the most common disease with neurologic disability arising between early- to mid-adulthood. MS is approximately twice as common in females than in males. Ten percent of cases begin before the age of 18.

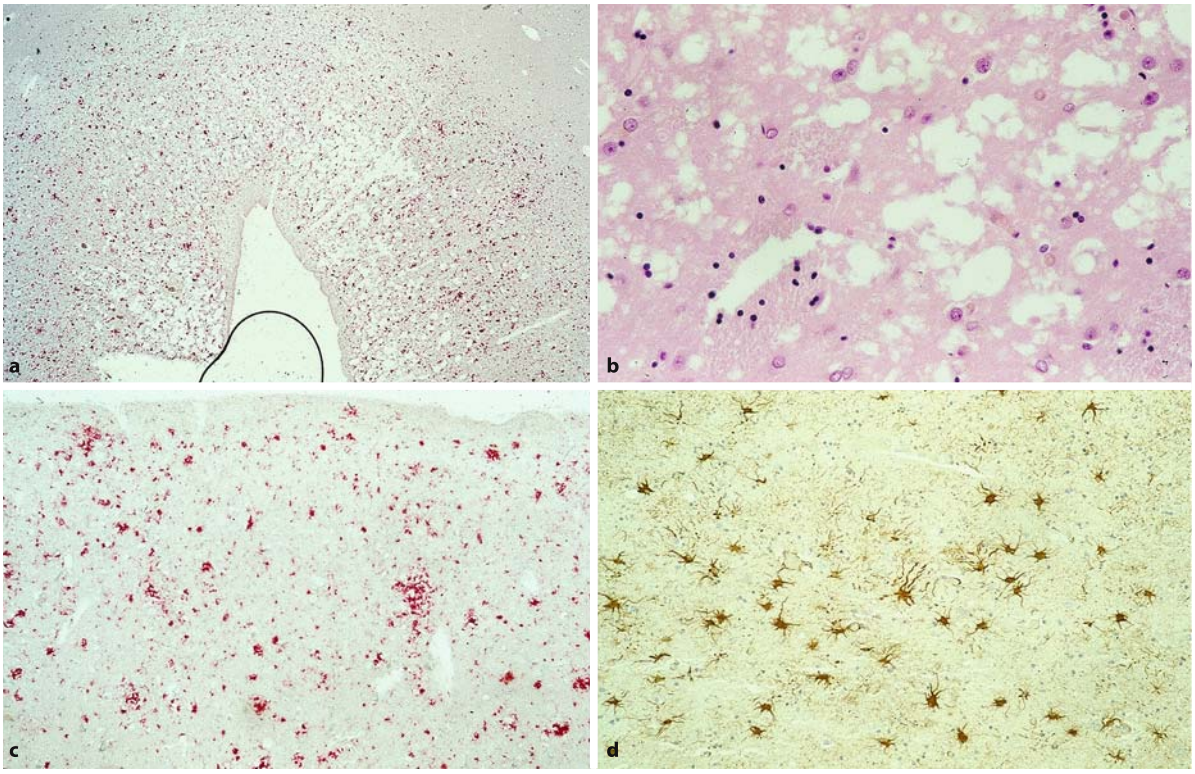

Fig. 29.15a–d. Creutzfeldt–Jakob–Disease (see Oehmichen et al. 2001). **a, b** The cortical structures are marked by a loss of neurons and a vascuolar degeneration of the neuropil; **c** in the gray matter granular and plaque-like prion-protein (Gö 138) reactive deposits are demonstrable as well as **d** a strong astrocytic reaction in the white and gray matter (**a, b** H&E; **c** Gö 138 reactivity; **d** GFAP reactivity; magnification **a** ×50; **b** ×1,000; **c, d** ×300)

The *pathogenesis* is unknown as is the mechanism of tissue damage. This disease is by most investigators believed to involve an autoimmune attack on the brain and spinal cord initiated by CD4+ T-cells specifically attacking some as yet unidentified brain antigen (Raine 1994; Williams et al. 1995). There is an immense literature and there are a lot of findings and hypotheses, which are excellently summarized by Prineas et al. (2002).

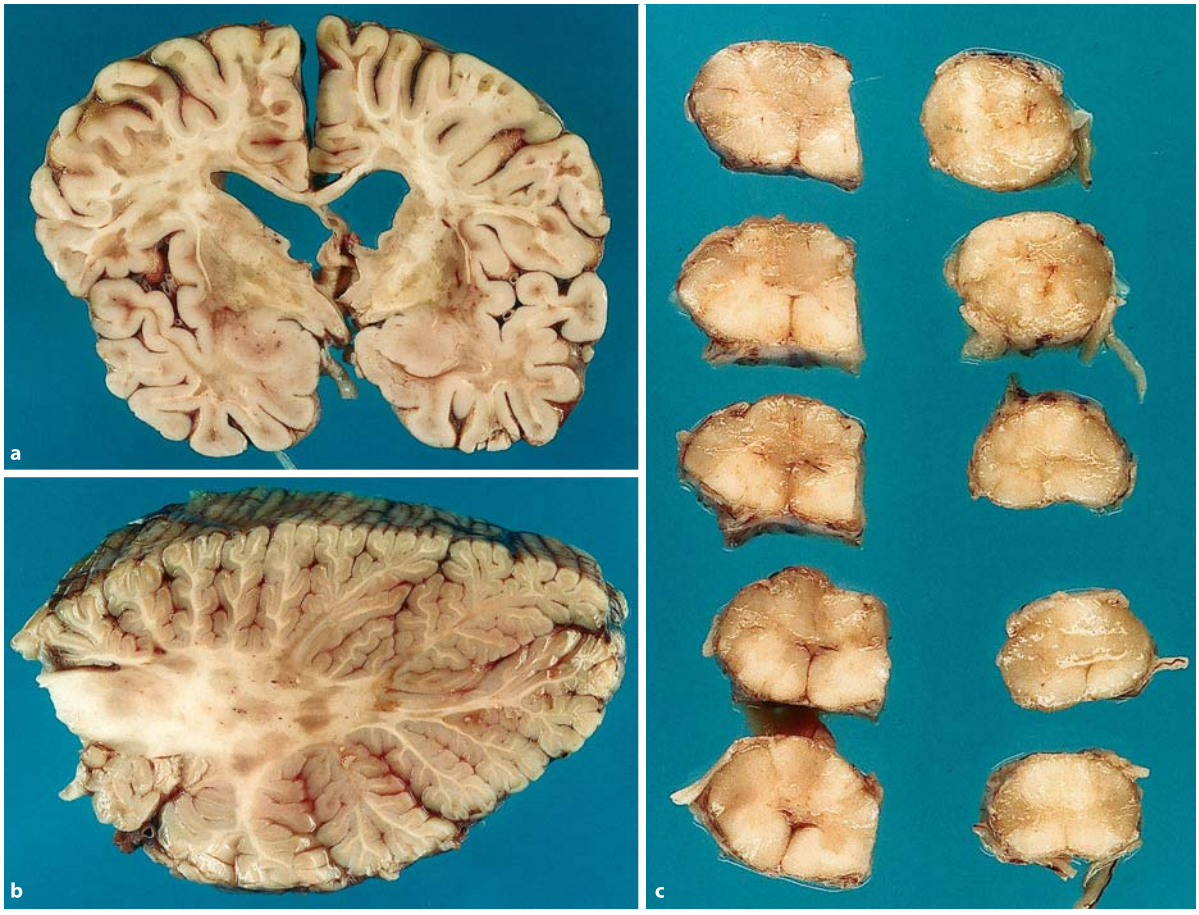

Fig. 29.16a–c. Multiple sclerosis. Disseminated foci of demyelination (plaques) in the white matter of **a** the cerebrum, **b** the cerebellum, and **c** the spinal cord

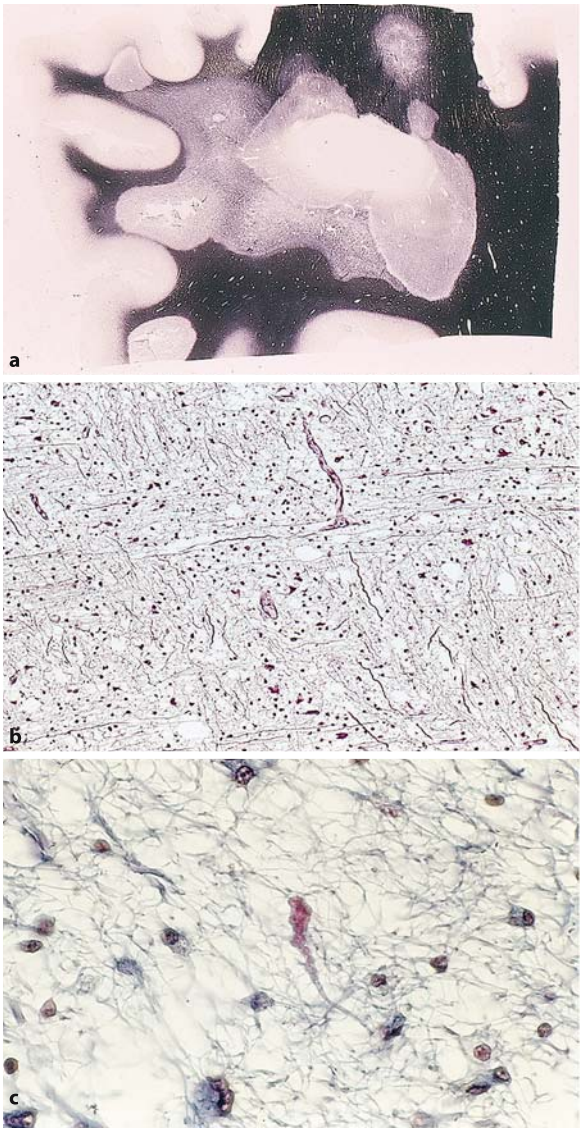

Fig. 29.17a–c. Multiple sclerosis. **a** Demyelination as demonstrated by myelin-stain; **b** inflammatory cells in a subacute phase of the demyelination process; **c** astrocytic accumulation as the final stage (**a** Weigert-Pal stain, **b, c** Holzer stain; magnification **b** ×100, **c** ×1,000)

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Nutritional and Metabolic Insults 30

Nutritional and metabolic intoxicants inflict special types of exogenous and endogenous insults on the nervous system. The majority of these intoxicants are "endogenous" neurotoxins. The insults may also result from deficiencies in energy, vitamins, water, and electrolytes secondary to functional decompensation of organs such as liver and kidney. The final diagnosis of almost all of these toxins and deficiencies cannot be made by the neuropathologist, but requires the expertise of the clinician (medical history) and pathologist (autopsy) aided by clinical–biochemical or molecular findings. At best, neuropathological examination can confirm the diagnosis and specify the type of insult of the nervous system. Such an examination can also document the neurological and/or psychopathological deficits that were present during life.

Kunze (2002) recently provided the following *definition* of metabolic encephalopathies: "Encephalopathies are diffuse multifocal cerebral states that can be caused by any of a large number of organ dysfunctions and factors. They represent functional brain disturbances that initially are not associated with morphological correlates. Primary encephalopathies can be attributed to a variety of genetically defined disturbances of carbohydrate, amino acid, and lipid metabolism. Secondary or metabolic encephalopathies are induced by systemic diseases, hypoxic–ischemic states, organ dysfunction of the liver, kidney, and lung, as well as by a variety of toxic agents. Although encephalopathy patients do not always experience *neuropathological changes*, patients with vascular and specific hepatic encephalopathies tissue often exhibit cerebral ischemia, edema, and tissue necrosis. At the cellular level astrocytes may undergo morphological changes and resemble Alzheimer type II cells."

Morris and Ferrendelli (1990) have published a thorough survey of metabolic encephalopathies and their causes. The basic pathophysiology of encephalopathy is still not known. A probable cause is a disturbance of the blood–brain barrier, but this may be only one of a number of explanations.

The *clinical features* of encephalopathies vary in both quantity and quality. Predominant among the global symptoms are slight cognitive disturbances and confusion, especially in the early stages. During later phases of disease, symptoms can include severe confusional states, altered consciousness, autonomic dysfunctions, and psychomotor hyperactivity. Severe encephalopathy can feature global brain stem signs with pathological reflexes, abnormalities of muscle tone, oral and facial automatisms, tremor, changes in spontaneous movements, and multifocal myoclonus. Among the focal cerebral symptoms are the various neurological signs of the hemispheres and/or brain stem. They generally do not predominate but are combined with global signs.

Our remarks in the following will be limited to the principal types of encephalopathy. Moreover, some of the diseases discussed here are examined in their relation to children in Part V (pp. 407 ff).

30.1 Starvation and Malnutrition

30.1.1 Protein Deficiency

An active adult requires 1,500 to 2,000 calories per day to maintain body mass. A 40% loss of original body mass can be fatal; the outcome depends in large part on the speed of loss. If sufficient fluids are available, food deprivation can lead to death within 50–60 days. Water deprivation is fatal in about 10 days, even fewer if there are high ambient temperatures.

Clinical Features. There are two basic patterns of starvation due to inadequate intake of calories and protein (Knight 1996).

- *Wet type starvation* features edema of the face, trunk, and limbs with pleural effusions and ascites. It is usually due to hypoproteinemia. The caloric intake in these types of starvation is sometimes sufficient (as in kwashiorkor).
- *Dry type starvation* is characterized by loss of half the normal body mass and leg edema; the clinical picture features feeble pulse, hypotension, and cyanosis.

Pathology. The principal autopsy findings include a negative relationship between body mass and length. The gastrointestinal tract is usually empty and the parenchymal organs are atrophic. There is sometimes a complete lack of macroscopically visible fat deposits in the abdominal walls and chest, with massive loss of muscle mass. In the mesentery the amount of fat is reduced. Elevated levels of ketone bodies are found in urine and blood (Hawkins et al. 1971).

Neuropathology. Lindenberg and Haymaker (1982) state that the brains of cachectic persons are often moist and soft. They harden poorly during fixation and easily shrink during dehydration and embedding. Despite the grave changes induced by malnutrition in various other organ systems, the *brains of cachectic adults* exhibit surprisingly few changes. The fully developed brain appears to be resistant to the effects of malnutrition (Harper and Butterworth 1997). MRI examinations of victims of anorexia nervosa (Deniker et al. 1986) and kwashiorkor (Gunston et al. 1992) show dilatation of the ventricles and sulcal widening, apparently reversible phenomena. During prolonged starvation the brain's energy requirements are met in part by ketone body metabolism (Owen et al. 1967).

Malnourishment of the mother during gestation and/or lactation can result in delayed *development of the fetal brain* (Perez-Torrero et al. 2001) and lead to congenital brain malformations (Anderson et al. 1958) such as anencephaly, hydrocephalus, encephalocele, and spinal bifida. If malnourishment persists beyond pregnancy to the early phase of postnatal development, it can cause delayed cell proliferation (Zamenhof et al. 1971; Torrero et al. 1999), diminished neocortical dendrogenesis, a reduction in the number of dendritic spines (Salas 1980; Escobar and Salas 1995; Andrade et al. 1996), plus a drop in the synapse-to-neuron ratio (Bhide and Bedi 1985). The development of child's brain will be retarded as observed by several teams (Stoch and Smythe 1967; Winick and Rosso 1969; Viteri 1981; Mize et al. 1984; Listernick et al. 1985; Udani 1992); in particular, the brain mass will be reduced (Brown 1966). Specific alterations associated with starvation during infancy and childhood are not described.

30.1.2 Vitamin Deficiencies

Malnourishment can also lead to vitamin deficiencies, sometimes in combination with marasmus.

Thiamine deficiency is relatively common in alcoholics and is known to induce "beriberi" or Wernicke–Korsakoff syndrome (see Gropman et al. 1998 – see p. 376).

Niacin (nicotinic acid) *deficiency* is also encountered in alcoholics (p. 380) as well as in tuberculosis patients. It can lead to "pellagra," which is characterized by dermatitis, diarrhea, and dementia. Its cerebral symptoms include clouding of consciousness, confusion, and myoclonic jerks. Macroscopically the brain appears normal; histologically, neurons in the pontine nuclei and dentate nuclei of the cerebellum appear ballooned and exhibit a central chromatolysis (Harper and Butterworth 2002). The neurons also feature eccentric nuclei and a loss of Nissl substance. The niacin deficiency may be a main symptom of child neglect (Piercecchi-Marti et al. 2004). In alcoholic populations most cases were reported with lesions seen especially in pontine nuclei and in the cerebellar dentate nuclei (Hauw et al. 1988).

Vitamin B12 deficiency affects patients with Addison's pernicious anemia and diseases of the intestine. It can arise after gastric surgery. Among its first clinical signs are bilateral sensory disturbances in the feet, later in the hands and fingers. Mental changes include depression, confusional states, and neurasthenia. Macroscopically the brain is normal,

but the spinal cord may appear shrunken. Microscopically demyelination is noted in the white matter of the posterior and lateral columns of the spinal cord.

Vitamin E deficiency is rare, being observed only after prolonged malabsorption. Clinically its symptoms resemble those of Friedreich's ataxia. Neuropathologically the posterior columns, especially the fasciculus cuneatus, exhibit a marked axonal degeneration.

30.1.3 Disturbances of Glucose Metabolism

Metabolic disturbances in diabetes mellitus are common and can cause acute psychomotor alterations and acute death as well as chronic alterations of the nervous and vascular systems (Cameron et al. 2001). Therefore, neurological complications in diabetes mellitus are frequent which affect sensorimotor, autonomic, and the central nervous system. Some 30% of hospitalized and 20% of community-dwelling diabetes patients have peripheral neuropathy; the annual incidence rate is approximately 2%. The primary risk factor is hyperglycemia.

The distal symmetric sensorimotor neuropathy is marked by pain, paresthesia, and sensory loss. Cardiac autonomic neuropathy may contribute to myocardial infarction, malignant arrhythmia, and sudden death. The pathology is multifactorial and involves oxidative stress, advanced glycation end products, polyol pathway flux, and protein kinase C activation (Simmons and Feldman 2002; Duby et al. 2004). All contribute to microvascular disease and nerve dysfunction.

Autonomic neuropathy is a frequent feature of diabetic neuropathy and the source of many significant problems including postural hypotension, gastroparesis, diarrhea, constipation, neurogenic bladder, and male impotence (Greene et al. 1992; Ross 1993). The neuropathologic alterations of autonomic ganglia have been extensively investigated in animal experiments and documented (Schmidt et al. 2003). The structural alterations, i.e., neuritic dystrophy expressed by markedly swollen axons and dendrites, are focused on prevertebral neuropathological alterations of autonomic ganglia. A chronic involvement of the central nervous system will be induced by chronic or transient states of hyperglycemia/hypoglycemia as well as – secondarily – due to a vascularly caused reduction of cerebral blood flow. The sequelae of permanent hypoglycemic or hyperglycemic processes causing death will be described below.

30.1.3.1 Hypoglycemic Encephalopathy

Some basic principles associated with hypoglycemic encephalopathy are described elsewhere (Chap. 13, pp. 286 ff).

Pathophysiology. Hypoglycemic encephalopathies can be caused by an insulin overdose, whether intentional (i.e., homicidal or suicidal) or accidental, or by failed gluconeogenesis in patients with hepatic disease. Neurological deficits in diabetics can result from vascular disorders (including changes in the blood–brain barrier) or other types of metabolic disturbances, including hyperglycemia, hyperosmolality, repeated hypoglycemic episodes, neuroendocrine or neurochemical changes, acidosis, and ketosis (Mooradian 1997).

The brain is supplied with energy by the oxidative metabolism of glucose. Four ATP molecules are produced by glycolysis, a further 38 by oxidative metabolism, for a total of 42 ATP molecules produced by each glucose molecule that totally combines with oxygen to form carbon dioxide and water. With few exceptions, the brain burns glucose as a fuel. The infant brain is somewhat protected against hypoglycemia by its ability to oxidize lactate (Thurston et al. 1983). During starvation, the brain utilizes ketone bodies circulating at elevated levels (Hawkins et al. 1971); the markedly hypoglycemic brain burns ketones as well (Ghajar et al. 1982).

It was once thought that both hypoxia- and hypoglycemia-induced lack of oxidative metabolism could cause neuronal degeneration. It is now known that hypoglycemic cell changes can be prevented by pharmacological antagonists of NMDA excitatory receptors (Wieloch 1985; Papagapiou and Auer 1990).

Clinical Features. Hypoglycemia is associated with psychopathological changes ranging in severity from cognitive impairment to coma. The effects of hypoglycemia can be ameliorated by optimizing blood glucose levels. In addition to acute neurological deficits, chronic deficits may also occur, diabetic neuropathy in particular. The secondary changes of diabetes, diabetes-associated hypertension, hypercholesterolemia, and arteriosclerosis, are also possible.

Neuropathology. Because both hypoglycemia and ischemia cause a selective neuronal necrosis in the cerebral cortex, hippocampus, and caudate nucleus (Auer et al. 1984), it can be very difficult to differentiate between these two insults in the human brain. Animal experiments, however, have shown that they can differ in their morphological sequelae (Auer and Siesjö 1988 – see Chap. 13, pp. 287 f). Hypoglycemia produces tissue alkalosis, whereas hypoxia causes acidosis. Because hypoglycemia does not induce

acidosis, which is critical to the pathogenesis of cerebral infarction, it does not result in the pan-necrosis (death of astrocytes as well as neurons, or infarction) seen in ischemia. Hypoglycemia differs from hypoxia/ischemia in the following ways:

Hypoglycemia is associated with neither (1) infarction nor (2) neuronal degeneration in the cerebellar cortex or brain stem (Auer and Sutherland 2002), (3) distribution of the neuronal necrosis in the cerebral cortex is superficial, a finding that contrasts with the selective neuronal necrosis in hypoxia/ischemia (see Chap. 13, pp. 286 ff), and (4) the granule cells of the dentate gyrus are subject to necrosis caused by the extracellular overflow of large quantities of aspartate, as the granule cells contain excitatory receptors.

There is also evidence of additional axonal injury as demonstrated by evoked compound action potentials (CAP): glucose withdrawal leads to delayed CAP failure (Brown et al. 2001). Dolinak et al. (2000) observed significant axonal injury in 13 cases of hypoglycemic encephalopathy even in the absence of elevated intracranial pressure. In one case injured axons were distributed in a pattern like that seen in diffuse axonal injury.

30.1.3.2 Hyperglycemia

Hyperglycemic states can be as detrimental to the brain as hypoglycemic states, although only under hypoxic conditions. It is known that higher blood glucose levels can have a detrimental effect on the outcome of human global ischemia (i.e., cardiac arrest). Longstreth showed that mean glucose levels were 341 mg/100 ml blood in patients who did not awaken versus 262 mg/100 ml blood in patients who did awaken (Longstreth and Inui 1984). Of those patients who did awaken after cardiac arrest, mean blood glucose levels were 286 mg/100 ml in those with persistent neurological deficits versus 251 mg/100 ml in those without permanent neurological disability. In focal ischemia (Pulsinelli et al. 1983), stroke (Kagansky et al. 2001) or near drowning (Ashwal et al. 1990) findings are similar. Brain hyperglycemia is associated with a reduction in cerebral O_2 and glucose metabolism, giving rise to all the signs of toxic edema (cytotoxic hypoxidosis) (Bodechtel and Erbslöh 1958). *Morphologically*, the associated selective parenchymal necrosis was stated to resemble that seen in hypoglycemia (see above). The author could observe one case of death caused by hyperglycemia which expressed a distinct necrosis of the putamen.

30.1.3.3 Diagnosis

Postmortem diagnosis of hypoglycemic encephalopathy is based on biochemical analysis of urine, CSF, and vitreous humor. Patients with hyperglycemia have elevated blood levels of ketone and acetone: diabetic ketoacidosis or non-ketotic hyperglycemic, hyperosmolar coma in patients with mild, often non-insulin-dependent diabetes. At autopsy the sum of the glucose and lactic acid levels in CSF (or in vitreous humor) of individuals with hypoglycemia and hyperglycemia can be an indication of the glucose levels at the time of death (Traub 1969). Lactate and glucose sums >400 mg/dl in CSF and >450 mg/dl in vitreous humor (Ritz and Kaatsch 1990) or >500 mg/dl in CSF and >650 mg/dl in vitreous humor (Kugler and Oehmichen 1986) may contribute to hyperglycemia-related acute death, whereas sums clearly <50 mg/dl are a sign of a fatal hypoglycemic situation. Because glycosylated hemoglobin (HbA1c) (Kugler and Oehmichen 1986; Winecker et al. 2002) and haptoglobin glycosylation (Ritz et al. 1996) remain stable after death, their postmortem levels can provide information on glucose levels in the days immediately preceding death, and thus on the quality of diabetic therapy.

30.2 Dissociation of Water and Electrolyte Balance

30.2.1 Dehydration

Incidence. As mentioned above, an adult can survive without water for about 10 days, children for less, especially if the ambient temperature is high. In children, dehydration is often caused by fever, gastroenteritis, or neglect, in the elderly by a lack of thirst. Dehydration can result in an electrolyte imbalance, with an attendant risk of sudden death due to hyperkalemic cardiac arrhythmia.

Clinical Features. Both infants and adults suffering from dehydration have deeply sunken eyes reflecting the loss of water and orbital fat, dry internal organs and mucous membranes, and diminished skin turgor. The skin becomes dry and wrinkled and stays ridged when pinched due to the loss of subcutaneous fluid and fat. Infants exhibit a sunken fontanel.

Pathology. As in life, the skin is wrinkled and dry and remains ridged when pinched between the fingers. Internal organs appear shrunken (except the brain). Feces in the rectum will be inspissated on account of the dehydration. The intestinal lining may be ulcerated by faecoliths. The diagnosis of dehydration can be confirmed by clinical–biochemical analyses (Coe 1977, 1989) of the vitreous humor for the presence of

the so-called dehydration pattern of simultaneously elevated vitreous sodium (>155 mmol/l) and chloride (>135 mmol/l) combined with moderate elevation of urea nitrogen (400–1,000 mg/l).

Neuropathology (see p. 505)**.** The high hematocrit associated with dehydration (Niaza et al. 1994) entails an elevated risk of *stroke* because the hyperviscosity of the hypercellular blood can diminish blood flow to levels liable to cause multiple small infarcts (Tohgi et al. 1978; Kirkham 1999). Dehydration-induced *sinus thrombosis*, invariably present if the veins are affected, can lead to thrombosis of superficial cortical veins. Initially the only change may be extreme congestion. Later, subarachnoid hemorrhage develops with multiple hemorrhagic infarcts that cause considerable tissue destruction if they become confluent (Friede 1989). Patients are at risk of cerebral thrombosis of the large intracranial veins, which is fatal in most cases.

30.2.2 Hypernatremia

Clinical Features. Hypernatremia is caused by extreme water loss (diabetes insipidus, diarrhea) or massive infusions of hypertonic solutions. It is associated with serum osmolality >330 mmol/kg and serum sodium concentrations >160 mmol/l. The neurological manifestations, which include seizures, myoclonus, focal deficits and coma, are superimposed on the systemic signs of dehydration (see above).

Pathophysiology and Neuropathology. Hypernatremic encephalopathy originates in the transudation of water from the intracellular milieu to extracellular hyperosmolar compartments. The result is cell shrinkage and loss of brain volume, with stretching and even tearing of small bridging vessels anchored to the dura on the skull's inner table. If tearing does occur, the resulting intracranial hemorrhage is a major complication that may account for the permanent sequelae of hypernatremic encephalopathy (Young and Truax 1979).

In 1959, Adams, Victor and Mancall described four patients with non-inflammatory demyelination in the central pons, two with a rapidly evolving flaccid quadriplegia and two without symptoms (Adams et al. 1959). It is now common knowledge (p. 610) that pontine myelinolysis (see below) can develop after excessively rapid correction of chronic hyponatremia (Brunner et al. 1990); however, this neurological event is not recognized as a complication of hypernatremia when arising from a normonatremic baseline. Following the hypothesis that myelinolysis will occur after induction of a more significant osmotic gradient than when starting from a hyponatremic state, Soupart et al. (1996) succeeded in inducing severe demyelinating lesions in rats similar to the histologic changes observed in hyponatremia-related myelinolysis.

If the extracellular osmolality increases slowly, brain cells can adjust to their changing environment by augmenting concentrations of idiogenic osmoles, which are intracellular, osmotically active particles. The osmoles consist mainly of amino acids (glutamate, glutamine, and aspartate) that prevent water from leaving the intracellular space. Remarkably, during chronic hyperosmolality the intracellular idiogenic osmoles may induce acute water intoxication if the extracellular space becomes suddenly normoosmolar due to precipitous rehydration with hypotonic fluids.

30.2.3 Hyponatremia and Water Intoxication

Hyponatremia is defined as the drop of serum sodium levels from a normal level of about 140 mmol/l to below 125 mmol/l. Adrogué and Madias (2000) recently surveyed the causes and consequences of hyponatremia. It is associated with normal, low or high tonicity (Gennari 1998). Hypotonic hyponatremia represents a relative excess of water in relation to existing sodium stores whether low, normal or high. Water retention usually results from conditions that impair renal water excretion. If excretion is normal or near normal, excessive water intake is the most common cause (primary polydipsia). The importance of hyponatremia is consistently underestimated. Rat experiments on acute and chronic hyponatremia showed that major determinants of mortality were gender, age, and the cerebral effects of vasopressin (Arieff et al. 1995).

Incidence. The literature on hyponatremia consists mainly of individual case reports. A case study on fatal child abuse by water intoxication was published by Arieff and Kronlund (1999 – see below). Athletes are especially prone to excessive water intake to prevent dehydration and exertional heat illness, which has resulted in a rise in the number of hyponatremia cases (Gardner 2002). Keating et al. (1991) reviewed the cases of 34 children treated at St. Louis (Missouri) Children's Hospital between 1975 and 1990 for water intoxication being manifestly the result of abuse. In postmenopausal women chronic symptomatic hyponatremia is a major contributor to morbidity and mortality. Intravenous sodium chloride treatment produced significantly better outcomes than fluid restriction when given for respiratory insufficiency (Ayus and Arieff 1999).

Pathogenesis. Although it is the most common electrolyte disorder, hyponatremia rarely results from excessive water intake unless the kidney cannot excrete free water, or because of protein retention in patients with liver cirrhosis or who have undergone orthotopic liver transplantation (Papadakis et al. 1990; Wszolek et al. 1999). Hypotonic hyponatremia mainly manifests as CNS dysfunction and increases in severity with the amount and rapidity of the decline in serum sodium levels. It causes water to enter the brain, resulting in brain edema and intracranial hypertension and possible brain injury. Fortunately, the solutes leave brain tissues within a matter of hours, thus inducing water loss and ameliorating the brain swelling (Verbalis and Gullans 1991).

Pathology and Clinical Features. According to Coe (1977), water intoxication is marked by a specific pattern of low vitreous sodium (<130 mmol/l), low chloride (<105 mmol/l), and relatively low potassium (<15 mmol/l). Arieff and Kronlund (1999) described three cases of fatal child abuse by forced water intake (>6.0 l). All of the victims presented to hospital with hypoxemia and hyponatremia; they experienced seizures, emesis, and coma. None of the three children were treated for hyponatremia because the forced water intoxication was not revealed to medical personnel. At autopsy all three were found to have aspiration pneumonia and *cerebral edema*.

A recent investigation (Saeed et al. 2002) gives a catamnestic review of 42 adult patients suffering severe hyponatriemia. Nine patients had central nervous symptoms and four of these patients died in hospital. The authors recommended that the diagnosis requires an accurate drug history, clinical examination, and assessment of fluid volume, plus the measurement of urinary electrolytes and osmolality in a spot urine sample. Neuropathological findings are not described.

Neuropathology. The CNS features a pronounced brain edema.

30.2.4 Hyponatremia and Central Pontine Myelinolysis

Central pontine myelinolysis (CPM) is a rare complication of hyponatremia characterized by non-inflammatory demyelination. It has been shown in controlled experimental conditions to be an osmotic instability of myelin reproducible after rapid correction of hyponatremia (Lien et al. 1991; Laureno and Karp 1997).

Pathogenesis. CPM was originally assumed to be almost exclusively a consequence of chronic alcohol abuse, since it is often associated with Wernicke–Korsakoff syndrome. But many non-alcoholics are also affected, usually patients with severe liver disease (Goebel and Zur 1972), especially after liver transplantation (Estol et al. 1989), severe burns (McKee et al. 1988), severe electrolyte disorders, malnutrition, or anorexia. It can also be caused by tubulopathy, water intoxication, or abuse of diuretics in individuals with anorexia nervosa (Amann et al. 2001). The signal pathogenetic factor is over-correction of chronic hyponatremia with hypertonic saline (Norenberg et al. 1982; Soupart et al. 2000). This hypothesis has been questioned though by a number of authors (Bird et al. 1990; Papadakis et al. 1990; Ashrafian and Davey 2001; Leens et al. 2001) and alternative hypotheses proposed, such as hypophosphatemia (Peters et al. 1993), but the central pathogenetic factor from animal and human studies is rapid correction of hyponatremia (Klineschmidt-DeMasters and Norenberg 1981, 1982; Norenberg et al. 1982).

Incidence. Pathological–anatomical studies indicate that this disease picture is relatively rare. CT and MRI techniques meanwhile allow detection of more cases during early stages as well as observation of complete recovery (Wakui et al. 1991).

Clinical Features. The clinical features include spastic tetraparesis, pseudobulbar paralysis, and locked-in syndrome and are a reflection of damage to the descending motor tracts. MRI of the brain reveals prolonged T1 and T2 relaxation in a characteristically shaped area of the central pons. The extent of recovery varies, ranging from substantial to none (Pirzada and Ali 2001).

Neuropathology (Fig. 18.5 – p.380)**.** The localization of the myelinolysis is highly characteristic. It usually occurs in the center of the base of the pons, extending rostrally from just beneath the midbrain through the upper two-thirds of the pons. The myelinolysis occurs symmetrically about the midline rostrocaudal axis and can be easily recognized on myelin-stained sections as a sharply demarcated area of pallor within the basis pontis (Harper and Butterworth 1997). The first sign is a demyelination process with preservation of axons followed by an inflammatory reaction with conspicuous preservation of the neurons. The myelinosis is usually accompanied by osmosis-induced pontine glial cell swelling and cell death (Ashrafian and Davey 2001). Within freshly demyelinated lesions the GFAP immunolabeling of astrocytic cytoplasm is drastically reduced. In both recent and old lesions, immunostaining of vimentin reveals differential intracytoplasmic decoration of dystrophic and hypertrophic astrocytes (Gocht and Lohler 1990). Other microscopic alterations depend on the age of the lesion. Very severe lesions exhibit

complete necrosis of the central zone. Extrapontine lesions can occur in the thalamus, striatum, cerebellum, and in the cerebral white matter (Wright et al. 1979; Goldman and Horoupian 1981; Estol et al. 1989). Extrapontine demyelination without actual central pontine myelinolysis has now been described as well (Okeda et al. 1986).

30.3 Hepatic Encephalopathy

Hepatic encephalopathy exhibits both neurologic and psychopathologic symptoms. One characteristic neuropsychiatric feature in the majority of patients is the potential for complete recovery. The conditions under which hepatic encephalopathy may arise (see Harper and Butterworth 2002) were summed up by the Working Party at the 11th World Congress of Gastroenterology in Vienna (1998 – see Ferenci et al. 2002): (1) acute fulminant hepatic failure, (2) portal-systemic congestion (bypass of the liver related to portosystemic shunts without intrinsic liver disease), and (3) chronic liver disease (cirrhosis, portal hypertension or familial hepatolenticular degeneration = Wilson's disease), (4) Reye's syndrome, which constitutes a special form of hepatic encephalopathy and will be described below, and (5) bilirubin encephalopathy, which is discussed in Part V, "Pediatric Neuropathology" (pp. 452 ff).

Clinical Features. The clinical features differ between patients with symptomatic encephalopathy and patients with minimal encephalopathy, which has no discernible symptoms of brain dysfunction (Ferenci et al. 2002). The neurological findings in *symptomatic encephalopathy* usually pertain only to the patient's motor and mental status. Characteristic of the altered mental status is impairment of the sleep–wake cycle, of attention, cognition, orientation, and consciousness. The neurologic status features dysarthria, increase in tone, hypomimia, slow or clumsy rapidly alternating movements, tremor, ataxia, increased deep tendon reflexes, and impairment of posture or postural reflexes. Differential diagnosis must exclude concomitant neurological influences such as Wernicke's disease, other types of metabolic disease, and drug intoxication (alcohol, sedatives, etc.). The symptoms of *minimal encephalopathy* are subclinical and include euphoria or anxiety, lack of awareness, shortened attention span, and impaired performance of addition (Ferenci et al. 2002).

Pathophysiology. Hepatic encephalopathy is caused by elevated levels of endogenous neurotoxins. It has various possible causes, prominent among them being hyperammonemia, altered amino acid ratios, an increase in the aromatic amino acid to branched-chain amino acid ratio, plus benzodiazepine excesses in certain brain areas (Mullen and Kaminsky-Russ 1996; Butterworth 1997). The prime candidate for the causative neurotoxin in hepatic encephalopathy is ammonia (Butterworth 2000; Felipo and Butterworth 2002). Consequently, astrocytes – where ammonia is mainly metabolized – probably play a key, perhaps a dominant, role in the pathogenesis of hepatic encephalopathy. Norenberg (1994) hypothesized that toxins affect the astrocytes, while abnormal glial function disturbs the microenvironment and glial–neuronal interactions. Acting together, these factors lead to disordered neuronal activity. The evidence today suggests that changes in neurotransmission may also contribute to this type of encephalopathy (Butterworth 2001). Such changes may be due to a depletion of cerebral energy (Rao and Norenberg 2001). The only brain cells that contain glutamine synthetase for ammonia removal are astrocytes, which thus have a high affinity for the glutamate transporters EAAT-1 and EAAT-2 as shown in the rat forebrain. The macroscopic brain changes include a cerebral edema and intracranial hypertension. Alterations also occur in the astrocytes themselves (see below).

30.3.1 Fulminant Hepatic Failure

Rapid onset of severe inflammatory or necrotic liver disease leads precipitately to stupor and coma, or to delirium, mania or seizures. Cytotoxic brain swelling is the salient pathological feature, with an attendant risk of cerebellar tonsillar herniation. Herniation can give rise to secondary hemorrhages in the brain stem. Hemorrhagic diathesis induces multifocal hemorrhages and hypoxia secondary to brain swelling.

30.3.2 Chronic Liver Disease and Portal-Systemic Bypass

Patients with cirrhotic liver disease slowly develop hepatic encephalopathy. Symptoms start with altered sleep patterns and progress through asterixis to stupor and coma. The liver cirrhosis generates a portal hypertension and in some cases a transjugular intrahepatic portosystemic stent shunt (Butterworth 2000). The clinical symptoms are often preceded by constipation, a dietary protein overload, or gastrointestinal bleeding.

Neuropathology. The brain appears macroscopically normal. It is disputed whether cirrhosis alone can

induce brain atrophy in the absence of simultaneous chronic alcohol abuse (see Lee et al. 1979 versus Acker 1986). Microscopically this form of encephalopathy is characterized by astrocytic (rather than neuronal) alterations termed Alzheimer II astrocytosis (astropathy). The astrocytes possess pale watery and enlarged nuclei with scant chromatin distributed around the periphery; they often have a distinct nucleolus. Expression of GFAP is unchanged or decreased depending upon the region of the brain (Norenberg et al. 1990). For example, there is decreased GFAP immunolabeling of cerebral cortical astrocytes in the cerebrum of chronic liver failure patients (Sobel et al. 1981) or following end-to-side portocaval anastomosis in rats (Norenberg 1977). GFAP immunolabeling of cerebellar Bergmann glia is unchanged (Kril et al. 1997).

Alzheimer II type astrocytes are seen mainly in deep layers of the cerebral cortex, in Bergman glial cells of the cerebellum, in the basis pontis, striatum, thalamus, globus pallidus, inferior olives, and dentate nucleus (Harper and Butterworth 2002). GFAP is not expressed by processes of Alzheimer type II or the perikaryon (Sobel et al. 1981; Norenberg 1990; Belanger et al. 2002). The nuclei in some cases become lobulated and are located in the gray matter, especially in the substantia nigra, dentate nucleus, and globus pallidus (Norenberg 1994). Alzheimer type II glia are not specific for hepatic encephalopathy, but occur in other metabolic encephalopathies such as hypocapnia, uremia, and in the early stages of anoxia and hypoglycemia, especially in infants. The common pathogenetic factor appears to be the elevated blood or brain ammonia (Norenberg 1994).

30.3.3 Familial Hepatolenticular Degeneration (Wilson's Disease)

Wilson's disease is a familial metabolic disorder transmitted in an autosomal recessive manner and characterized by liver cirrhosis in association with neuronal degeneration in the striatum. The responsible gene appears to code for a copper-transporting P-type ATPase and has been mapped to chromosome 13 (Bull et al. 1993). Starting at birth, patients with Wilson's disease have 10 to 50 times normal copper levels in the liver and a caeruloplasmin deficiency in the blood. The first clinical symptoms appear in the 5th year of life. Neurological symptoms include progressive rigidity, tremor, dysarthria, dysphagia, and dementia. Pathognomic of Wilson's disease is the so-called Kayser–Fleischer ring of brown pigmentation in the cornea.

Neuropathology. The ventricles are symmetrically dilated, especially close to the striatum, and the striatum appears brown or brick-red in color. The putamen often shows cavitation. Microscopically there is a proliferation of Alzheimer type II astrocytes and neuronal loss in the putamen, the globus pallidus, caudate nucleus, and thalamus. There is also an increase in the number of Opalski cells (no processes, large perikaryon, small nucleus) and Alzheimer type I cells (large, multinucleated astrocytes). Iron pigment is evident in macrophages. Enhanced pericapillary accumulation of copper is characteristic.

30.3.4 Reye's Syndrome

Reye's syndrome is marked by an association between encephalopathy and hepatomegaly. This is not a rare syndrome. The Center for Disease Control, Atlanta/Georgia, documented 655 cases in the years 1977 and 1978 alone, 32% of which were fatal (Starko et al. 1980). It does not appear to have a single cause, likely causes including toxic, infectious or metabolic insults. Short- and medium-chain fatty acids are thought to play a major role in the pathogenesis, with injury to the mitochondria of the liver producing the liver symptoms (Mamunes et al. 1974). Encephalopathy has been attributed among other causes to a hyperammonemia (DeLong and Glick 1982).

The *clinical manifestations* begin with vomiting, personality change, and somnolence progressing to convulsions and coma. Children between the ages of 2 and 16 are the main victims, although a few cases involving adults have been reported (Van Coster et al. 1991). Elevated levels of transaminases in blood is common, as is hypoglycemia (Reye et al. 1963).

Neuropathology. The brain alterations associated with Reye's syndrome feature a marked cytotoxic brain edema with distinct swelling of astrocytic foot processes (Blisard and Davis 1991). Frequent findings include acute, multifocal ischemic changes in the cerebral cortex, cerebellum, hippocampus, and basal ganglia (Pedal et al. 1984). The liver undergoes fatty degeneration. Electron microscopic demonstration of anomalous liver mitochondria is regarded as constituting proof of Reye's syndrome.

30.4 Uremic Encephalopathy

A number of acquired and genetically determined diseases are thought to affect the brain and kidney, among them vasculitides, paraproteinemias, microangiopathies, and von Hippel–Lindau disease. Independent of these diseases, uremic encephalopathy can also be caused by renal failure, which induces a rise in substances normally eliminated with the urine. Acute kidney failure can have a profound ef-

fect on the nervous system. Uremia affects both the central and peripheral nervous systems.

Pathophysiology. Uremia with accumulation of toxic substances causing encephalopathy can be attributed to a broad spectrum of pathogenic diseases, chronic renal diseases, or to acute renal failure as well. The four guanidino compounds known to accumulate in uremia are creatinine, guanidine, guanidinosuccinic acid, and methylguanidine. These substances have been shown in animal studies to induce behavioral alterations and long-lasting generalized convulsions (D'Hooge et al. 1992). In humans, uremia is associated with decreased brain oxygen consumption; in rodent models of acute renal failure, with diminished brain energy consumption (Mahoney et al. 1984). It has been proposed that encephalopathy is caused by derangements of amino acids (mainly glycine, glutamine, aromatic and branched-chain amino acids) plus a neurotransmitter imbalance (mainly GABA, dopamine, serotonin) (Biasioli et al. 1986). Encephalopathy has also been attributed to an extensive neuroendocrine disturbance (Handelsman and Dong 1993). Because uremia-associated neuropsychiatric symptoms are improved by either medical suppression of parathyroid hormones or parathyroidectomy (Cogan et al. 1978), it is also thought that parathyroid hormone is a CNS uremic toxin (Fraser 1992).

Moreover, as many as 40% of uremic patients receive ciclosporin, which may result in neurological side-effects. Five per cent of patients with uremia develop nerve injuries during renal transplantation and up to 45% of transplant patients suffer CNS infections, often fungal in type, that end in death (Burn and Bates 1998).

Classification. Four different types of encephalopathy are distinguished (Rob et al. 2001):

- *Uremic encephalopathy,* a complication of uremia that responds well to dialysis.
- *Dialysis encephalopathy syndrome* (see below), which results from acute aluminum intoxication associated with aluminum-containing dialysate.
- *Dialysis-associated encephalopathy/dementia*, which invariably involves elevated serum aluminum levels.
- *Age-related vascular dementia*, in particular, is as common among patients on long-term dialysis as among the general population.

Clinical Features. Uremic encephalopathy features signs of depressed brain function manifested as cognition and memory disturbances, and can progress over time to delirium, convulsions, and coma. Periods of dialysis may initially aggravate the encephalopathy, and are related to changes in metabolic states associated with ionic changes or diminished synaptic function. Symptoms of global cerebral involvement are also seen, including agitation and fluctuating disturbances of consciousness accompanied by hyperpnea (Kussmaul or Cheyne-Stokes type), multifocal myoclonus, hyperreflexia, asterixis, tremor, and brain stem signs with various types of nystagmus and muscle tone abnormalities (Kunze 2002). Uremic encephalopathies are marked by elevated serum creatinine, potassium, phosphates, as well as by metabolic acidosis and hypocalcemia. The peripheral nervous system can also be affected by renal failure, displaying a neuropathy with a predilection for axons that are large in diameter (Burn and Bates 1998; Kunze 2002). Dialysis or transplantation can reverse these processes. The myopathy accompanying renal failure resembles that of primary hyperparathyroidism and osteomalacia and is frequently associated with bone pain and tenderness (Burn and Bates 1998).

Pathology. Uremia/renal insufficiency and the underlying renal disease characterize the pathology. In cases with uncertain diagnosis, the uremia pattern (Coe 1977) should be assessed: marked elevations of vitreous and serum urea levels and creatinine without a significant rise in sodium and chloride values are specific to uremic encephalopathy.

Neuropathology. The main neuropathological finding of reversible cerebral edema is associated with rapid dialysis. Despite the steep drop in plasma urea levels, the retention of brain urea accounts for the rise in brain water (Silver 1995). Patients with chronic renal failure and hypertension, or patients receiving conservative treatment or hemodialysis were found to suffer from cerebral atrophy (Savazzi et al. 2001; Savazzi and Cusmano 2002). Subdural hemorrhages were found in 1–3% of 400 patients dying of chronic renal failure (Fraser and Arieff 1988). Variably pronounced, usually generalized neuronal degeneration has been reported to strike perivascular areas of demyelination and necrosis. The affected brain areas include the subcortical nuclei, cerebral cortex, the cerebellum, and nuclei of the brain stem. Alzheimer type II astrocytes are common (Norenberg 1994). In one case the affected internal capsules, periventricular white matter, and bilateral basal ganglia were hypodense on CT (Okada et al. 1991). Isolated cases have exhibited Wernicke's encephalopathy (Jagadha et al. 1987; Ihara et al. 1999) or – in patients with hemolytic uremic syndrome – involvement of the basal ganglia (Barnett et al. 1995; Theobald et al. 2001).

30.4.1 Dialysis Encephalopathy

Dialysis itself can induce neurological disorders such as Wernicke's encephalopathy, disequilibrium syndrome, and subdural hemorrhage. In patients with

chronic renal failure the use of long-term hemodialysis is associated with endemic lethal encephalopathy attributable to the high aluminum levels (Alfrey et al. 1976) in the dialysate. Modern techniques of water purification, however, are now able to avert such acute intoxication. Dialysis encephalopathy is characterized *clinically* by headache, nausea, EEG abnormalities, emesis, blurred vision, tremor, muscle twitching, hypertension, asterixis, seizures, dementia, disorientation, and myoclonic jerks. The clinical and neuropathological features of dialysis encephalopathy have led some authors to postulate an association between dialysis dementia, aluminum intoxication, and Alzheimer's disease.

Neuropathology. Biochemically, dialysis dementia features a conspicuous increase in the brain's aluminum content (see Chap. 17, pp. 339 f). Reusche (2002) used a simple and effective method for demonstrating neurofibrillary tangles and senile plaques to show that aluminum encephalopathy exhibits identical morphologic features to those found in Alzheimer's disease. He did not however provide any evidence of elevated aluminum levels in the brains of Alzheimer's patients (Reusche 1997).

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Aging and Brain Pathology 31

Physiological brain changes associated with the aging process do not lead to sudden, unexpected death; in fact the older the person, the less unexpected death becomes. As mean life expectancy has increased in the industrialized Western world, so has the exposure of the forensic neuropathologist to the normal changes and pathology of the aging brain. Neuropathological examination must make a clear distinction between age-related and disease-related alterations of brain tissue (Braak et al. 2002). The task of the forensic neuropathologist is to distinguish changes due to acute or chronic exogenous effects from changes attributable to physiological endogenous effects. Neuropathological findings can also provide additional – though limited – information regarding the psychopathological state of the deceased. For these reasons the editors have deemed it necessary to discuss the neuropathological aspects of aging and brain pathology in this Part on clinical neuropathology.

31.1 Basic Principles

31.1.1 Biology of Aging

The implications of aging both for individuals and societies transcend the bounds of any one field. Although aging is a multifactorial process, the forensic neuropathologist is confronted chiefly with the psychological and physiological concomitants of aging that render the elderly disadvantaged in society. The ongoing rise in the numbers of elderly people also poses an entirely different set of problems: the molecular and biochemical mechanisms underlying the aging process can only be understood to the extent that the multifactorial exogenous, endogenous (genetic), and autonomous processes affecting them are also identified.

The human body is comprised of 10 billion cells, the majority of which replicate themselves and are thus theoretically immortal. Regarding the cell's potential immortality Hayflick (1968) observed that after 50 replications (±10 replications) cultured fibroblasts lose their ability to divide. He concluded that human cells have a limited lifespan, termed under these model conditions the "Hayflick limit." Aging is thus an intrinsic process of the cell itself (Hayflick 2002).

The following three theories have attempted to explain this self-limited growth (for review see Oehmichen et al. 2002; Meissner 2003).

1. *Attrition theory* (Wei 1998). As catabolic products accumulate in human cells, they inhibit proliferation, perhaps due to oxidative damage to lipids and proteins or via somatic DNA mutations. Free radicals, for example, have been shown to

contribute to these alterations (Dizdaroglu 1998, 1999). So-called radical scavengers and antioxidants such as vitamins E and C are thought to counter the injurious effects of free radicals (Strasser et al. 1997).

The mitochondria are the site of intracellular energy metabolism. They possess their own, autonomously replicating mitochondrial DNA (mtDNA), which is liable to attack and damage by free radicals. Free radicals not only inflict point mutations and duplications, they also induce deletions. At least one of these deletions, the 4977 base pair deletion (common deletion), appears to be age dependent (Meissner et al. 1997, 1998). Such deletions are most readily demonstrated in post-mitotic cells, i.e., in muscle cells and brain cells, and also in mitotic cells such as astrocytes (Storm et al. 2002) or blood cells (Wurmb et al. 1998). In addition, aging mtDNA deletions are caused by several exogenous factors such as UV light, hypoxia, toxic influences, etc. (Wickens 1998), and accumulate in different tissues in an age-dependent manner.

2. *Theory of genetic control or so-called telomere theory* (Hayflick 1994; Holt et al. 1997; Hodes 1999; Kaye 2002). Normal human cells have a finite lifespan with a DNA-determined rate as well as limit to cell division and consequent programmed cell death (von Zglinicki 2000). The telomere theory states the following (Hodes 1999): the fusion of chromosomes is prevented by DNA sequences located at the end of chromosomes, i.e., by telomeres. Each division of the cell shortens the telomeres (Hamilton and Mestler 1969); this shortening accounts for the ability of single cells to divide. However, in cancer cells the telomeres are not shortened at division, in spite of uninhibited growth. This phenomenon is attributed to the presence of the enzyme telomerase in cancer cells, which is not present in most human cells. Transfection of telomerase into normal cells could also prolong their life (Bodnar et al. 1998; Parwaresch and Krupp 2002).
3. *Autonomous process theory.* An autonomous process of spontaneous modification of extracellular and cellular proteins occurs in a manner dependent of age. Among the "age modifications" of these proteins are oxidation, glycosylation, deamidation as well as isomerization and racemization. The abnormal, long-lived proteins created by these modifications accumulate over the course of life (Ritz-Timme 1999, 2002). Racemization of aspartic acid can serve as a "biological clock" for determining the age of permanent proteins that are not exchanged during life and thus for estimating the age of the organism itself, also within the brain (Shapira et al. 1988; Mori et al. 1994; Kenessey et al. 1995).

Aging obviously reflects the accumulation of endogenous and exogenous changes that increase the risk of disease and death (Harman 2002).

31.1.2 Neurobiology of Aging

The physiological processes contributing to the aging of the brain are reflected in qualitative *changes in memory* affecting both verbal and declarative memory as well as short-term and long-term memory. Verbal or declarative memory requires functioning of the hippocampus and limbic system, areas commonly damaged in Alzheimer's disease (AD). It can be tested by questioning subjects about facts, experiences, or specific time and place events. Short-term and long-term memory are best tested by means of verbal recall. The elderly consistently suffer a deficit of short-term memory, whether tested by verbal or non-verbal means, whereas age-dependent deficits in long-term memory are thought by most – but not all – researchers to be minimal.

As to *intellectual function* other than memory, both cross-sectional and longitudinal studies appear to show that persons who perform well in this regard when young also perform well when old. Although a modest decline in intellectual ability is thought by most authors to be part of the aging process, the decline may start later in life and be smaller in magnitude than once thought. It may also involve fewer of the many functions of which intelligence is composed. For example, there is an age-related decline in "fluid" intelligence, which is concerned with new problem solving, adaptation to new situations, and the discrimination and identification of stimuli and appropriate responses.

The effects of normal aging on human *cerebral physiology* remain largely unknown. Slower reaction times and prolonged latency of sensory-evoked potentials reflect slowed CNS conduction times as well as other possible slowing of "central processing" functions. Somatosensory-evoked potentials are often amplified, perhaps as compensation or due to a loss of inhibitory effects. The meaning of the age-related mild slowing of alpha activity on the electroencephalogram (EEG) is not known. Many apparently healthy elderly individuals show increased beta activity and anterior temporal slow waves in EEGs; some investigators however insist that there can be little or no abnormality in EEGs of the truly healthy.

31.1.3 Dementia and Delirium

Psychological alterations such as dementia and delirium are always associated with injury or disease

of the brain. Both dementia and delirium can be subsummed under the general heading of organic mental disorders (psychiatric diagnostic terminology) or the useful term *brain failure* associated with multiple diseases (Ross and Bowen 2002).

Dementia refers to global loss of intellectual and integrative brain functions in an alert patient. It may be acute in onset and remain static, as after cerebral anoxia, brain injury, or encephalitis. In most cases, though, it is gradual in onset and progressive. Dementia is one of the most disabling and costly diseases of aging (for review see Ross and Bowen 2002). Dementia may be confused with many disorders by the unwary. Although the elderly are much more likely to suffer from dementing syndromes and diseases than are persons under the age of 60, dementia is an age-related, not an age-induced disorder. Dementia should not be confused with the comparatively slight decline in mental function of healthy aging. Forgetfulness, which is common at all ages, usually does not result from disease but from such factors as inattention, poor motivation, distractibility, and stimulus interference or "system overload."

Delirium represents a confusional state associated with illusions and hallucinations attributable to global impairment of intellectual function associated with impairment of consciousness or awareness of the environment. Delirium is commonly acute in onset, fluctuating in course, and often reversible.

Frontal lobe lesions often lead to personality changes, such as loss of initiative, apathy, diminished insight, neglect of personal hygiene, and loss of social inhibitions. *Lesions of the temporoparietal region* of the dominant posterior hemisphere can cause fluent aphasia with poor comprehension, loss of the ability to write, read, or calculate, right–left disorientation, and difficulty naming fingers. *Damage of medial temporal lobes* (the amygdala and hippocampus in particular) and/or of *diencephalic structures* (mammillary bodies and the dorsomedial thalamus) are known to induce amnesic syndromes.

31.1.4 Classification of Age-Dependent Dementias

Age-dependent dementias are sometimes classified according to their topography, sometimes according to their pathogenesis. Topographically they are differentiated into cortical and subcortical types. Cortical type dementias, which include *Alzheimer's disease (AD)* and *Pick's disease*, exhibit distinct mental alterations such as apraxia, aphasia, and visuospatial difficulties. Subcortical dementias, including *Parkinson's disease* and *Huntington's disease*, feature moderate impairment of motor functions, such as posture and gait, with slowness of thinking, verbal responses, and movements but with preserved language and visuospatial orientation. The pathogenesis of these disorders is unknown, and they are described as "degenerative diseases." Based on the known pathogenesis, three additional age-related types of dementia can be distinguished:

- *Multiple cerebral infarctions*, which rarely constitute the only pathological finding in demented patients. The few exhaustively examined cases of multi-infarct dementia exhibited destruction of large volumes of brain tissue ranging from 50 to 100 ml. It is not known how much damage must occur to which critical areas of the brain before this multifocal disease produces dementia.
- *Subcortical arteriosclerotic encephalopathy*, or *Binswanger's disease*, is caused by ischemic lesions of deep hemispheric white matter; unlike multi-infarct dementia, it features a restricted location of infarctions.
- *Acquired immune deficiency syndrome (AIDS)*, which is associated with a high incidence of dementia (see pp. 593 f).

31.2 Morphology of the Aging Brain

Just as growth is a normal part of brain development in early life, so are a number of physiological changes part of the brain's aging toward the end of life (Braak et al. 2002). Certain brain diseases on the other hand affect the elderly only and can be distinguished from normal aging processes based on quantitative changes alone. Even if normal aging of the brain does not invariably involve significant neuronal loss, such loss under pathological conditions is the morphological hallmark of dementia. Recent data appear to indicate that the adult CNS has a remarkable capacity for self-repair (for review see Horner and Gage 2002; – see p. 66).

In the following, normal alterations associated with aging of the brain are presented, followed by a description of age-related diseases of the brain (pp. 625 ff).

31.2.1 Macroscopic Alterations

Three phenomena are typical of the gross changes of the brain:

- *Decrease in brain volume* – after age 65. The decline is diffuse and not focally emphasized. The decrease in cortical thickness is associated with cortical atrophy, loss of white matter with enlargement of the ventricles, the lateral ventricles in particular.

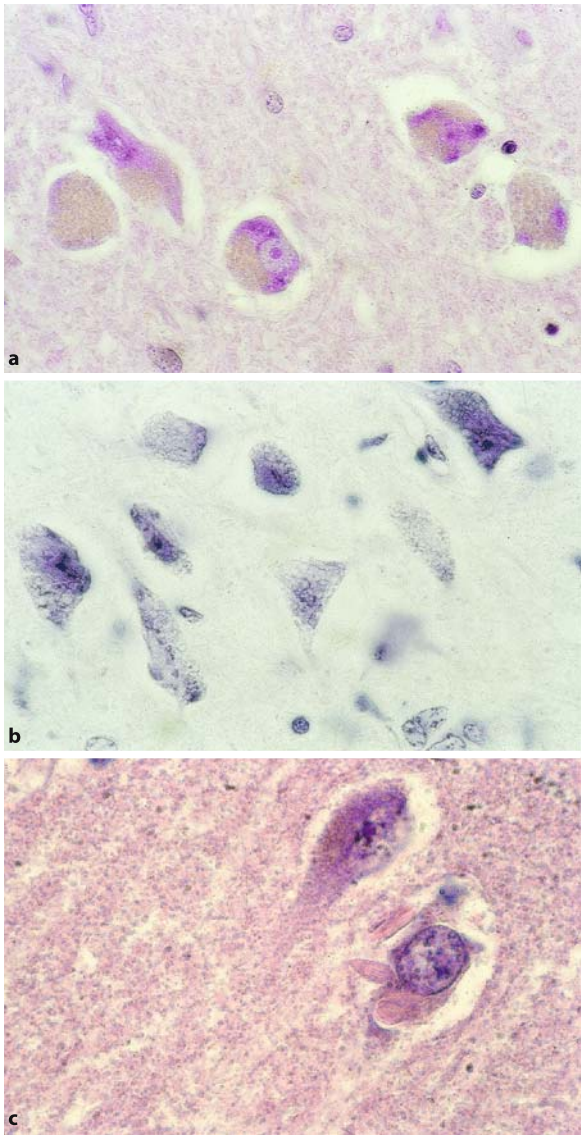

Fig. 31.1a–c. Age-dependent neuronal alterations. **a** Increase of lipofuscin-containing neurons, especially in neurons of the inferior olivary nucleus; **b** granulovacuolar degeneration and shrinkage of neurons; **c** Hirano body. (**a, c** H&E; **b** Nissl stain; magnification **a–c** ×1,000)

- *Loss of brain mass*: the normal adult brain loses about 30 g of mass up to the age of 60. A relatively rapid loss of brain mass begins after age 70 and can amount to as much as 200 g.
- *Atherosclerotic blood vessels and vascular lesions*: these changes are observed to some degree in almost every brain after age 70. Such changes are often associated with hypertension.

31.2.2 Microscopic Alterations

The age-related microscopic changes of the brain cover a diverse spectrum:

- *Loss of large neurons*, predominantly of cortical neurons. It is generally thought that while the healthy brain suffers little or no age-related neuronal loss (Haug 1977; Peters et al. 1998), patients with AD exhibit massive loss of neurons (Coleman and Flood 1987).
- *Shrinkage and atrophy of neurons* can result from loss of cytoplasmic RNA.
- *Aggregation of lipofuscin in neurons* (also in astrocytes and oligodendrocytes): lipofuscin is the end-product of lysosomal metabolism and consists of non-degradable proteins and lipids. The presence of lipofuscin in neurons is not associated with any functional changes (Mann and Yates 1987). Lipofuscin is found mainly in neurons of the inferior olivary nucleus (Fig. 31.1a), in the hippocampal area, and in the cerebellar dentate nucleus. It also occurs in anterior horn cells of the spinal cord.
- *Ubiquitin-reactive structures:* ubiquitin is a protein that acts as a marker for degradation by proteasome mechanisms. Such structures are a common feature of the aging brain in the form of granular bodies or intranuclear dot-like structures (Marinesco bodies) (Dickson et al. 1992) and are encountered mainly in neurons of the locus ceruleus and substantia nigra.
- *Granulovacuolar degeneration* is common in brains of the aged, especially of AD patients (Fig. 31.1b). It appears as a single or multiple granule-containing vacuole of 3–5 µm diameter residing in the cytoplasm of pyramidal cells of the hippocampus, preferentially in CA1.
- *Hirano bodies* are refractile, brightly eosinophilic, rod-shaped, ovoid, spherical or cylindrical structures located within neuronal processes (Fig. 31.1c). They most often lie immediately adjacent to hippocampal pyramidal cells, preferentially in CA1. They can be seen in normal aging.
- *Lewy bodies* are a relatively common incidental finding in brains of the elderly, their prevalence climbing from 3.8% to 12.8% between the sixth and ninth decades of life (Perry et al. 1990). They vary in size from 3 µm to 20 µm. Hyaline acidophilic inclusions can be visualized only by neutral or acidic dyes, being invisible in Nissl stain. *Classic Lewy bodies* are intraneuronal, rounded, eosinophilic inclusions with a hyaline core and a pale-staining peripheral halo (Fig. 31.8). They are characteristic of Parkinson's disease and are usually located in surviving neurons in the substantia nigra. *Cortical Lewy bodies* are also

found in Parkinson's disease and in "dementia with cortical Lewy bodies" as well as in various other diseases. They occur in neurons of the cerebral cortex (layers V and VI) (cf. Lowe and Leigh 2002). Lewy bodies react to antibodies to ubiquitin (Fig. 31.8c), neurofilament protein and α-synuclein.

- *Beta-amyloid precursor protein* (β-APP) can be demonstrated in dystrophic neurites of senile plaques (Cras et al. 1991; Wang and Munoz 1995).
- *Changes of the dendritic system and rearrangement of synapses* occur in aged brains under both physiological and pathological conditions (Masliah et al. 1993).
- *Neuropil threads* are neuropil structures distributed throughout the gray matter, the frequency of which is a marker of the degree of dementia (McKee et al. 1991). They appear to be involved in degeneration processes of the distal dendrites (Yamaguchi et al. 1990) or axons, especially in the entorhinal cortex or amygdala (Braak and Braak 1988), and are often associated with (a high number of) neurofibrillary tangle-bearing neurons. Neuropil threads express ubiquitin, tau antigen (Yamaguchi et al. 1990), and neurofilament protein.
- *Myelin sheaths* exhibit degenerative changes, such as the formation of splits containing electron-dense cytoplasm, and the formation of myelin balloons (Peters 2002). Moreover, *oligodendrocytes* increase in number with age, and a loss of nerve fibers from the white matter of the cerebral hemispheres is observed. All these alterations contribute to cognitive decline especially because of the consequent decrease in connections between neurons.
- *Cerebral white matter lesions,* so-called leukoaraiosis are common neuroradiological findings in elderly people (Kuo and Lipsitz 2004). These lesions are located at periventricular and subcortical areas and are associated with falls, executive cognitive impairment, depressive symptoms, and urinary incontinence.
- *Astrocytic changes* are characterized by an upregulation of glial fibrillary acidic protein (GFAP – Hansen et al. 1987).
- *Corpora amylacea* are spherical, laminated, basophilic to eosinophilic structures within astrocytic processes commonly located near the blood–brain or cerebrospinal fluid–brain interfaces (Mrak et al. 1997).
- *Resting microglia* will be activated (Sloane et al. 1999). Moreover according to observations by Streit et al (2004, see Streit 2004) a microglial dystrophy may be a sign of microglial cell senescence which is characterized by LN-3 immunohistochemistry-demonstrable abnormalities in cytoplasmic structure, including deramification, spheroid formation, gnarling, and fragmentation of processes.
- *Atherosclerosis* is an aging process of the vessels that affects about 75% of all persons aged 75 years and older. It is not associated with any primary functional impairments, which only arise if vessel occlusion leads to necrosis (pp. 543 ff).
- *Status lacunaris* is in most cases asymptomatic, but can in rare cases lead to hemiplegia or to extrapyramidal syndromes (pp. 548 ff).
- *Cerebral amyloid angiopathy* features deposition of amyloid Aβ40 in the lamina media of small to medium-sized arteries of the meninges and cortex (congophilic angiopathy). The amino acid sequences of cerebrovascular and plaque amyloid exhibit no homology to any other known protein and are virtually identical. Amyloid angiopathy can be demonstrated with thioflavin S or by immunohistochemical expression of Aβ42. Vessels exhibiting such changes chiefly occur in association with AD. Amyloid angiopathy can be the cause of atypical brain hemorrhages such as those seen in AD.

In a special study, Knopman et al. (2003) examined the neuropathological changes in brains of 39 longitudinally followed, cognitively normal elderly individuals (24 women, 15 men; age range 74–95 years, median 85 years). Only one subject had neocortical Lewy bodies. Small, old infarcts were common, but no subjects had more than two of these and none had a single large infarction. Thus, the majority of individuals who are cognitively normal near the time of their death have minimal amounts of tau-positive neuritic pathology [Braak stage <IV and neuritic plaques <6 per mm^2 (National Institute of Aging criterion) in the most affected neocortical region]. Few subjects with more severe AD pathology can be expected based on incidence rates of AD in the very elderly.

31.2.2.1 Neurofibrillary Tangles

Neurofibrillary tangles (NFTs) are fibrillary alterations (argentophilic fibrils) of the cytoplasm of neurons and the apical dendrites of neurons. They are relatively inconspicuous in Nissl or H&E stains, a faint marginal refractivity of fibrillary material becoming visible only by dimming the light. The nucleus is usually deformed and eccentric, while the Nissl bodies are displaced. NFTs appear sometimes flame-shaped, sometimes more globular. They can be demonstrated with silver techniques {according to Böck (1989), especially according to Bodian (1937) [see Ziesmer (1969)], Bielschowsky [see Ráliš et al. (1973)], and Gallyas (1971), as well as according to

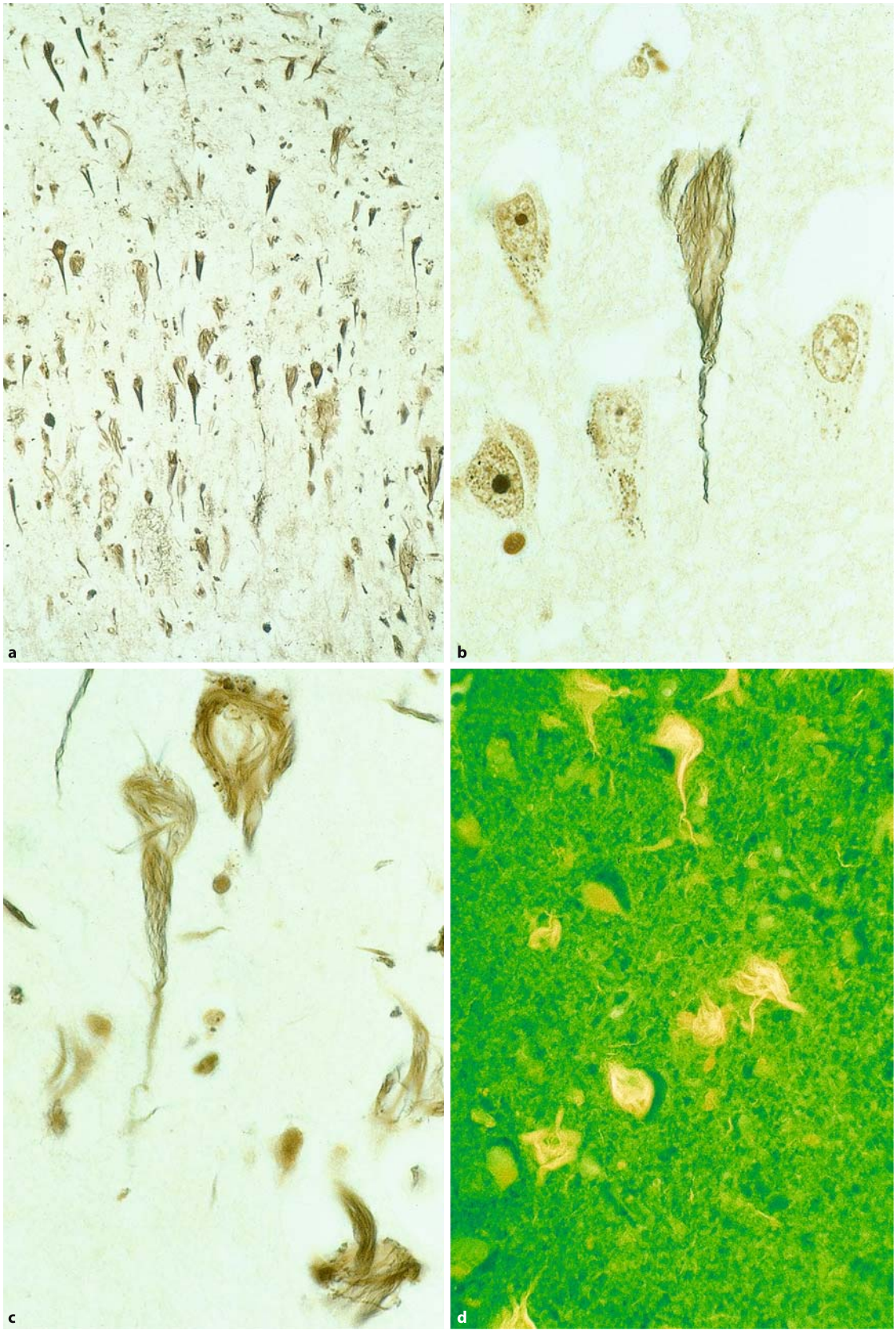

Fig. 31.2a–d. Neurofibrillary tangles in cortical neurons which are sometimes flame-shaped (**a**, **b**) and sometimes more globular (**c, d**). (**a–c** silver stain; **d** thioflavin S fluorescence; magnification **a** ×300; **d** ×500; **b, c** ×1,000)

Reusche (1991) – Fig. 31.2a–c}, or using fluorescence techniques [thioflavin S, see Fig. 31.2d – Vassar and Culling (1959)].

The fibrillary changes seen in normal aging brains as well as in brains of AD feature an aggregation of swollen fibrils, which suggests that the substrate for the disease process is provided by the cell's neurofibrillary framework. As AD progresses, thick bands increase in number and extend from the apical dendrite to just beneath the cytoplasmic membrane at the base of the cell, imparting a wicker basket-like appearance to the cell. In the final disease stages, residual masses may resemble triangles, spools, or torches.

Electron microscopic examination reveals paired filaments 10 nm in diameter wound helically around each other with crossovers at 80-nm intervals. They exhibit multiple phosphorylation sites and are associated with the microtubule-associated protein tau (Grundke-Iqbal et al. 1986). It is not known how native tau converts to paired helical filaments. The monoclonal antibody Alz50 recognizes a 68-kDa polypeptide called A68 (Wolozin et al. 1986) and is able to identify neurons with tangles or those that are liable to develop tangles (Hyman et al. 1988). The pathological tau protein causes the intracytoplasmic microtubule system to break apart and the neuron becomes non-functional (Iqbal et al. 1986).

The main sites of NFTs are the hippocampus, parahippocampus, amygdala, and layers II and IV of the cortex (Arnold et al. 1991). They occur in the physiologically aging brain, their concentration increasing exponentially with age (Price and Morris 1999). The number of NFTs is noticeably increased in persons with Down's syndrome, AD, lead encephalopathy, dementia pugilistica, etc. (Wisniewski et al. 1979). The results of recent investigations suggest that NFTs may constitute a pathological substrate of memory loss not only in AD but also in normal aging and mild cognitive impairment (Guillozet et al. 2003).

31.2.2.2 Senile Plaques

Senile plaques are found predominantly in the cerebral cortex. They are spherical, 4–200 µm in diameter, and feature extracellular deposition of the amyloid Aβ42. When fully developed, neuritic plaques possess a central core of amyloid, a peripheral group of neuronal processes, and both altered and unaltered neurites. The altered neurites constitute mainly axon terminals or preterminals. They contain paired helical filaments and altered cytoplasmic organelles. The amyloid core possesses immunoglobulins. On their periphery, neuritic plaques also have processes of microglial cells, fibrous astrocytes, and macrophages. Senile plaques assume various forms:

- *Neuritic plaques* (classic plaques) possess a concentric, target-like structure with a well-formed amyloid core surrounded by radially oriented swollen neuronal processes (Fig. 31.3).
- *Perivascular oriented plaques* are concentric and usually associated with amyloid angiopathy.
- *Primitive plaques* are spherical and comprised of dense granular amyloid deposits.
- *Diffuse plaques* lack thickened neurites or well-defined amyloid cores and appear more amorphous (Fig. 31.3b, c).
- *Burned out plaques* feature an amyloid core devoid of surrounding structures.

Biochemically the amyloid deposits in the plaques consist of the proteins Aβ42 and Aβ40 (Glenner and Wong 1984). The molecular processes underlying formation of the plaques are the subject of intensive ongoing research.

Senile plaques occur in the cerebral cortex, the hippocampal formation and entorhinal cortex, as well as in the basal ganglia and the cerebellar cortex. In some cases only plaques are present, in other cases only NFTs are demonstrated, but in most cases both pathological phenomena are associated (Fig. 31.4), often in combination with ubiquitin deposits, especially in and around the plaques (Fig. 31.4c).

31.3 Pathology of the Aging Brain

The gross changes associated with the various age-related brain diseases are described below. Whereas some of the disorders exhibit specific morphological changes, others are characterized by quantitative changes alone.

Classification of age-related brain disorders will be problematic. Since the pathogenetic background of similar disease pictures can be as unknown as it is diverse, and since numerous transitional forms exist, the differential diagnosis must be largely phenomenological. In the following, brain diseases described as degenerative disorders are distinguished from vascular diseases, although both share the clinical features of "dementia." The disease pictures of degenerative disease are differentiated according to the lesion's localization, generalized lesions for example would be typical of AD, frontotemporal lesions of Pick's disease. A recently introduced classification is based on biochemical criteria (Kretzschmar and Neumann 2000; Mirra and Heyman 2002): intracellular deposition of tau protein in AD and Pick's disease, of α-synuclein in Parkinson's disease, of polyglutamine in Huntington's chorea, and of ubiquitin in amyotrophic lateral sclerosis; extracellular deposition of pathologic protein in prion disease and AD.

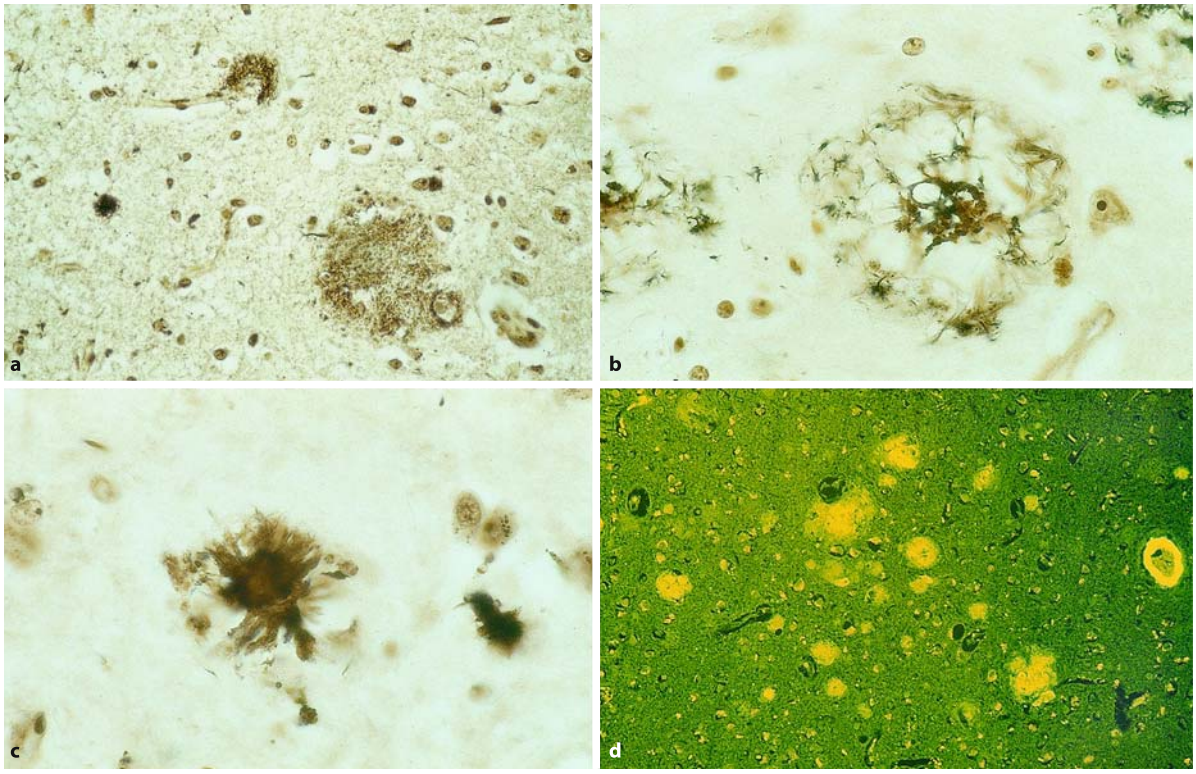

Fig. 31.3a–d. Senile plaques in the cerebral cortex. Fully developed neuritic plaques which were demonstrated by silver stain (**a–c**) and by thioflavin S fluorescence (**d**) (magnification **a–c** ×1,000; **d** ×300)

Age-related diseases associated with primary age-independent motoric, sensory, and/or focal deficits due to degenerative alterations will not be described here (see textbooks of clinical neuropathology; for vascular diseases, see Chap. 28, pp. 542 ff).

31.3.1 Alzheimer's Disease (AD)

AD is the most common cause of dementia in the elderly. Prior to age 65 dementia is a rare phenomenon and is designated "presenile dementia" or "Alzheimer's Disease." After age 80, one in five individuals suffers from so-called senile dementia or dementia of Alzheimer's type, after age 90 one in two individuals is affected (Kawas and Katzman 1999).

31.3.1.1 Clinical Features

The onset of AD is frequently subtle and difficult to date and describe. In the early stages many integrative behaviors are affected. Although the first symptom is often forgetfulness, changes in mood or personality, impoverished language and intellectual fatigue may herald onset of the illness. Only rarely does the disease begin with signs of focal cortical dysfunction such as dressing apraxia, aphasia, or spatial disorientation with concurrent retention of other intellectual functions.

Numerous defects become evident as the dementia progresses, affecting judgment, reasoning, memory, orientation, and the ability to use language, to calculate, and to think abstractly. Routine tasks may be performed tolerably well, but the patient fails when confronted by new or altered circumstances. Alzheimer's patients are prone to denial and confabulation or to hide their shortcomings. The clinical picture may be dominated by emotional changes such as depression, a fatuous euphoria, or a wide range of personality changes that can be the most distressing element for family and friends. AD leads in its advanced stages to devastation of a human being from cumulative loss of the brain's adaptive, integrative, and intellectual functions. AD victims eventually become completely helpless.

Even though a large percentage of cases can be correctly diagnosed using psychological tests and imaging techniques, especially based on the exclusion of other dementing disorders (Miller et al. 2002), the diagnosis of AD can only be confirmed by neuropathological, i.e., by postmortem, examination (Jellinger et al. 1992; Klatka et al. 1996). There are no biological markers in blood or CSF (for review see Frank et al. 2003; in contrast to Hulstaert et al. 1999). The

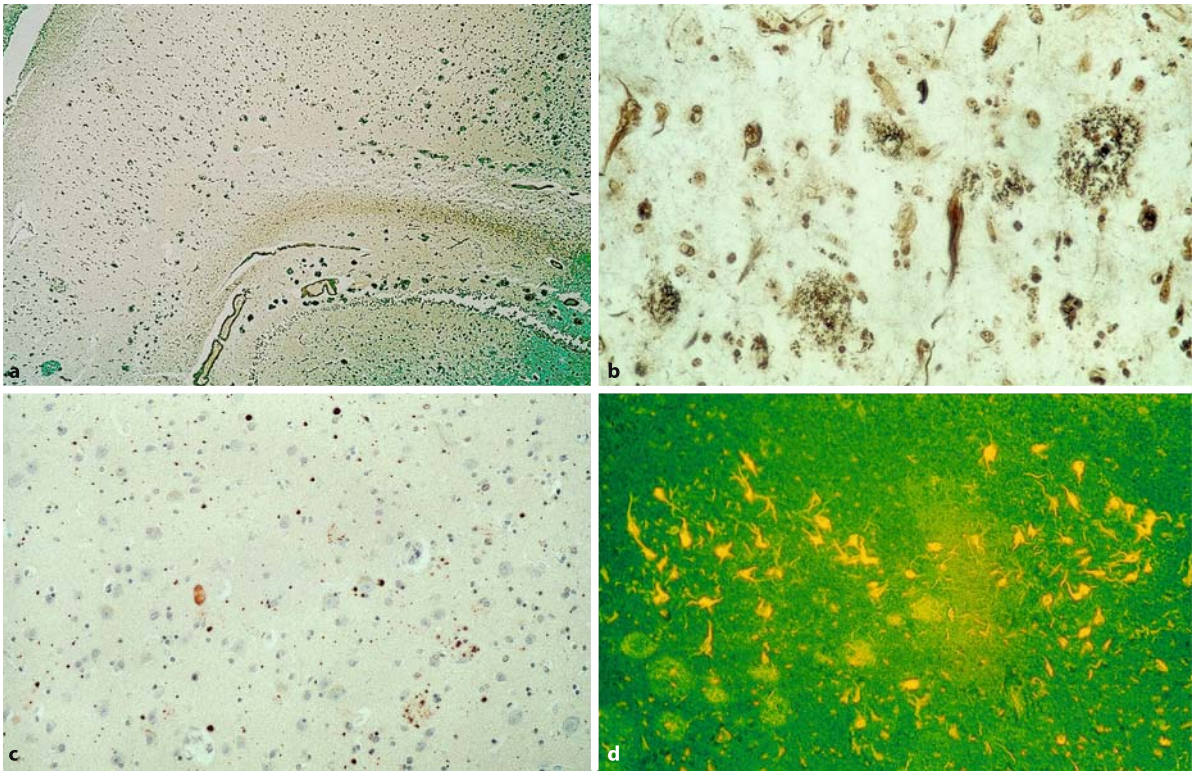

Fig. 31.4a–d. Neurofibrillary tangles and senile plaques in Alzheimer's disease (*AD*) brain. **a** Aggregation of plaques in the hippocampal area; **b** demonstration of different types of plaques, i.e., primitive, and diffuse plaques; **c** demonstration of ubiquitin-reactive spots in the plaques as well as disseminated within the neuropil; **d** aggregated plaques, fibrillary tangles and fluorescent amyloid containing material in vascular walls as seen by thioflavin S fluorescence (magnification **a** ×200; **b** ×500; **c, d** ×300)

prerequisite for correct neuropathological diagnosis, however, is the presence of a clinical dementia, otherwise even demonstration of the criteria presented below cannot confirm the diagnosis of AD.

A question of particular importance for patients and their families is the expected survival time following diagnosis of AD. Brookmeyer et al. (2002) estimate that patients, their families, and caregivers can plan on a median survival time of 7–10 years if the illness is diagnosed when the patient is in his sixties or early seventies, of 3 years or less for patients in their nineties.

31.3.1.2 Neuropathology and Diagnostic Criteria

Gross findings are independent of disease stage and generally non-specific. Cortical atrophy and an increase in ventricular system volume (Fig. 31.5) are common. When combined with the appropriate clinical psychopathological and neurological features, a tentative diagnosis of AD can be made.

Microscopically a loss of neurons and synapses (Coleman and Yao 2003; Scheff and Price 2003) is evident, with proliferation and activation of astrocytes and microglia, the presence of senile plaques, neurofibrillary tangles, amyloid angiopathy, neuropil threads, and granulovacuolar degeneration (see Figs. 31.1, 31.4, 31.5d, 31.6). All of these microscopic features are non-specific for AD. Diagnostically relevant are the senile plaques, i.e., diffuse and neuritic plaques in neocortical regions (McKeel et al. 2004), and neurofibrillary tangles, i.e., changes also commonly associated with the normal physiological aging process independent of dementia.

Early Microscopic Alterations. Mild cognitive impairment correlates closely with widely distributed diffuse and neuritic plaques combined with a marked increase in the number of tangles (Price and Morris 1999). Giannakopoulos et al. (1997) found an association between extensive hippocampal alterations and age-related memory impairment, as well as between extensive tangle formation in the neocortical association areas of the temporal lobe and development of AD. They found no correlation between senile plaque density and the severity of dementia.

The following criteria are *diagnostically relevant* for a manifest AD:

- Clinically confirmed dementia.
- Microscopic alterations quantitatively in excess of age-appropriate threshold values: the num-

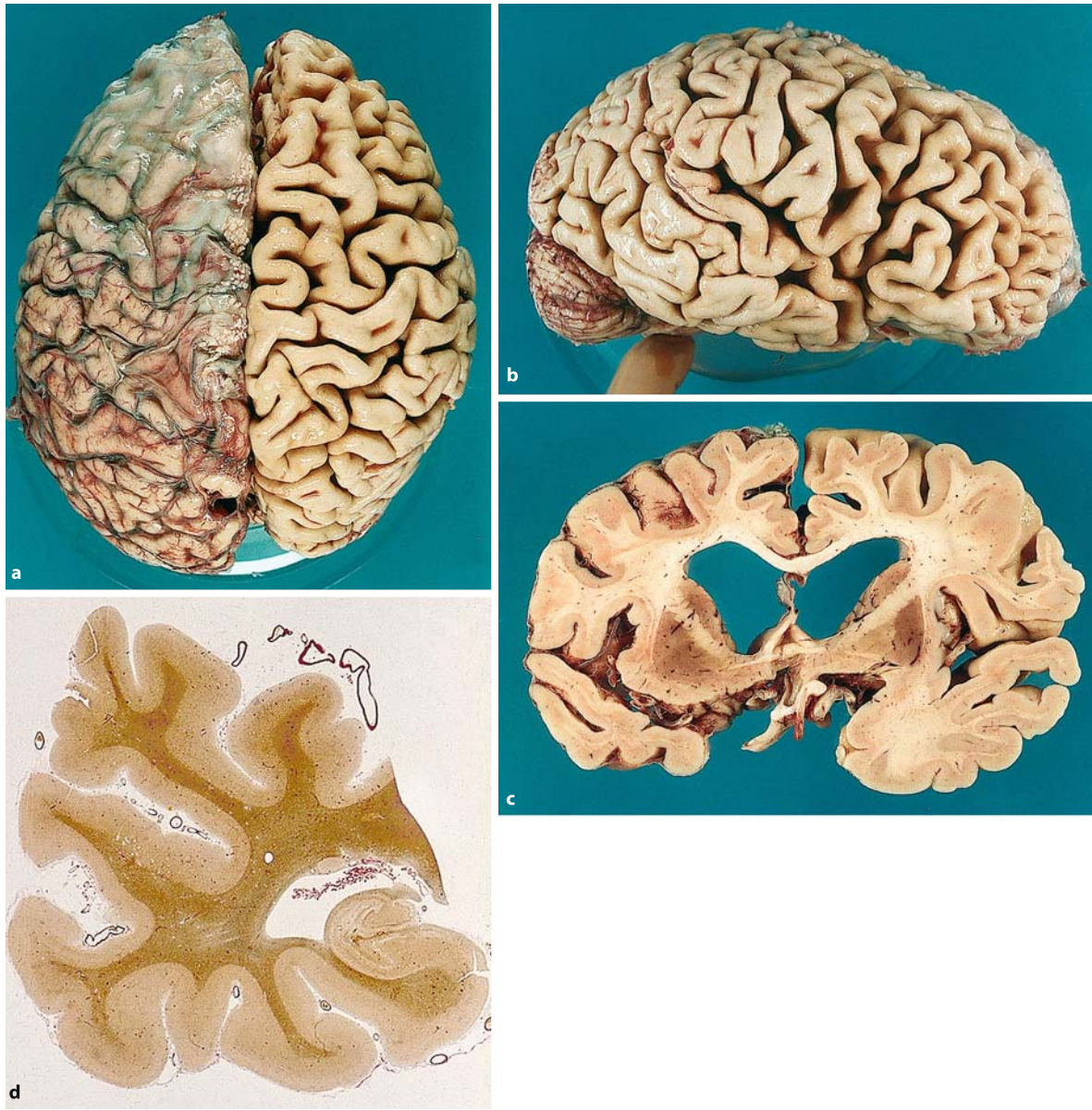

Fig. 31.5a–d. The brain in Alzheimer's disease. **a, b, d** Generalized cortical atrophy and (**c**) increase in ventricular system volume. Distinct cortical alterations are seen by the naked eye after a silver staining procedure, expressing plaques within the cortical structures (magnification ×5)

ber of senile plaques and neurofibrillary tangles exceeds that in control populations of the same age.

- Demonstration of *neuritic plaques*: AD can be diagnosed only if this type of plaque is present.
- *Neurofibrillary tangles* in combination with senile plaques – located mainly in neocortical areas – are a hallmark of AD. They are also found in the subcortical nuclei of cases involving progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome; Steele et al. 1964), but their morphology is then globose, not flame-shaped.
- *Loss of synapses* (and/or *loss of dendrites*) correlates closely with the extent of dementia and can be demonstrated using antibodies against synaptophysin (or MAPII). Quantification of the extent of the loss, however, can be problematic.

In essence, *neuropathological diagnosis* of AD is a question of degree, or quantity. Three commissions have proposed diagnostic criteria to take this into account:

1. National Institute of Aging (NIA) protocol (see Khachaturian 1985).

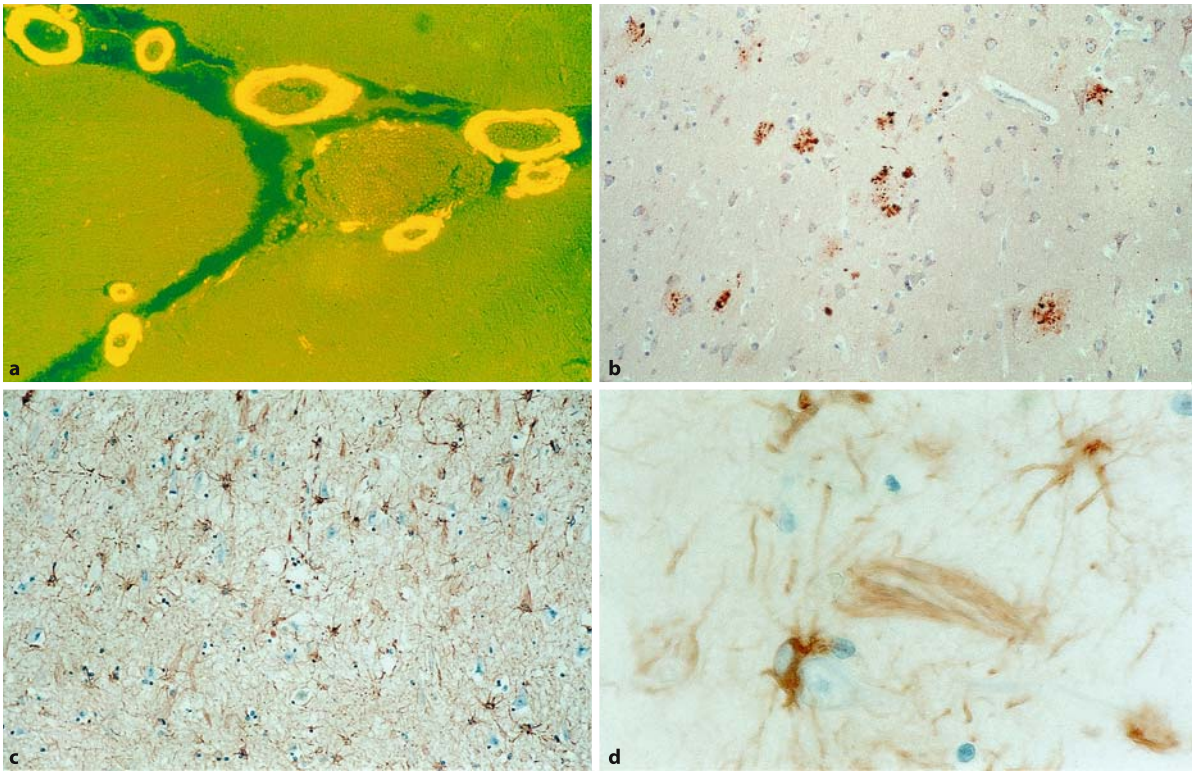

Fig. 31.6a–d. Vessels and glial cells in Alzheimer's disease. **a** Beside a distinct increase in neurofibrillary tangles and senile plaques often an amyloid angiopathy is demonstrable; **b** an increase in activated major histocompatibility complex (*MHC*) class II reactive microglia aggregated within the plaques occurs, and **c, d** astrocytes – associated with neurofibrillary tangles in one neuron (**a** thioflavin S, **b** MHC-class II-reactivity, **c, d** GFAP reactivity; magnification **a** ×100; **b** ×500, **c** ×300, **d** ×1,000)

2. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol (see Mirra et al. 1993, 1994), developed in an attempt to standardize the neuropathological diagnosis of AD by promoting a common language and providing correlations between clinical and other data (Heyman et al. 1997).
3. The NIA and Reagan Institute protocol (see Hyman and Trojanowski 1997), which incorporates both the staging of Braak and Braak (1991) and the quantification of the CERAD protocol.

All protocols are based on the assumption that neuritic plaques represent the most important diagnostic lesions, NFTs being merely a supplementary, less important phenomenon. If the number of neuritic plaques exceeds that of an age-matched control population, and if NFTs are present, then AD can be diagnosed (Jellinger 1998).

For pragmatic reasons the CERAD protocol is generally recommended today (Heyman et al. 1996; Newell et al. 1999; see also NIA 1997). The patient's age and density of plaques in the most heavily affected neocortical sections (frontal, temporal or parietal cortex) are used to calculate an age-related plaque score (see Table 31.1).

Concomitant vascular lesions – usually cerebral infarcts – are found in a considerable subset of AD patients. Patients whose AD is combined with a vascular pathology suffer greater overall severity of dementia with worse performance on language and cognitive function tests (Heyman et al. 1998).

31.3.1.3 Pathogenesis

A leading hypothesis holds that diminished cholinergic neurotransmitter function is one of the factors responsible for the intellectual decline associated with both physiological aging and AD. The most striking reduction in both normal aging and AD involves basal forebrain-derived cholinergic afferents to the cerebral cortex. Chemical markers of presynaptic cholinergic systems in the cerebral cortex of the healthy aged also undergo modest reductions, whereas almost all AD patients exhibit marked reductions. The most striking abnormality is the decline in activity of the presynaptic enzyme choline acetyltransferase (Hansen et al. 1988), which is necessary for acetylcholine (ACh) production. In cortical biopsy samples from AD patients, ACh synthesis is diminished versus controls. The degree of intellec-

Table 31.1. Age-related plaque scores according to the Consortium to Establish a Registry for Alzheimer's Disease (*CERAD*) protocol. The score is based on the patient's age and number of plaques in the most heavily affected neocortical section. The concentration of neuritic plaques is assessed semiquantitatively, and the density converted into an age-related CERAD 0, A, B, or C plaque score. (*0* No plaques, *A* histologic findings are uncertain evidence of AD, *B* histologic findings suggest AD, *C* histologic findings indicate AD). Source: Mirra et al. 1991

Age at death (years)	Frequency of plaques			
	None	Sparse	Moderate	Frequent
<50	0	C	C	C
50–75	0	B	C	C
>75	0	A	B	C

tual impairment in AD appears to be related to the degree of choline acetyltransferase deficiency.

It was recently suggested that AD is caused by the gradual aggregation of the abnormal cytoskeletal tau protein into insoluble fibrillary material (Trojanowski and Lee 2002). The sequence of destruction in AD begins in predisposed cortical induction sites then spreads in predictable succession to other cortical areas and subcortical nuclei (Braak et al. 2002). This process closely resembles the inverse sequence of cortical myelination. An anomalous immunological expression in the same regions is directly responsible for neuronal death. Another molecular mechanism of neuronal cell loss includes the association of an endogenous neurotoxin, nitric oxide, which is produced by inducible nitric oxide synthase (Markesbery and Carney 1999; Kimura et al. 2002). Based on these findings, theoretical therapeutic strategies towards AD have been proposed and met with partial success (see Morris et al. 2002).

Eikelenboom et al. (2002; see also McGeer and McGeer 2001; Vehmas et al. 2003) showed that senile plaques are linked to an intense immunological reaction. This suggests that the reactive process underlying AD is similar to that of Creutzfeldt–Jakob disease (prion disease), i.e., both diseases should be regarded as cerebral proteopathies (Walker and LeVine 2000) and inflammatory diseases.

Fewer than 10% of cases are thought to be *genetically determined*: autosomal dominant inheritance of early-onset familial AD (chromosome 21: APP; chromosome 14: presenilin I; chromosome 1: presenilin II) (see Lautenschläger et al. 1999; St. George-Hyslop 2000). With increasing age, Down's syndrome patients with trisomy of chromosome 21 always develop AD neuropathology, because the APP gene is located on chromosome 21.

Moreover, the apolipoprotein E (ApoE4) is known to be one of the main genetic risk factors for late-onset AD (Saunders et al. 1993). The ApoE4 genotype, like brain injury, is associated with an elevated risk of AD. Recently Bretsky et al. (2003) stated that epsilon4 allele either may function as a risk factor for cognitive impairment in normal aging across a broad spectrum of domains or may exert detectable effects early in a long prodromal AD trajectory.

If ApoE4 affects neuronal viability and branching, and if response to brain injury differs in E4-patients, then the association between mechanical brain injury and AD may vary with the presence of the ApoE4 allele. O'Meara et al. (1997) showed that ApoE4 is an independent risk factor that neither changes nor confounds the association. The susceptibility to AD conferred by ApoE4 apparently does not elevate the risk associated with brain injury (see also pp. 105 ff).

The great majority of AD patients become ill with the sporadic type of AD after age 65. The true cause of the disease in these cases remains unknown.

31.3.2 Neurofibrillary Tangles and Dementia

Bancher and Jellinger (1994; Jellinger and Bancher 1998) describe a type of neurodegenerative dementia which occurs after age 80 and is characterized clinically by delusions and depression. The diagnosis can only be made postmortem: senile plaques are lacking, but numerous NFTs are present, especially in the pyramidal neurons of the hippocampal area.

31.3.3 Dementia Pugilistica

Repeated impact to the head as suffered by boxers can lead to diffuse brain atrophy. Microscopically, the salient feature is fibrillary degeneration of neu-

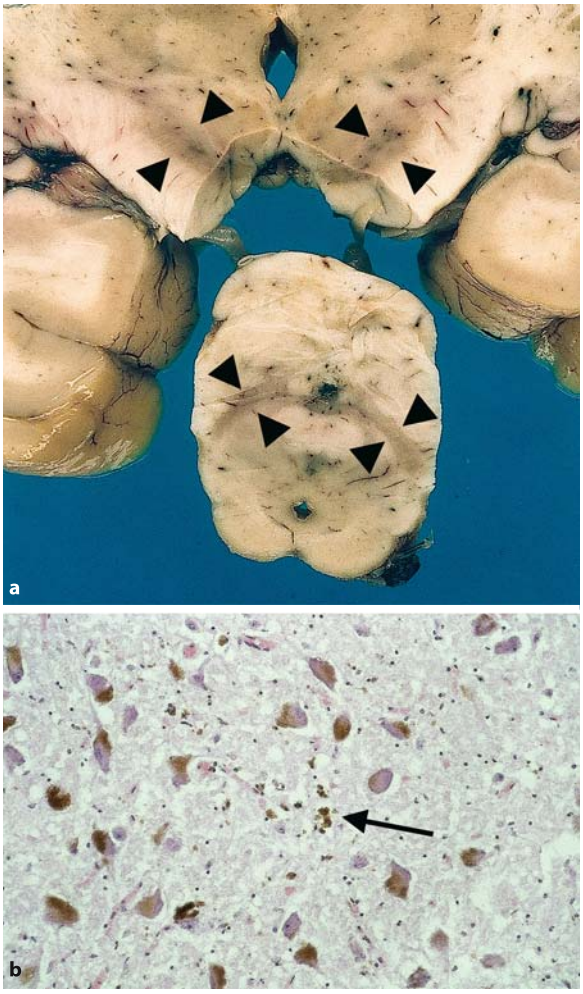

Fig. 31.7a, b. Parkinson's disease is (**a**) macroscopically characterized by a loss of pigmented (neuromelanin-bearing) neurons, especially in the substantia nigra and the locus ceruleus. *Arrow heads* mark the shadow of the substantia nigra. (**b**) Microscopically the loss of neuronal pigmentation is seen as well as a perivascular aggregation of pigment (*arrow*; H&E; magnification ×500)

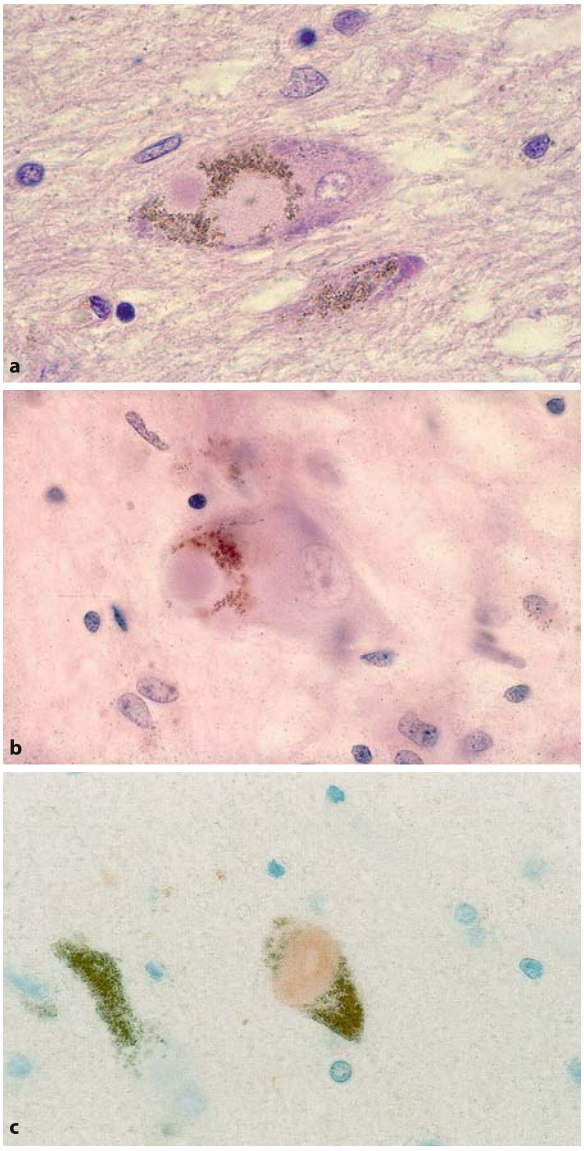

Fig. 31.8a–c. Lewy body in the substantia nigra. **a, b** Lewy bodies demonstrated by H&E stain, which **c** are reactive for ubiquitin (magnification **a–c** ×1,000). **a, b** Figures kindly provided by Professor Dr. E. Reusche, Lübeck

rons in the temporal allocortex and isocortex. Facultative senile plaques are also encountered.

31.3.4 Dementia in Parkinson's Disease (PD)

The clinically salient feature of Parkinson's disease (PD) is the development of extrapyramidal movement disturbances (Lowe and Leigh 2002). *Clinical diagnosis* of PD requires the presence of two out of three of the following features: resting tremor, bradykinesia, and rigidity. The clinical picture may also include autonomic dysfunction, dysphagia, or dementia. Median times of survival are 10.3 years and 13.4 years (Elbaz et al. 2003). The risk of developing dementia is almost twice as high in PD patients with severe extrapyramidal symptoms than in controls (Marder et al. 1995).

The *principal pathological feature* of idiopathic PD is dopaminergic neuron loss in the substantia nigra (Fig. 31.7) and other pigmented brain stem nuclei associated with Lewy bodies and accompanied by neuromelanin uptake by macrophages and gliosis. In the early phases of the disease Lewy bodies are seen in the anterior olfactory nucleus and dorsal motor nucleus of the vagal and glossopharyngeal nerves (Tredici et al. 2002; Braak et al. 2003).

Pathological inspection can confirm *diagnosis* if Lewy bodies (Fig. 31.8) can be demonstrated in two unilateral 7-µm sections from the middle portion

of the substantia nigra. Should Lewy bodies not be found upon first inspection, two further sections should be examined. If Lewy bodies are still not found, Lewy body PD can be excluded in most cases (Gibb and Lees 1989).

Pathogenesis. PD is inherited in a Mendelian fashion in only a few families, in some of which the responsible genes have been identified (Foltynie et al. 2002); the remaining patients having symptomatic PD or mixed forms. Approximately 10–15% of patients with idiopathic PD suffer from dementia (Mayeux et al. 1990). Hughes et al. (1993) found in a clinicopathological study of 100 PD cases that AD was the underlying pathology in 29%, that numerous cortical Lewy bodies were present in 10%, and that 6% may have had a vascular cause. In 55% no definite additional pathology could be found. Lewy bodies (Hurtig et al. 2000) and Lewy neurites (Churchyard and Less 1997) can be readily demonstrated using antibodies to α-synuclein and ubiquitin. Three types of dementia have been distinguished in PD:

- Dementia associated with AD
- Dementia associated with Lewy bodies
- Dementia associated with subcortical atrophy

31.3.5 Lewy Body Dementia

Single or multiple Lewy bodies are found in the cytoplasm of neuromelanin-containing neurons (see above). The Lewy body appears to be principally made of α-synuclein, a presynaptic protein; it also contains ubiquitin and some components of the proteasome. This suggests that alteration of protein catabolism may be involved in its formation. They may also coexist with NFTs.

Disorders involving Lewy bodies are the second most common cause of dementia in aging adults after AD. But Levy bodies are neither specific for PD nor for dementia (Jellinger 2004, 2005). A few work groups have questioned whether Lewy body dementia represents a distinct entity since there is considerable overlap of morphological and clinical features between AD and PD on the one hand, and AD and Lewy body dementia on the other (Ditter and Mirra 1987; Lopez et al. 2000; for a contrasting view see Stern et al. 2001). McKeith et al. (1996) have put forth criteria that allow a differentiation of Lewy body dementia based on both clinical features and neuropathological findings.

Clinical Features. These include motor features of Parkinsonism, impaired problem solving and visuospatial skills, diminished attention, cognitive function fluctuations, and well-formed visual hallucinations.

Neuropathological Features. Pallor of the substantia nigra features is more predictive of Lewy body diseases than pallor of the locus ceruleus. *Microscopically*, the degeneration exhibited by the substantia nigra represents the loss of neuromelanin-bearing neurons, which is free of pigment within astrocytes and macrophages and in the neuropil. The most striking finding is that some of the residual pigmented neurons contain typical Lewy bodies. The locus ceruleus, nucleus basalis Meynert, and the dorsal nucleus of the vagus may contain similar Lewy bodies. Less distinctive in appearance are cortical Lewy bodies, which – as mentioned – can best be demonstrated with antibodies to α-synuclein and ubiquitin.

In addition to Lewy bodies in the cortex and brain stem, the following findings are also common: spongiform changes within the neuropil, cell loss and gliosis in the locus ceruleus, the substantia nigra, and nucleus basalis of Meynert, Lewy neurites, senile plaques, and neurofibrillary tangles.

31.3.6 Frontotemporal Dementia (Pick's Disease)

The chief morphological and clinical *diagnostic hallmark* of Pick's disease is a frontotemporal atrophy (Kertesz and Munoz 2002) in association with such core symptoms as apathy, personality change, blunted emotions, loss of insight as well as inhibition (Lund and Manchester Groups 1994). This is a rare disease. Onset begins between ages 45 and 65 and leads to death within 5–10 years. The disease usually occurs sporadically, but a few familial cases of Pick's disease have been described, usually with an autosomal dominant type of inheritance (Morris et al. 2001). According to Constantinidis (1985 – see also Dickson 2001), the following types can be distinguished (a contrasting classification was made by the Workgroup on Frontotemporal Dementia and Pick's Disease – McKhann et al. 2001):

- Type A: Classic Pick's disease (Fig. 31.9), typically featuring limbic and frontotemporal degeneration in association with Pick cells and bodies.
- Type B: characterized by parietal and superior frontal atrophy in combination with ballooned neurons in the absence of Pick bodies. Patients with type B Pick's disease sometimes exhibit extrapyramidal signs indicative of corticobasal degeneration.
- Type C: a clinically and pathologically heterogeneous group, possessing neither ballooned neurons nor Pick bodies.

Clinical Features. Clinically three psychopathological syndromes are distinguished (Neary et al. 1998 – for more details, see McKhann et al. 2001):

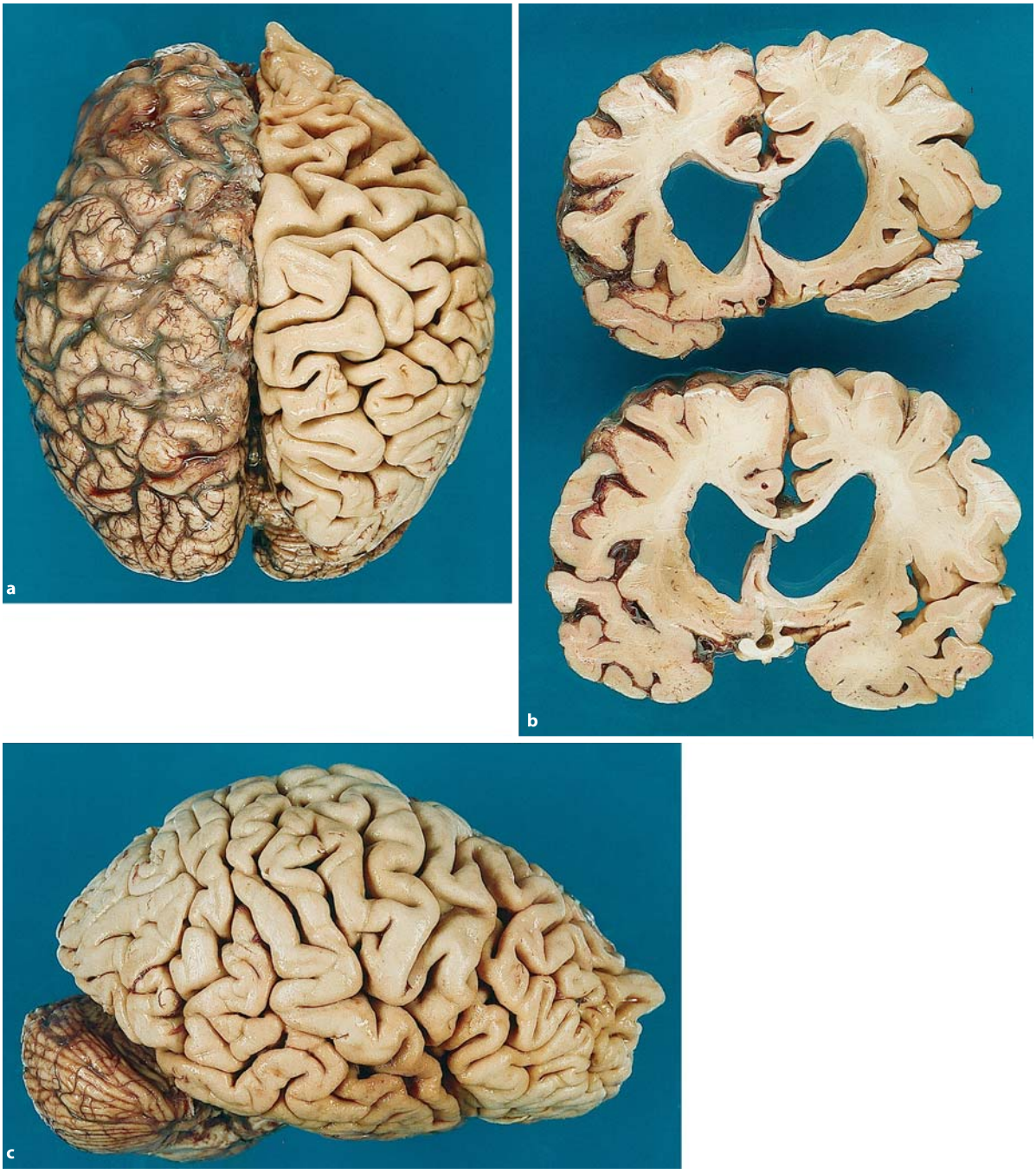

Fig. 31.9a–c. The brain in frontotemporal dementia (Pick's disease). The brain is characterized by a frontotemporal atrophy (**a, b**) as well as by a marked hydrocephalus (**c**)

- *Frontotemporal dementia:* characterized by a frontal syndrome in association with behavioral disorders and disinhibition.
- *Progressive non-fluent aphasia*, which resembles primary progressive aphasia.
- *Semantic dementia:* progressive fluent dysphasia combined with impairment of semantic verbal memory.

Definitive clinical diagnosis is made by CCT or MRI scan demonstration of a lobar distribution of the atrophy and the different clinical symptoms with regard to AD.

Neuropathological Features. Macroscopically Pick's disease features a limited frontotemporal atrophy with relative sparing of the precentral and postcentral gyri and posterior aspect of the superior

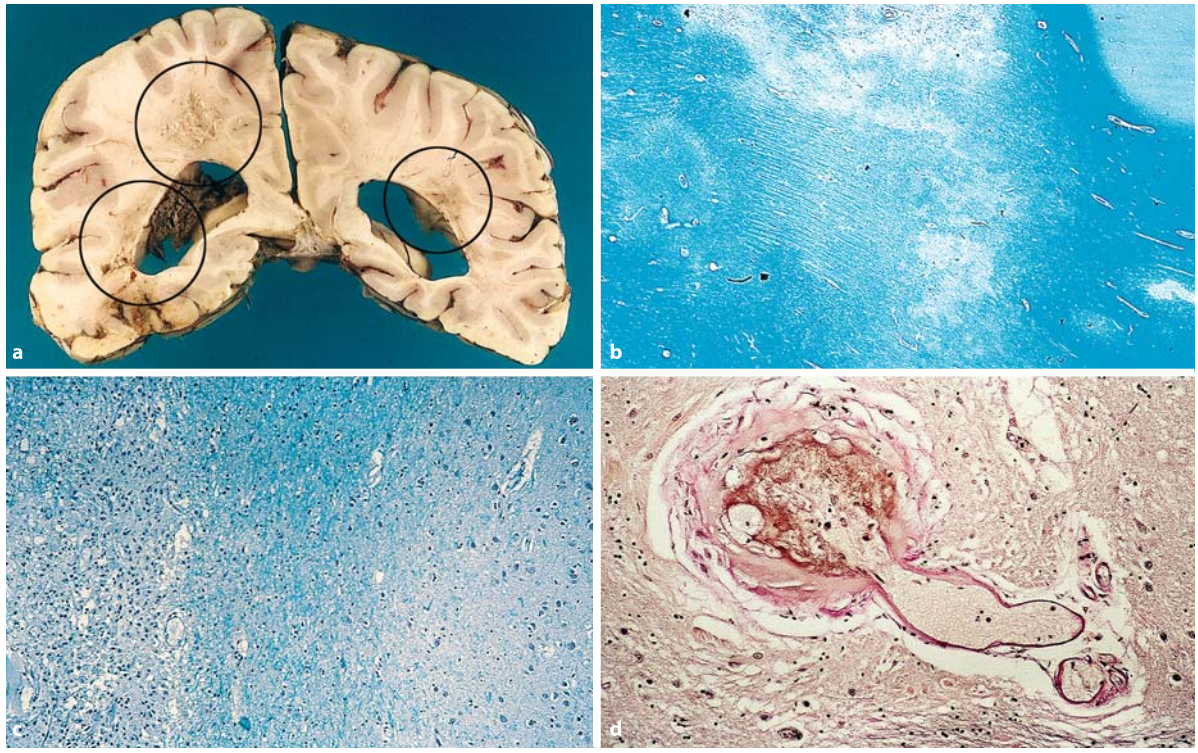

Fig. 31.10a–d. Subcortical infarcts in vascular dementia. **a** Macroscopically a multifocal demyelination is demonstrable (*circles*) associated with focal demyelination (**b, c**) and atherosclerotic and hyalinotic vessel disease (**d**) (**b, c** luxol fast blue; magnification **b** ×100; **c** ×300; **d** ×500)

temporal gyrus, with brain mass reduced by up to 750 g. The cortical ribbon is thinner than usual upon sectioning and the gray–white junction indistinct. Gliosis may render the cortical gray matter firm. The ventricles are dilated and the subcortical white matter is attenuated, retracted, gray, and usually soft (Dickson 2001).

Microscopy reveals evidence of Pick cells and Pick bodies combined with astrocytosis, spongiosis of the parenchyma, and massive loss of neurons.

- *Pick cells* are defined as ballooned and eosinophilic neurons. Their appearance is comparable to that seen in retrograde degeneration. The central cytoplasm has a lavender hue in H&E stain. The nucleus appears displaced, slightly chromophilic, and flattened. The Nissl bodies are confined to the periphery.
- *Pick bodies* are isotropic and argentophilic intraneuronal cytoplasmic inclusions comprised of a small eosinophilic core within a basophilic cytoplasm. In contrast to Lewy bodies, Pick bodies possess no halo. Pick bodies are preferentially located in the pyramidal cell layer of the hippocampus and dentate granule cells.

Both Pick cells and Pick bodies are reactive with antibodies to phosphorylated neurofilaments and – sometimes – with ubiquitin.

31.3.7 Vascular Dementia

The etiological category "vascular dementia" encompasses forms of clinical dementia attributable to hemorrhagic or ischemic cerebrovascular diseases or to ischemic–hypoxic brain lesions of cardiovascular origin (Román 2002). After AD, vascular dementia is the principal cause of dementia (Prencipe et al. 1997; Knopman et al. 2002).

Clinical Features. In contrast to the dementias described above, vascular dementia is characterized by a sudden onset, usually associated with the sequelae of a stroke, episodic worsening of the disease picture, and a tendency to decompensation. The *diagnosis* is usually based on imaging techniques and/or SPECT or PET assessment of cerebral blood flow and cerebral metabolism (cf. Román and Goldstein 1993).

Pathogenetically there are different causes which lead to an identical clinical feature (Esiri et al. 1997): vascular dementia. Commonly the disease is mor-

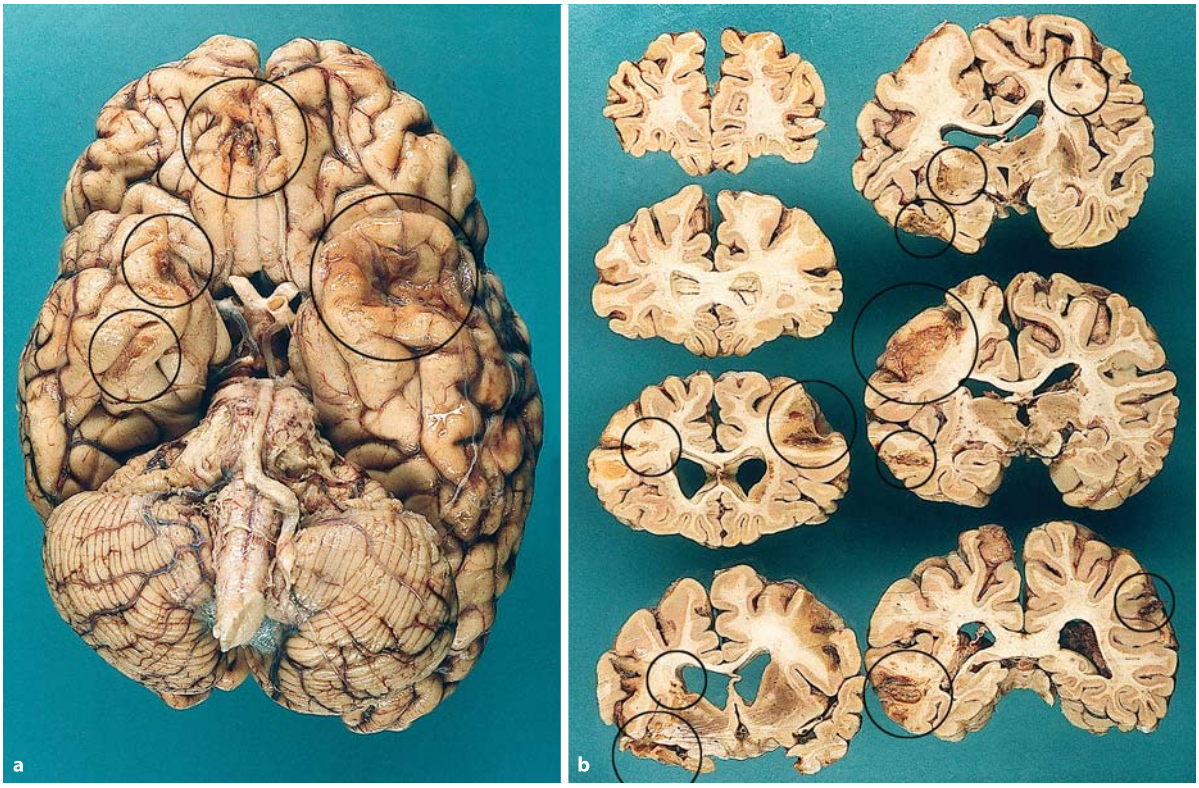

Fig. 31.11a, b. The brain in multi-infarct dementia. **a** The external surface of the brain is characterized by several scars which (**b**) are also demonstrable on the frontal sections – marked by *circles*. A distinct external atrophy associated with hydrocephalus internus

phologically characterized by multiple infarcts, especially in deep parts of the brain and/or white matter (subcortical infarcts – Bogousslavsky 1993). The infarcts are caused by atherosclerosis, vasculitides, coagulation disturbances, hypertensive angiopathy or certain sporadic or hereditary arthropathies such as small vessel disease, "classic" Binswanger's disease or cerebral autosomal dominant arteriopathy with subcortical infarcts (CADASIL) (for review: Ostrow and Miller 1993; Aharon-Peretz et al. 2002). The different pathomechanisms may overlap. The brains exhibit enlargement of the lateral ventricles, severe atherosclerotic or hyalinotic alterations of the vessel's wall and shrunken as well as softened white matter associated with an état criblé (Fig. 31.10), i.e., a loss of myelin and multiple small infarcts in the white and deep gray matter. Binswanger's disease (van Swieten and Caplan 1993) in particular is strongly associated with a history of hypertension, affecting men and women aged 50–70 years, and is characterized by an extensive pallor of myelin.

The following types are to be distinguished:

- Arteriosclerosis of large precerebral arteries.
- Microangiopathies of parenchymal vessels secondary to diabetes mellitus or arterial hypertension.
- Cardiopathies with an associated risk of thromboemboli.
- Coagulation disorders.
- Vascular diseases such as vasculitis, amyloidosis, leukoencephalopathy, and CADASIL.

Román (2002) published a complete list of the various pathological lesions known to cause vascular dementia. Knopman and coworkers (2002) could demonstrate that 11% of 482 dementia patients had bilateral gray matter lesions considered critical on imaging, and 10% had experienced onset or worsening of their dementia within 3 months of stroke. They also found that 18% of the patients had one or the other of these features, while only 4% had both.

A special type of vascular dementia may be the multi-infarct dementia, though it will be difficult to classify this type as an autonomous disease. The disease picture is characterized by: (1) at least two brain infarcts, chiefly in the regions supplied by the median or posterior cerebral arteries, with (2) comparatively extensive destruction of brain tissue (50–100 ml – see Tomlinson et al. 1970), which alone can readily explain the dementia (see Fig. 31.11). The morphological sequelae of vascular diseases are described elsewhere (pp. 541 ff).

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