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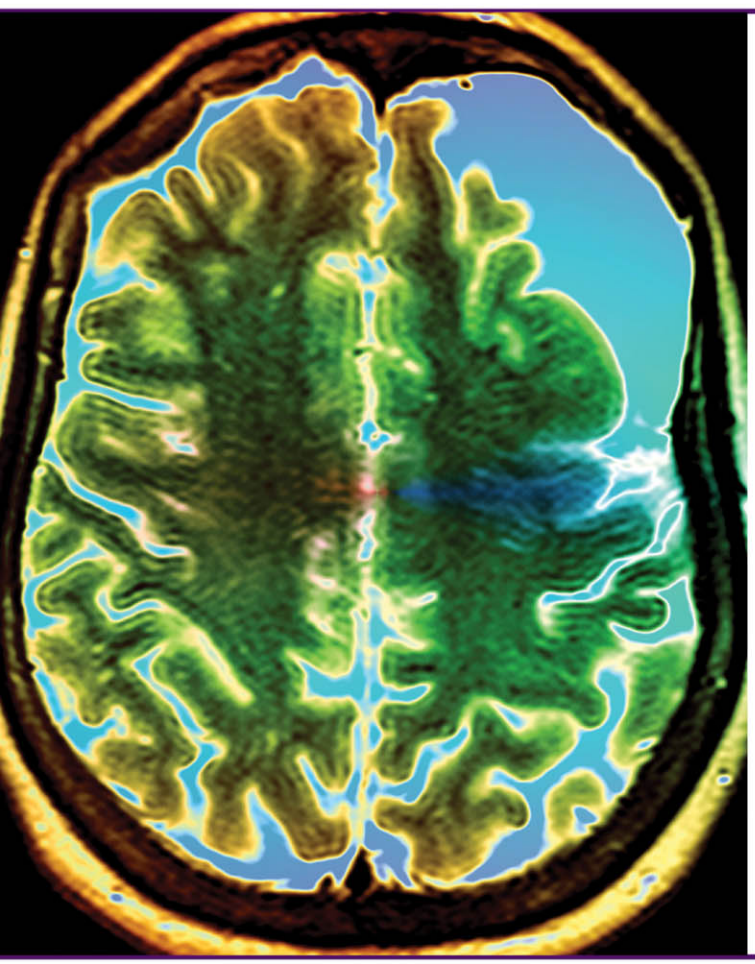
Specialty Board Review

# Neurology

SECOND EDITION



- More than 1200 questions and answers
- Complete explanations for correct and incorrect answers
- Covers all topics tested on the boards, including psychiatry
- Designed to sharpen differential diagnosis skills

NIZAR SOUAYAH

McGraw-Hill
SPECIALTY BOARD REVIEW

# Neurology

**Second Edition**

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# Contents

# Preface

My experience in teaching medical students, neurology residents, and fellows has been that they love multiple-choice questions combined with didactic teaching. For that reason I developed several board-style questions at the end of most of my recent lectures, encouraging my listeners to memorize the provided information.

The idea of this review initially arose when I was studying for the neurology board myself. I was surprised by the lack of review books in a question-and-answer format to help me assess my progress and identify areas of weakness. The few neurology reviews that did have multiple-choice questions were intended for medical students preparing for the USMLE, but they lacked the deep, broad coverage needed for the neurology board exam.

Additional impetus for this book came from my years of teaching. Many of my students, residents, fellows, and even colleagues asked me whether there was a book in question-and-answer format that could be used as a tool in preparing for neurology board certification/recertification. The format of the present work simulates the board exam and serves as an excellent tool for identifying areas of strength and weakness and sharpening knowledge that has already been acquired.

In preparing a second edition of this book, I was driven not only by recent changes in the question format of the neurology board exam and the steady advances in nearly all aspects of neurology over the past five years but also by the response my work had received from its readers. I am grateful for their positive comments. As I reviewed the first edition in preparation for the second, I recognized clearly all the very significant and exciting changes had recently occurred in the neurology and neurosciences fields.

This book is not designed to substitute for the didactic lectures, seminars, and conferences offered during residency or fellowship training but rather to augment residents' experimental learning, reinforce their self-assessment and growth, and better prepare them for the certification examination of the American Board of Psychiatry and Neurology.

The book is divided into 17 chapters, including one devoted to psychiatry and another to localization signs, thus providing comprehensive coverage of the neurology board topics. The content represents almost a total rewrite of the previous edition, with new questions in the new neurology board format as well as numerous illustrations, including color illustrations, and updated answers using the current literature for references to reflect the most recent advances.

The best way to go through this book is to follow these steps:

- First read the question without reading the answer choices (A to E) and guess the answer based on the information offered by the question.
- Then read the answer choices (A to E); these may confirm or refute the answers you have already developed. If your first answer proves wrong, choose another from the remaining choices.
- Go to the answer section of the chapter, check if your answer is correct, and read the answer.

The answers offer a comprehensive review of the different question choices. Whether or not you answered the question correctly, I strongly advise you to go in depth through the incorrect choices to find out why they are incorrect by consulting the answer references or other references. They will enlarge the knowledge provided by the question and help to identify any hidden weakness in your knowledge base.

I am indebted to my family, who allowed me the luxury of time to produce this second edition and who carried most of my personal daily workload with understanding.

I am also grateful for the assistance of the editorial and publishing staff of McGraw-Hill throughout the preparation of this second edition.

I hope you have fun studying for the neurology board via the multiple-choice question-and-answer study approach.

Nizar Souayah, MD

*To my son, Sami: let your dreams be your guide through this life.*
*To my daughters, Leila and Nora: keep your dreams alive.*
*Achievement requires faith, hard work, determination, and persistence.*
*To my wife, Sonia: without your help and sacrifice this would not have been possible.*
*To my parents: for your love, great affection, inspiration, and patience.*

CHAPTER 1

# Anatomy and Physiology of the Central and Peripheral Nervous System

## Questions

**1.** Which of the following sensory pathways projects outside the thalamus?

(A) The visual pathway
(B) The auditory pathway
(C) The vibration sense pathway
(D) The olfactory pathway
(E) The temperature sense pathway

**2.** Damage to the area indicated by the arrow in Figure 1-1 causes

(A) ipsilateral blindness
(B) homonymous hemianopia
(C) bitemporal hemianopia
(D) superior quadrantic hemianopia
(E) inferior quadrantic hemianopia

**3.** All fibers in the posterior funiculus are

(A) primary afferent fibers
(B) fibers that establish synapses in lamina III of the cervical enlargement
(C) unimodal afferents
(D) ascending fibers
(E) activated by nociceptors

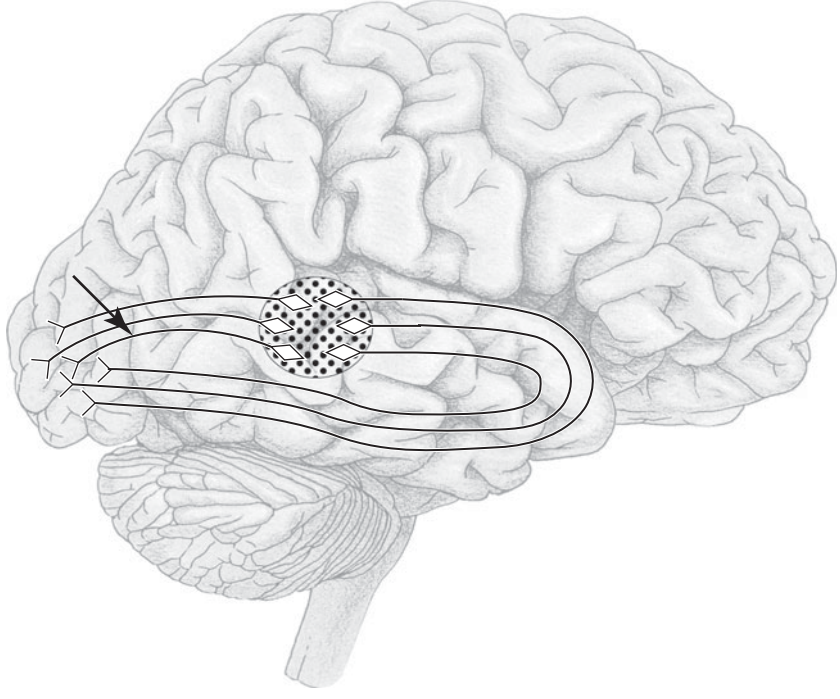

**FIG. 1-1.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

**4.** Which of the following pathways is used for propioception of the hindlimb but not for vibration of the hindlimb?

(A) The dorsal spinocerebellar tract
(B) The spinocervical tract
(C) The ventral spinocerebellar tract
(D) The lateral spinothalamic tract
(E) The rubrospinal tract

**5.** The long thoracic nerve innervates the

(A) serratus anterior muscle
(B) rhomboid muscle
(C) levator scapulae
(D) supraspinatus muscle
(E) infraspinatus muscle

**6.** The axillary nerve

(A) arises from C7–C8
(B) innervates the deltoid muscle by its inferior branch
(C) is a pure motor nerve
(D) is one whose injury may lead to weakness of arm adduction
(E) may be affected in isolation in 10% of cases in neuralgic amyotrophy

**7.** A musculocutaneous nerve lesion affects

(A) hand sensation
(B) supination with the forearm extended
(C) supination with the elbow in flexion
(D) wrist extension
(E) upper arm abduction

**8.** Which of the following is a compression site of the radial nerve?

(A) The suprascapular notch
(B) The carpal tunnel
(C) The spinoglenoid notch
(D) The elbow posterior to the medial epicondyle
(E) The spiral groove in the posterior aspect of the humerus

**9.** The rhomboid muscles are innervated by the

(A) long thoracic nerve
(B) suprascapular nerve
(C) axillary nerve
(D) dorsal scapular nerve
(E) subclavian nerve

**10.** To differentiate between a lesion of the upper brachial plexus and one of the lateral cord, the most useful muscle to test is the

(A) teres minor
(B) biceps
(C) pronator teres
(D) flexor carpi radialis
(E) abductor pollicis brevis

**11.** To differentiate between a lesion of the lower trunk and one of the medial cord, the most useful muscle to test is the

(A) flexor pollicis longus
(B) abductor pollicis brevis
(C) abductor digiti minimi
(D) extensor indicis proprius
(E) first dorsal interosseous

**12.** To differentiate between lesions of the middle trunk and those of the posterior cord, the most useful muscle to test is the

(A) triceps
(B) pronator teres
(C) anconeus
(D) extensor digitorum communis
(E) extensor indicis proprius

**13.** The lateral division of the sciatic nerve innervates the

(A) semimembranosus
(B) long head of the biceps femoris
(C) semitendinosus
(D) short head of the biceps femoris
(E) adductor magnus muscle

**14.** In carpal tunnel syndrome, the median nerve is entrapped

(A) beneath the flexor retinaculum ligament
(B) above the flexor retinaculum ligament
(C) at the hamate bone
(D) in Guyon's canal
(E) on the radial side of the wrist at the level of the styloid process

**15.** The sartorius muscle is innervated by the

(A) obturator nerve
(B) femoral nerve
(C) genitofemoral nerve
(D) superior gluteal nerve
(E) inferior gluteal nerve

**16.** The structure indicated by the broken arrow in Figure 1-2 is the

(A) hypoglossal nucleus
(B) nucleus ambiguus
(C) medial longitudinal fasciculus
(D) facial nucleus
(E) nucleus solitarius

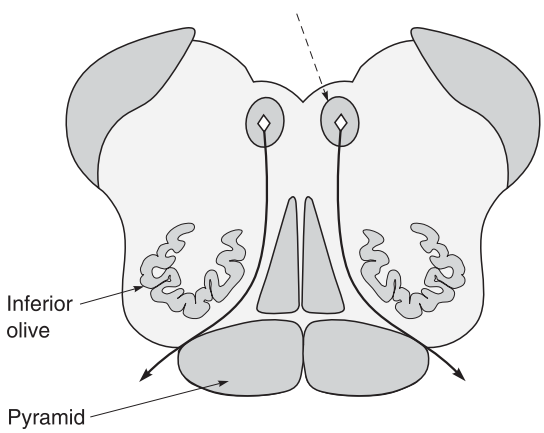


**FIG. 1-2.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

**17.** Which of the following structures is involved in vertical saccades?

(A) The parietal cortex
(B) The cerebellar vermis
(C) The caudate nuclei
(D) The interstitial nucleus of the medial longitudinal fasciculus
(E) The fastigial nucleus

**18.** Information regarding eye position reaches the abducens nucleus from neuronal integrator neurons coming from the

(A) rostral interstitial nucleus of the medial longitudinal fasciculus
(B) interstitial nucleus of Cajal
(C) parapontine reticular formation
(D) red nucleus
(E) nucleus prepositus hypoglossi

**19.** The gaze-holding neural integrator for vertical gaze is located in the

(A) interstitial nucleus of Cajal
(B) medial vestibular nucleus
(C) nucleus prepositus hypoglossi
(D) red nucleus
(E) rostral interstitial nucleus of the medial longitudinal fasciculus

**20.** Which of the following cranial nerves exits the brainstem from its dorsal aspect?

(A) The oculomotor nerve
(B) The facial nerve
(C) The trigeminal nerve
(D) The glossopharyngeal nerve
(E) The trochlear nerve

**21.** The perihypoglossal nuclei are involved in

(A) extraocular movement
(B) proprioceptive innervations of the tongue
(C) motor innervation of the tongue
(D) pain sensation of the posterior third of the tongue
(E) pharyngeal gag reflex

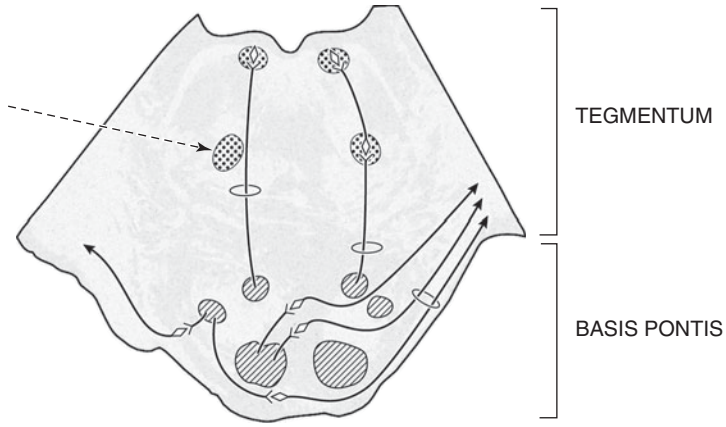


**FIG. 1-3.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

**22.** The nucleus ambiguus

(A) is the dorsal motor nucleus of the vagus
(B) receives general somatic afferent fibers from the external ear
(C) has neurons that convey special visceral efferent impulses to the pharynx
(D) is involved in epiglottic taste sensation
(E) receives fibers that convey thermal sensation from the posterior third of the tongue

**23.** Cardiorespiratory control is partially conveyed by the

(A) nucleus ambiguus
(B) nucleus solitarius
(C) pontine reticular nuclei
(D) restiform body
(E) spinal trigeminal nucleus

**24.** Taste sensation is conveyed by

(A) the facial nerve, the cochleovestibular nerve, and the glossopharyngeal nerve
(B) the cochleovestibular nerve, the glossopharyngeal nerve, and the vagus nerve
(C) the facial nerve, the glossopharyngeal nerve, and the vagus nerve
(D) the glossopharyngeal nerve, the vagus nerve, and the spinal accessory nerve
(E) the facial nerve, the spinal accessory nerve, and the hypoglossal nerve

**25.** Damage to the structure indicated by the broken arrow in Figure 1-3 causes

(A) ipsilateral hemiplegia
(B) anosognosia
(C) internuclear ophthalmoplegia
(D) ipsilateral facial weakness
(E) impaired salivary secretion

**26.** The semilunar ganglion conveys

(A) proprioceptive fibers of the trigeminal nerve
(B) pain sensation from the face
(C) the jaw reflex
(D) the corneal reflex
(E) taste in the anterior two thirds of the tongue

**27.** The structure indicated by the arrow in Figure 1-4 is

(A) the trigeminal nerve
(B) the facial nerve
(C) the abducens nerve
(D) the trochlear nerve
(E) the oculomotor nerve

**28.** Proprioceptive impulses from the muscles of mastication and the periodontal memebrane are conveyed by the

(A) mesencephalic nucleus of the trigeminal nerve

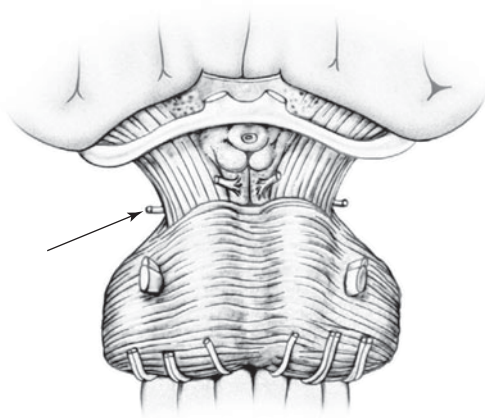

**FIG. 1-4.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

(B) interpeduncular nucleus
(C) dorsal tegmental ncleus
(D) rubrospinal tract
(E) medial lemniscus

**29.** The structure indicated by the arrow in Figure 1-5

(A) conveys fibers from the red nucleus to the spinal cord
(B) conveys auditory fibers
(C) conveys kinesthetic fibers
(D) conveys fibers of pain and temperature sensation
(E) conveys fibers supplying the superior oblique muscle

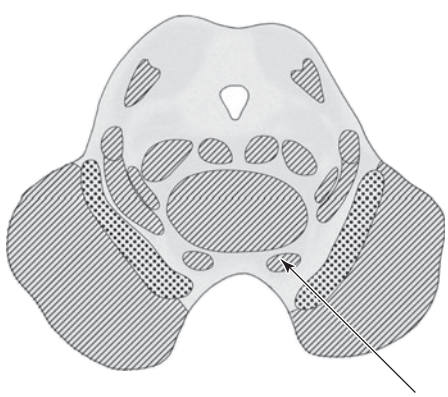

**FIG. 1-5.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

**30.** Noradrenergic innervations to most of the nervous system is provided by the

(A) substantia nigra
(B) locus ceruleus
(C) dorsal raphe nucleus
(D) red nucleus
(E) ventral tegmental nucleus

**31.** The structure indicated by the arrow in Figure 1-6 is the

(A) interstitial nucleus of Cajal
(B) nucleus of Darkschewitsch
(C) nucleus of the posterior commissure
(D) oculomotor nucleus
(E) red nucleus

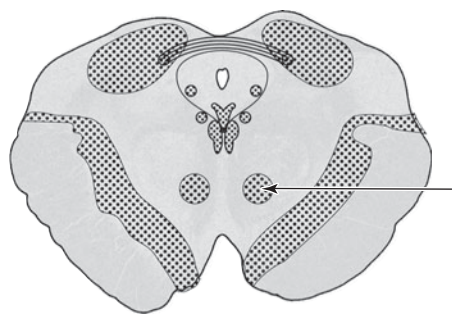

**FIG. 1-6.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

**32.** The Marcus Gunn phenomenon

(A) is caused by a lesion of the oculomotor nerve
(B) is characterized by prolonged pupillary contraction in response to light
(C) is characterized by a paradoxical dilatation of the affected pupil that occurs when light is shone in the symptomatic eye after having been shone in the normal eye
(D) preserves the consensual light reflex
(E) is associated with damage to the ciliary ganglion

**33.** A waddling gait is seen with

(A) a cerebellar lesion
(B) an acute vestibular lesion
(C) Guillain-Barré syndrome
(D) hip muscles weakness
(E) a corticospinal tract lesion

**34.** The anterior interosseous nerve innervates the

(A) pronator teres and pronator quadratus
(B) flexor digitorum profundus I and II and flexor pollicis longus
(C) flexor pollicis longus and abductor pollicis brevis
(D) first dorsal interosseous and abductor digiti minimi
(E) flexor carpi radialis and pronator quadratus

**35.** The posterior interosseous nerve innervates the

(A) supinator muscle
(B) triceps muscles
(C) anconeus muscle
(D) extensor carpi radialis longus
(E) brachioradialis

**36.** The tensor fasciae latae is innervated by the

(A) superior gluteal nerve
(B) inferior gluteal nerve
(C) sciatic nerve
(D) obturator nerve
(E) femoral nerve

**37.** The deep peroneal nerve supplies sensory innervation to

(A) the lateral distal lower leg
(B) the dorsum of the foot
(C) the skin in the web between the first and second toes
(D) the lateral heel
(E) no part of the body because it is a pure motor nerve

**38.** Which of the following neurological structures travels outside the cavernous sinus?

(A) The sympathetic carotid plexus
(B) The oculomotor nerve
(C) The mandibular branch of the trigeminal nerve
(D) The trochlear nerve
(E) The abducens nerve

**39.** Which of the following is TRUE about the trigeminal nerve?

(A) The spinal nucleus of the trigeminal nerve subserves light touch on the ipsilateral side of the face.
(B) The motor nucleus of the trigeminal nerve lies in the pons medial to the sensory nucleus and sends axons to the maxillary division of the trigeminal nerve.
(C) The three divisions of the trigeminal nerve converge at the Gasserian ganglion.
(D) The mesencephalic nucleus of the trigeminal nerve subserves pain and temperature on the ipsilateral side of the face.
(E) The mandibular division of the trigeminal nerve subserves sensation to the ipsilateral angle of the mandible.

**40.** Which of the following pairs of cranial nerves travel through the internal auditory canal?

(A) Vestibulocochlear and trigeminal
(B) Facial and trigeminal
(C) Facial and optic
(D) Facial and vestibulocochlear
(E) Vestibulocochlear and vagus

**41.** The taste fibers of the anterior two thirds of the tongue have their neurons of origin in the

(A) sensory nucleus of the trigeminal nerve
(B) motor facial nucleus
(C) superior salivary nucleus
(D) inferior salivary nucleus
(E) geniculate ganglion

**42.** A 40-year-old man developed chronic pain in the right forearm that lasted for hours each day. Neurological examination demonstrated normal sensation, mild weakness on right forearm pronation, and weak flexion of the terminal phalanges of the right thumb as well as the index and middle fingers. An attempt to make a full circle by applying the end phalanx of the thumb to that of the index finger with firm pressure showed consistent weakness. Which of the following structures is affected?

(A) The right anterior interosseous nerve
(B) The right median nerve at the upper axilla
(C) The right ulnar nerve
(D) The right radial nerve
(E) The right musculocutaneous nerve

**43.** The substantia gelatinosa of the spinal cord is located in

(A) lamina I
(B) lamina II
(C) lamina IV
(D) lamina VII
(E) lamina IX

**44.** The neostriatum is formed by the

(A) caudate nucleus and globus pallidus
(B) putamen and globus pallidus
(C) substantia nigra and olfactory tubercles
(D) caudate nucleus and putamen
(E) caudate nucleus and subthalamic nucleus

**45.** The direct circuit loop between the basal ganglia and the cortex is

(A) cerebral cortex → striatum → internal globus pallidus → substantia nigra pars reticulata → dorsal thalamus → cerebral cortex
(B) cerebral cortex → striatum → external globus pallidus → substantia nigra pars reticulata → dorsal thalamus → cerebral cortex
(C) cerebral cortex → striatum → internal globus pallidus → dorsal thalamus → cerebral cortex
(D) cerebral cortex → striatum → external globus pallidus → substantia nigra pars compacta → dorsal thalamus → cerebral cortex
(E) cerebral cortex → striatum → internal globus pallidus → subthalamic nucleus → internal globus pallidus → dorsal thalamus → cerebral cortex

**46.** The indirect circuit loop between the basal ganglia and the cerebral cortex is

(A) cortical fibers → striatum → external globus pallidus → subthalamic nucleus → internal globus pallidus → dorsal thalamus → cerebral cortex
(B) cortical fibers → striatum → external globus pallidus → internal globus pallidus → dorsal thalamus → cerebral cortex
(C) cortical fibers → striatum → external globus pallidus → substantia nigra pars reticulata → dorsal thalamus → cerebral cortex
(D) cortical fibers → striatum → external globus pallidus → subthalamic nucleus → substantia nigra pars compacta → dorsal thalamus → cerebral cortex
(E) cortical fibers → striatum → external globus pallidus → subthalamic nucleus → internal globus pallidus → substantia nigra pars compacta → dorsal thalamus → cerebral cortex

**47.** The superior cerebellar peduncle contains one cerebellar afferent, which is the

(A) ventral spinocerebellar tract
(B) pontocerebellar tract
(C) dorsal spinocerebellar tract
(D) olivocerebellar fibers
(E) reticulocerebellar fibers

**48.** The dentate nucleus sends efferent projections to the

(A) red nucleus
(B) ventrolateral nucleus of the thalamus
(C) vestibular nucleus
(D) pontine reticular nucleus
(E) oculomotor nucleus

**49.** The cerebellar cortex contains

(A) pyramidal cells
(B) Purkinje cells
(C) fusiform cells
(D) horizontal cells of Cajal
(E) hair cells

**50.** The source of noradrenergic projection to the cerebellum is the

(A) dorsomedial nucleus of the hypothalamus
(B) locus ceruleus
(C) raphe nucleus
(D) thalamus
(E) inferior olivary nucleus

**51.** The emboliform nucleus sends efferent projections to the

(A) nucleus ambiguus
(B) nucleus solitarius
(C) vestibular nucleus
(D) pontine reticular nucleus
(E) red nucleus

**52.** The learning of complex motor tasks and motor plasticity are two functions that mainly involve the

(A) olivocerebellar climbing fibers
(B) mossy fibers
(C) emboliform nuclei
(D) motor cortical area
(E) parallel fibers from granular cell axons

**53.** The fastigial nucleus sends efferent projections to the

(A) nucleus ambiguus
(B) nucleus solitarius
(C) vestibular nucleus
(D) superior olive
(E) locus ceruleus

**54.** The tuberoinfundibular hypothalamic tract arises from the

(A) arcuate nuclei
(B) mammillary nuclei
(C) fornix
(D) paraventricular nucleus
(E) supraoptic nucleus

**55.** The most likely neurotransmitter for cerebellar climbing fibers is

(A) acetylcholine
(B) glutamate
(C) aspartate
(D) dopamine
(E) glycine

**56.** The only efferent fibers from the cerebellar cortex come from the

(A) axons of Purkinje cells
(B) mossy fiber projections
(C) parallel fibers
(D) climbing fibers
(E) axons of Golgi cells

**57.** Hyperphagia is caused by a lesion in the

(A) ventromedial nucleus
(B) supraoptic nucleus
(C) anterior nucleus
(D) arcuate nucleus
(E) mammillary nucleus

**58.** Which of the following extraocular muscles is innervated by a nucleus located on the contralateral side?

(A) Superior rectus
(B) Inferior rectus
(C) Medial rectus
(D) Lateral rectus
(E) Inferior oblique

**59.** Which of the following cranial nerve nuclei are sources of special visceral efferents?

(A) Oculomotor nuclei
(B) Trochlear nuclei
(C) Abducens nuclei
(D) Motor nuclei of the facial nerve
(E) Hypoglossal nuclei

**60.** The parasympathetic innervation of the parotid gland is provided by the

(A) facial nerve
(B) vestibulocochlear nerve
(C) glossopharyngeal nerve
(D) vagus nerve
(E) spinal accessory nerve

**61.** Which of the following is true about the trigeminal nerve nuclei?

(A) The trigeminal nerve has two sensory nuclei.
(B) Pain and temperature are carried predominantly by the spinal nucleus of the trigeminal nerve.
(C) Most small fibers afferent of the spinal tract of the trigeminal nerve end in the main sensory nucleus of that nerve.
(D) The motor nucleus of the trigeminal nerve innervates the muscles of mastication via its maxillary division.
(E) The motor nucleus of the trigeminal nerve contains only alpha motor neurons.

**62.** The sole output neurons of the cerebellar cortex are

(A) pyramidal cells
(B) granular cells
(C) Purkinje cells
(D) horizontal cells
(E) fusiform cells

**63.** The principal efferent neuron layer of the cerebral neocortex is

(A) layer II
(B) layer III
(C) layer IV
(D) layer V
(E) layer VI

**64.** Thalamocortical afferents have their main terminals in the cerebral cortex layer number

(A) I
(B) II
(C) III
(D) IV
(E) V

**65.** The extrathalamic cortical modulatory system, using acetylcholine as a neurotransmitter, arises from the

(A) midbrain raphe
(B) locus ceruleus
(C) ventral midbrain
(D) nucleus basalis of Meynert of the basal forebrain
(E) hypothalamic nuclei

**66.** Prosopagnosia is associated with

(A) a lesion of the posterior parietal association cortex
(B) a lesion of the temporal association cortex
(C) a lesion of the prefrontal association cortex
(D) labile emotion
(E) a problem-solving deficit

**67.** Which of the following arteries supplies the medial part of the lateral geniculate body?

(A) The ophthalmic artery
(B) The anterior communicating artery
(C) The anterior choroidal artery
(D) The posterior choroidal artery
(E) The middle cerebral artery

**68.** Which of the following cranial nerves is responsible for eye closure?

(A) The oculomotor nerve
(B) The trochlear nerve
(C) The abducens nerve
(D) The facial nerve
(E) The spinal accessory nerve

**69.** Which of the following structures receives afferents responsible for taste sensation in the anterior two thirds of the tongue?

(A) The submaxillary ganglion
(B) The pterygopalatine ganglion
(C) The superior salivary nucleus
(D) The geniculate ganglion
(E) The submandibular ganglion

**70.** Which of the following arteries supplies the intracranial part of the facial nerve?

(A) The middle meningeal artery
(B) The superior cerebellar artery
(C) The posteroinferior cerebellar artery
(D) The anteroinferior cerebellar artery
(E) The posterior auricular artery

**71.** The third-order neurons of the auditory pathway terminate at the

(A) inferior colliculus
(B) auditory radiation
(C) medial geniculate body
(D) lateral geniculate body
(E) dorsal portion of the cochlear nucleus

**72.** The glossopharyngeal nerve crosses the jugular foramen with the

(A) facial and vestibulocochlear nerves
(B) vestibulocochlear and vagus nerves
(C) vagus and spinal accessory nerves
(D) vestibulocochlear and spinal accessory nerves
(E) facial and spinal accessory nerves

**73.** Glomus jugulare tumors may cause

(A) ipsilateral trapezoid weakness
(B) vertigo
(C) diplopia
(D) ipsilateral tongue deviation
(E) blepharospasm

**74.** Which of the following arteries supplies the midbrain?

(A) The vertebral artery
(B) The superior cerebellar artery
(C) The anteroinferior cerebellar artery
(D) The posteroinferior cerebellar artery
(E) The recurrent artery of Heubner

**75.** Which of the following is true about ion channel sequestration in central nervous system axons?

(A) Sodium and potassium channel clustering causes an inhibition of proper electrical signal generation in the central nervous system.
(B) Sodium channel clustering is located within the juxtaparanodal axonal region.
(C) Sodium channel clustering is initiated by Schwann cells in the peripheral nervous system.
(D) Shaker-type potassium channels are clustered in the node of Ranvier and may serve to inhibit sodium channel clustering.
(E) Axonal sodium channel expression decreases in multiple sclerosis.

**76.** Which of the following proteins is found in noncompact myelin of the peripheral nervous system?

(A) Connexin 32
(B) Myelin basic protein
(C) Proteolipid protein (PLP)
(D) Peripheral myelin protein 22 (PMP22)
(E) Myelin-oligodendrocyte-specific protein

**77.** Schwann cells

(A) ensheathe multiple axons
(B) make multiple myelin sheaths for different axons
(C) express myelin-oligodendrocyte glycoprotein
(D) do not have a basal lamina
(E) are responsible for myelin synthesis in the central nervous system

**78.** Which of the following characteristics is common to astrocytes and oligodendrocytes?

(A) Class I major histocompatibility complex (MHC) expression
(B) Class II MCH expression
(C) Expression of costimulatory molecules
(D) Expression of complement components
(E) Expression of myelin basic protein

**79.** The resting membrane potential in a typical neuron is

(A) −50 mV
(B) −70 mV

(C) −80 mV
(D) −30 mV
(E) −40 Mv

**80.** Which of the following types of axons has the fastest conduction velocity?

(A) Ia
(B) Ib
(C) II
(D) III
(E) IV

**81.** Neurulation does not occur when the embryo is exposed to colchicine because

(A) it inhibits induction
(B) it inhibits anterior neuropore closure
(C) it inhibits posterior neuropore closure
(D) it induces microfilament-based contraction
(E) it induces the depolymerization of microtubules

**82.** After fertilization, the anterior neuropore closes at

(A) 14 days
(B) 20 days
(C) 18 days
(D) 24 days
(E) 28 days

**83.** Failure of the anterior neuropore to close causes

(A) anencephaly
(B) spina bifida
(C) meningocele
(D) meningomyelocele
(E) tethered cord syndrome

**84.** Failure of the forebrain to undergo cleavage results in

(A) anencephaly
(B) holoprosencephaly
(C) myelodysplasia
(D) meningoencephalocele
(E) spina bifida

**85.** Which of the following brain structures derives from the telencephalon?

(A) The internal capsule
(B) The cerebral aqueduct of Sylvius
(C) The thalamus
(D) The fourth ventricle
(E) The third ventricle

**86.** The diencephalon develops into the

(A) cerebral cortex
(B) fourth ventricle
(C) cerebral aqueduct of Sylvius
(D) olfactory bulb
(E ) thalamic nuclei

**87.** Defects in the closure of the posterior neuropore cause

(A) spina bifida
(B) anencephaly
(C) tethered cord syndrome
(D) holoprosencephaly
(E) lissencephaly

**88.** Which of the following cells derives from the neural crest?

(A) Radial glial cells
(B) Neuroblasts
(C) Schwann cells
(D) Purkinje cells
(E) Astrocytes

**89.** Which of the following structures derives from the basal plate?

(A) General somatic efferent
(B) General visceral afferent
(C) General somatic afferent
(D) Special visceral afferent
(E) Special somatic afferent

**90.** Which of the following structures sends afferents to the mammillary body?

(A) The medial temporal cortex
(B) The retinal pregeniculate nucleus
(C) The nucleus of locus coeruleus
(D) The arcuate nucleus
(E) The supraoptic nucleus

**91.** The anterior thalamic nuclei receive afferent connections from the

(A) lateral geniculate body
(B) basal ganglia
(C) spinal cord
(D) mammillary body
(E) cerebellum

**92.** The dorsomedial nucleus of the thalamus receives afferent connections from the

(A) frontal lobe
(B) occipital lobe
(C) fornix
(D) mammillary body
(E) spinal cord

**93.** The medial geniculate body sends efferents to the

(A) calcarine cortex
(B) temporal gyrus of Heschl
(C) cerebellum
(D) mammillary body
(E) spinal cord

**94.** Anencephaly results from

(A) a defect of prosencephalization
(B) failure of the anterior neuropore to close
(C) failure of the posterior neuropore to close
(D) failure of secondary neurulation
(E) defective development of the neural crest

**95.** Secondary neurulation defects cause

(A) tethered cord syndrome
(B) anencephaly
(C) prosencephaly
(D) congenital hydrocephalus
(E) Dandy–Walker malformation

**96.** Heterotopia is caused by

(A) failure of secondary neurulation
(B) disrupted migration of immature neurons
(C) abnormal migration of neural crest cells
(D) failure of the posterior neuropore to close
(E) failure of the anterior neuropore to close

**97.** Which of the following structures pass through the jugular foramina?

(A) The facial nerve
(B) The cochleovestibular nerve
(C) The hypoglossal nerve
(D) The vagus nerve
(E) The trigeminal nerve

**98.** Which of the following arteries supply the thalamus?

(A) The middle cerebral artery
(B) The anterior choroidal arteries
(C) The posterior choroidal artery
(D) The anterior cerebral artery
(E) The superior cerebellar artery

**99.** Which of the following structures is a part of the Papez circuit?

(A) The medial lemniscus
(B) The nucleus ambiguous
(C) The hypothalamus
(D) The hippocampus
(E) The lateral geniculate body

**100.** The fibers of the medial lemniscus terminate in a somatotropic manner within the

(A) ventral posterolateral nucleus
(B) ventral posteromedian nucleus
(C) lateral dorsal nucleus
(D) midline nuclei
(E) reticular nucleus

**101.** Which of the following hypothalamic nuclei is responsible for body temperature control?

(A) The supraoptic nucleus
(B) The paraventricular nucleus
(C) The suprachiasmatic nucleus
(D) The preoptic nucleus
(E) The anterior nucleus

**102.** Brodmann area 6 of the cerebral cortex corresponds to the

(A) frontal eye field
(B) Broca convolution
(C) premotor somatosensory cortex
(D) angular gyrus
(E) supramarginal gyrus

**103.** In the medulla, the vascular supply of the medial lemniscus is provided by

(A) penetrating branches of the basilar artery
(B) the posterior cerebral artery
(C) the posterior spinal artery
(D) the anterior spinal artery
(E) the superior cerebellar artery

**104.** The thalamocortical cells and fibers arising from the ventral posterolateral nucleus

(A) conveys inhibitory input to the cortex
(B) are gluteminergic neurons
(C) are GABAergic neurons
(D) terminate in the auditory cortex
(E) receive ascending input from the trigeminothalamic tract

**105.** The cell bodies of the trigeminal primary afferent neurons are located in the

(A) semilunar ganglion
(B) nucleus ambiguus
(C) red nucleus
(D) nucleus solitarius
(E) cuneate nucleus

**106.** The Aδ nociceptive primary afferent fibers target

(A) Rexed laminae I, II, and IV
(B) Rexed laminae II and V
(C) Rexed laminae I and II
(D) Rexed laminae I and V
(E) Rexed laminae IV and V

**107.** Which of the following is true about the ascending pathway for sympathetic afferents?

(A) The cell bodies of origin of sympathetic fibers are located in the posterior root ganglia at about levels S2 to S4.
(B) The sympathetic afferent fibers terminate in spinal cord laminae I and V.
(C) The sympathetic afferent fibers enter the spinal cord via the anterior root.
(D) The sympathetic afferent fibers are formed by large myelinated fibers.
(E) The input originating from physiological receptors travels primarily in sympathetic afferent fibers.

**108.** The restiform body is supplied by the

(A) anteroinferior cerebellar artery
(B) posteroinferior cerebellar artery
(C) superior cerebellar artery
(D) posterior cerebral artery
(E) basilar artery

**109.** Mossy fibers

(A) are the only afferent fibers of the cerebellar cortex
(B) originate from the inferior olivary nucleus
(C) utilize glutamate as a neurotransmitter
(D) are inhibitory to granule cerebellar cells
(E) synapse exclusively with the Purkinje cerebellar cells

**110.** The climbing cerebellar fibers

(A) are cerebellar efferent fibers
(B) excite Purkinje cells
(C) originate from the locus ceruleus
(D) terminate exclusively withn the granule layer of the cerebellum
(E) use norepinephrine as a neurotransmitter

**111.** The parasympathetic postganglionic cell bodies of the oculomotor nerve are located in the

(A) pterygopalatine ganglion
(B) submandibular ganglion
(C) otic ganglion
(D) ciliary ganglion
(E) inferior salivary nucleus

**112.** The parasympathetic preganglionic cell bodies of the facial nerve are located in the

(A) Edinger-Westphal nucleus
(B) inferior salivatory nucleus
(C) otic ganglion
(D) nucleus ambiguus
(E) superior salivatory nucleus

**113.** The anterior group of the thalamus has reciprocal connection with

(A) mammillary bodies
(B) amygdaloid nucleus
(C) auditory cortex
(D) striatum
(E) visual cortex

**114.** The prefrontal cortex has reciprocal connection via the anterior thalamic peduncle with the

(A) anterior nuclear group of the thalamus
(B) dorsomedial nucleus of the thalamus
(C) lateral posterior nucleus of the thalamus
(D) lateral geniculate body
(E) cerebellum

**115.** The medial geniculate nucleus

(A) is a relay thalamic nucleus in the auditory system
(B) receives fibers from the optic tract
(C) receives input from the somatosensory cortex
(D) is involved in motor corrdination
(E) is a part of the limbic system

**116.** The only cerebellar neuron that sends its axons outside the cerebellum is the

(A) basket cell
(B) stellate cell
(C) golgi cell
(D) granule cell
(E) Purkinje cell

**117.** The structure indicated by the arrow in Figure 1-7 is the

(A) optic chiasm
(B) hypothalamic sulcus
(C) pituitary gland
(D) lamina terminalis
(E) mammillary body

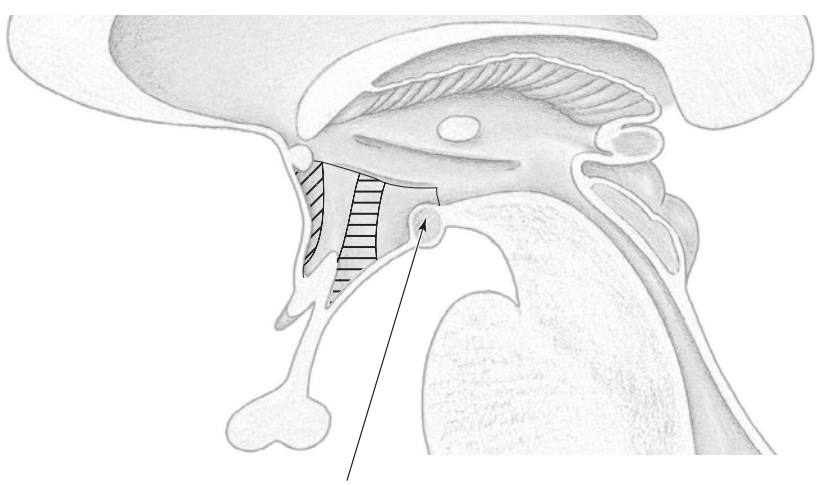

**FIG. 1-7.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

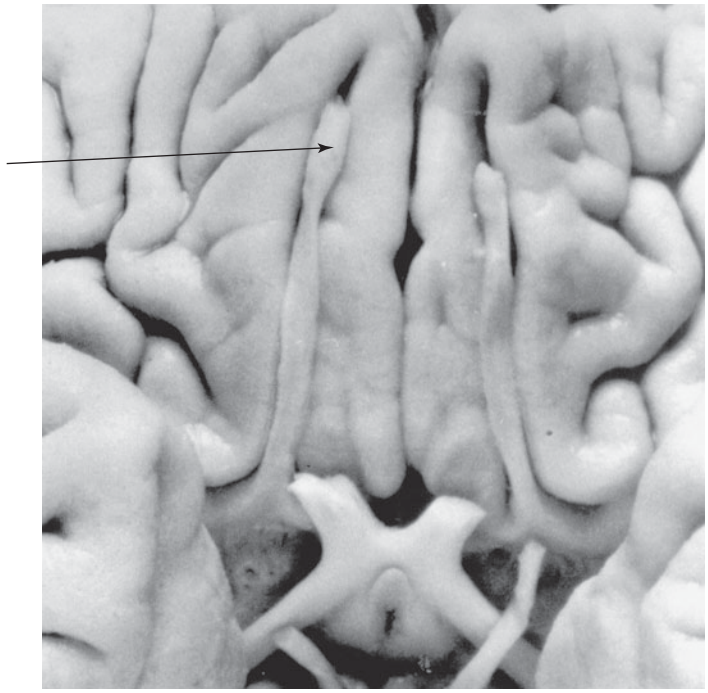

**FIG. 1-8.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

**118.** The structure indicated by the arrow in Figure 1-8 is the

(A) optic nerve
(B) olfactory bulb
(C) optic chiasm
(D) optic tract
(E) oculomotor nerve

**119.** The structure indicated by the arrow in Figure 1-9 is the

(A) cingulate gyrus
(B) corpus callosum
(C) cingulate sulcus
(D) parahippocampal gyrus
(E) subcallosal gyrus

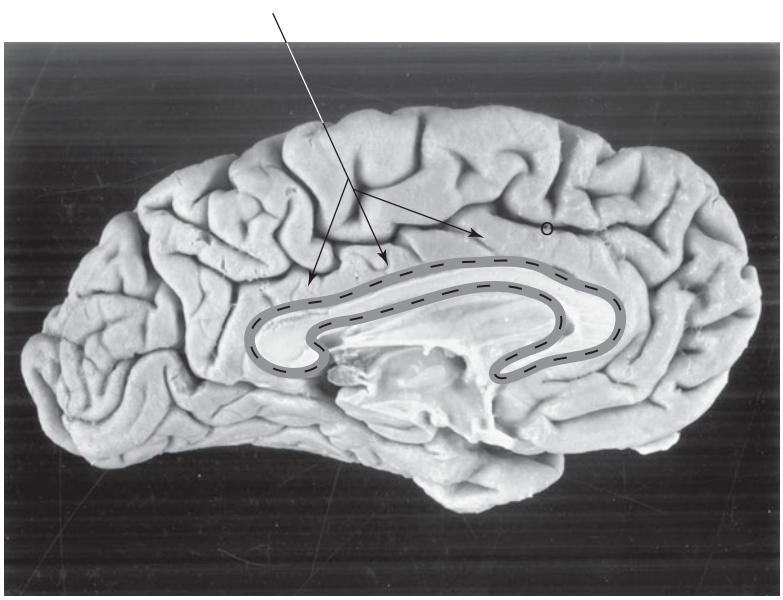

**FIG. 1-9.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

**120.** The first intracranial branch of the internal carotid artery is the

(A) anterior cerebral artery
(B) anterior choroidal artery
(C) recurrent artery of Heubner
(D) superior cerebellar artery
(E) ophthalmic artery

**121.** The anterior limb and genu of the internal capsule are supplied by the

(A) middle cerebral artery
(B) recurrent artery of Heubner
(C) superior cerebellar artery
(D) vertebral artery
(E) anteroinferior cerebellar artery

**122.** The structure indicated by the arrow in Figure 1-10 is the

(A) postcentral gyrus
(B) intraparietal sulcus
(C) central sulcus
(D) cingulate sulcus
(E) precentral gyrus

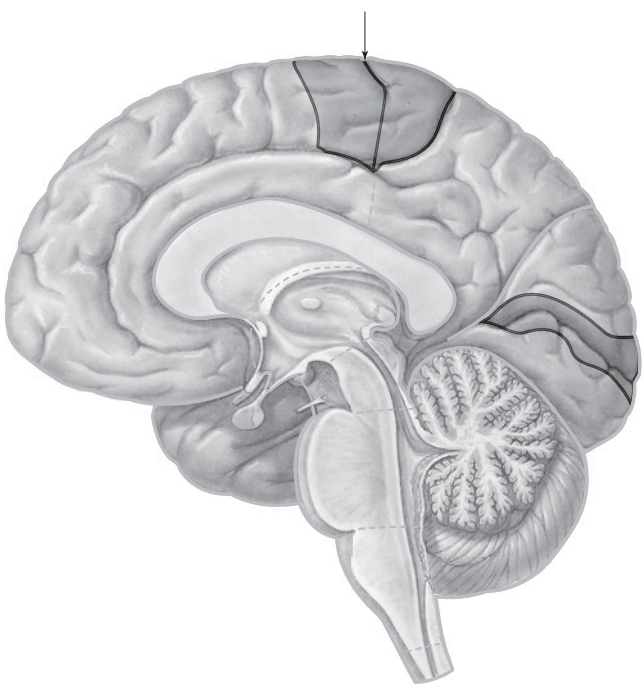

**FIG. 1-10.** (Reproduced with permission from Martin JH. *Neuroanatomy. Text and Atlas.* 3rd Ed. New York: McGraw-Hill; 2003.)

**123.** Each of the lateral ventricles is connected to the third ventricle by the

(A) cerebral aqueduct
(B) foramen of Magendie
(C) foramen of Luschka
(D) quadrigeminal cistern
(E) foramen of Monro

**124.** The structure indicated by the arrow in Figure 1-11 is the

(A) vertebral artery
(B) basilar artery
(C) anteroinferior cerebellar artery
(D) anterior spinal artery
(E) superior cerebellar artery

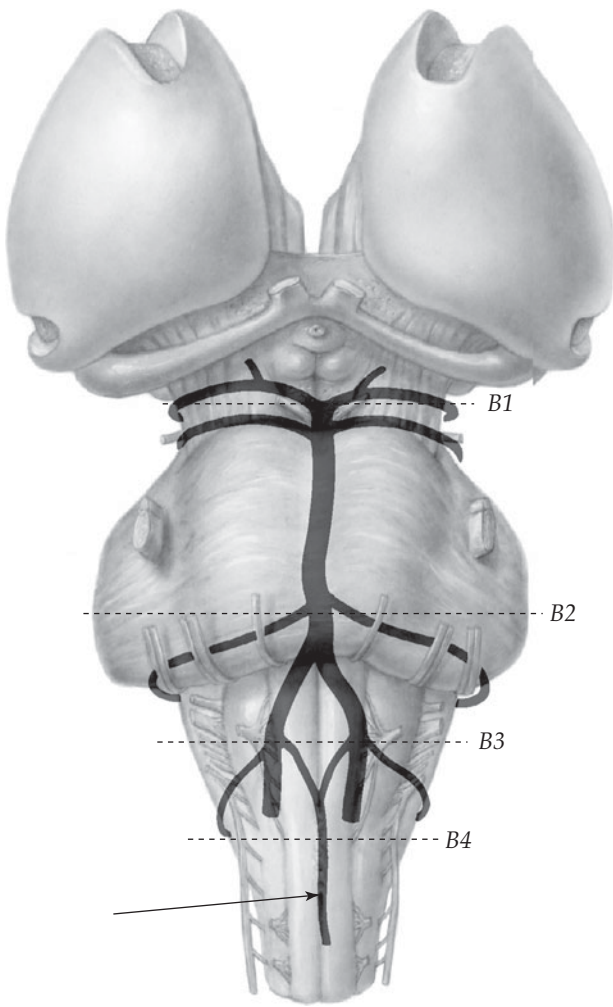


**FIG. 1-11.** (Reproduced with permission from Martin JH. *Neuroanatomy. Text and Atlas.* 3rd ed. New York: McGraw-Hill; 2003.)

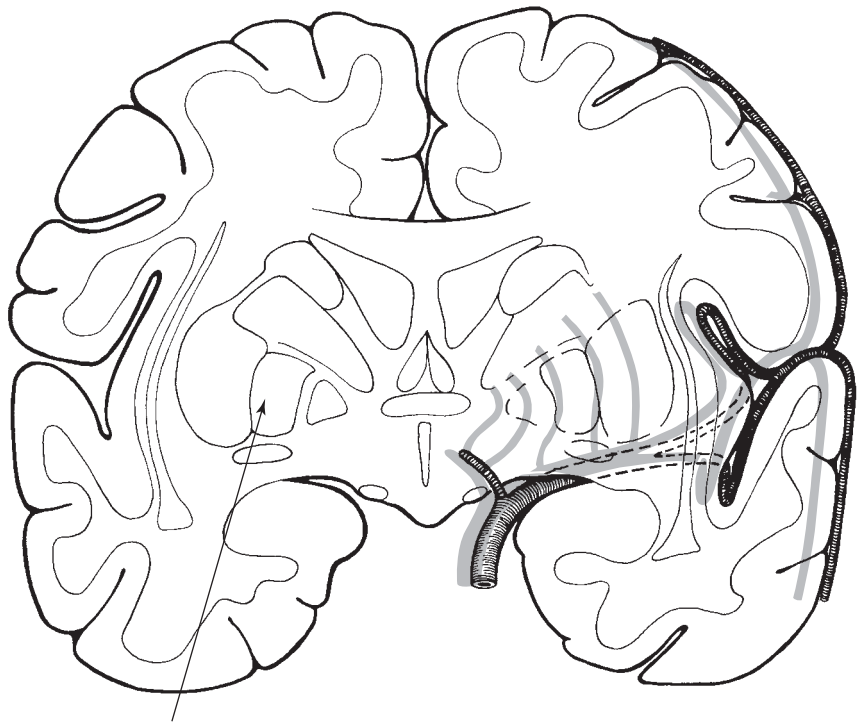

**FIG. 1-12.** (Reproduced with permission from Martin JH. *Neuroanatomy. Text and Atlas.* 3rd ed. New York: McGraw-Hill; 2003.)

**125.** The structure indicated by the arrow in Figure 1-12 is the

(A) insular cortex
(B) midbrain
(C) corpus callosum
(D) lateral geniculate body
(E) globus pallidus

**126.** Although the cerebrospinal fluid is mainly secreted by the choroid plexus, it is also secreted by the

(A) inferior sagittal sinus
(B) the capillary–astrocyte complex
(C) dura mater
(D) pineal gland
(E) pia mater

**127.** The first central nervous system relay for taste is located in the

(A) nucleus ambiguus
(B) solitary nucleus
(C) lateral geniculate nucleus
(D) medial geniculate nucleus
(E) red nucleus

**128.** The preganglionic neurons that innervate the parotid gland originate from the

(A) inferior salivary nucleus
(B) superior salivary nucleus
(C) Edinger–Westphal nucleus
(D) dorsal motor nucleus of the vagus
(E) solitary nucleus

**129.** Clarke's nucleus

(A) is located in the caudal medulla
(B) relays somatic sensory information from the upper limbs to the cerebellum
(C) gives rise to the dorsal spinocerebellar tract
(D) receives afferent fibers that course in the cuneate fascicle
(E) gives rise to crossed fibers that enter the cerebellum via the superior cerebellar peduncle

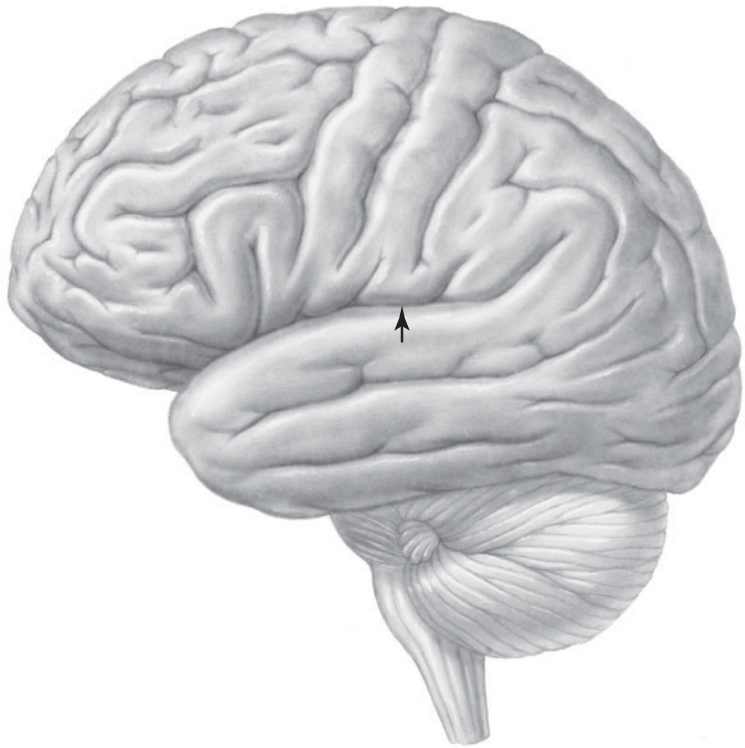

**FIG. 1-13.** (Reproduced with permission from Martin JH. *Neuroanatomy. Text and Atlas.* 3rd ed. New York: McGraw-Hill; 2003.)

**130.** The inferior olivary nucleus hosts neurons of the

(A) cerebellar climbing fibers
(B) cerebellar mossy fibers
(C) cerebellar parallel fibers
(D) reticulospinal fibers
(E) trigeminal cerebellar fibers

**131.** The structure indicated by the arrow in Figure 1-13 is the

(A) lateral sulcus
(B) angular gyrus
(C) central sulcus
(D) precentral sulcus
(E) middle frontal gyrus

**132.** The structure indicated by the arrow in Figure 1-14 is the

(A) red nucleus
(B) oculomotor nerve
(C) mammillary body
(D) pineal gland
(E) substantia nigra

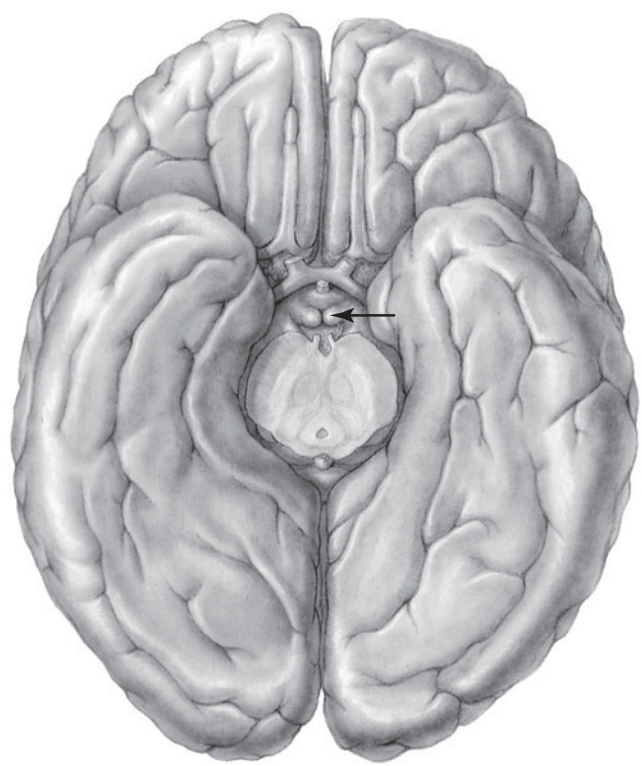

**FIG. 1-14.** (Reproduced with permission from Martin JH. *Neuroanatomy. Text and Atlas.* 3rd ed. New York: McGraw-Hill; 2003.)

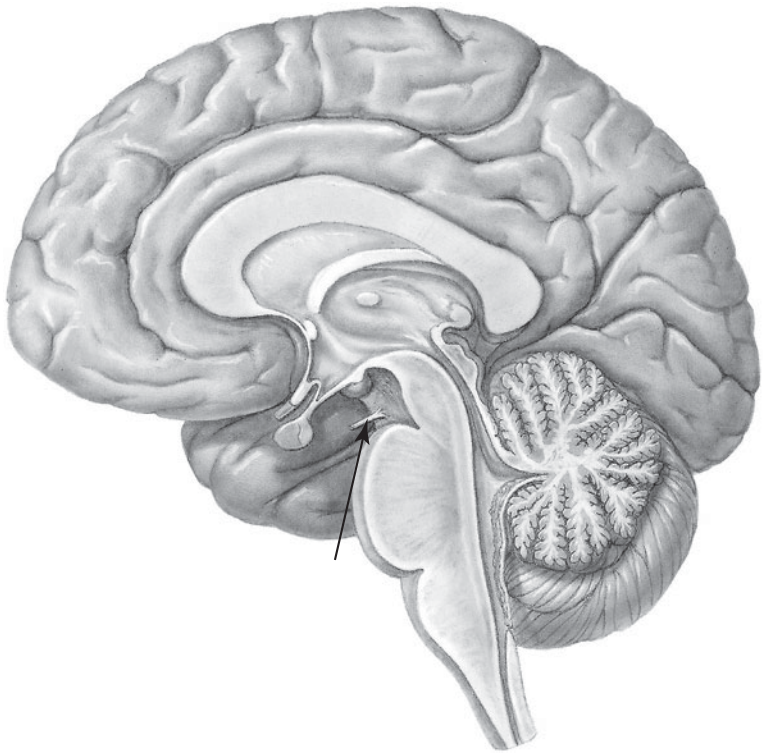

**FIG. 1-15.** (Reproduced with permission from Martin JH. *Neuroanatomy. Text and Atlas.* 3rd ed. New York: McGraw-Hill; 2003.)

**133.** The structure indicated by the arrow in Figure 1-15 is the

(A) trigeminal nerve
(B) oculomotor nerve
(C) facial nerve
(D) abducens nerve
(E) trochlear nerve

**134.** The structure indicated by the arrow in Figure 1-16 is the

(A) oculomotor nerve
(B) trigeminal nerve
(C) abducens nerve
(D) hypoglossal nerve
(E) vagus nerve

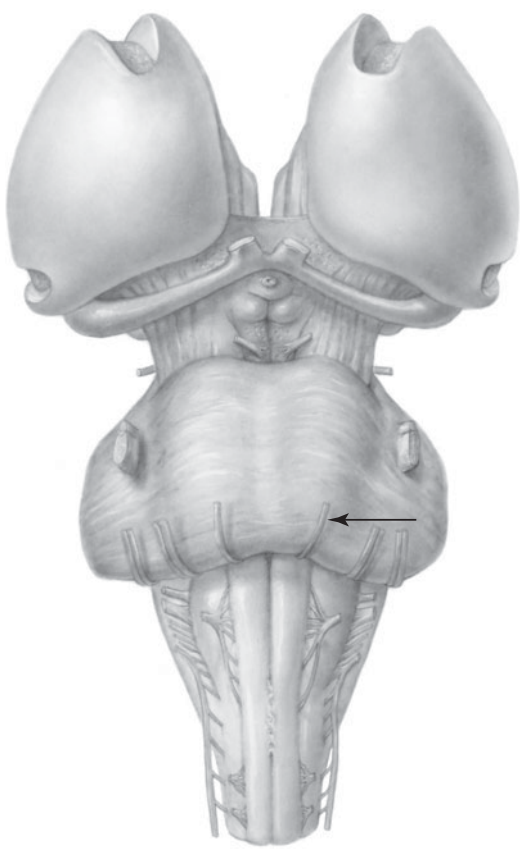

**FIG. 1-16.** (Reproduced with permission from Martin JH. *Neuroanatomy. Text and Atlas.* 3rd ed. New York: McGraw-Hill; 2003.)

**135.** The structure indicated by the arrow in Figure 1-17 is the

(A) trigeminal nerve
(B) abducens nerve
(C) facial nerve
(D) oculomotor nerve
(E) trochlear nerve

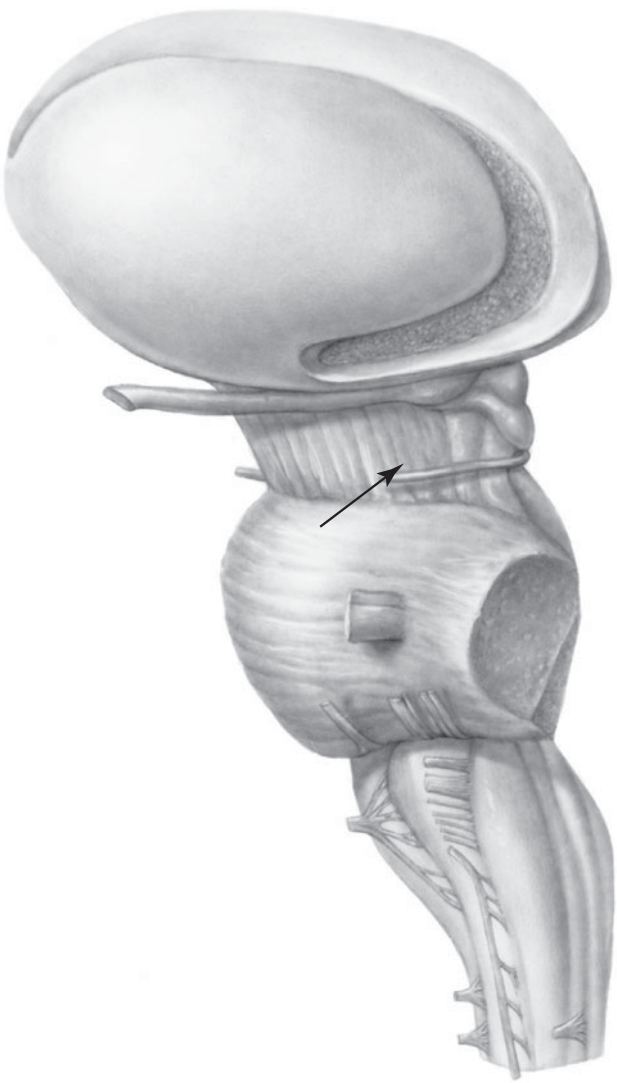

**FIG. 1-17.** (Reproduced with permission from Martin JH. *Neuroanatomy. Text and Atlas.* 3rd ed. New York: McGraw-Hill; 2003.)

**136.** The structure indicated by the arrow in Figure 1-18 is the

(A) pineal gland
(B) mammillary body
(C) superior colliculus
(D) trochlear nerve
(E) third ventricle

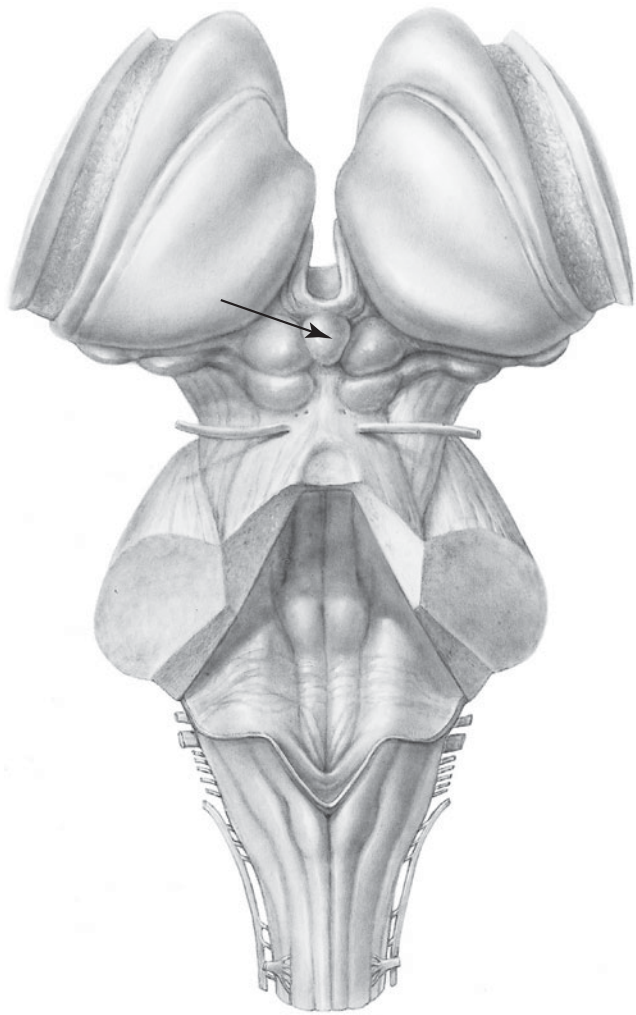

**FIG. 1-18.** (Reproduced with permission from Martin JH. *Neuroanatomy. Text and Atlas.* 3rd ed. New York: McGraw-Hill; 2003.)

**137.** The structure indicated by the arrow in Figure 1-19 is the

(A) pyramid
(B) reticular formation
(C) inferior cerebellar peduncle
(D) medial lemniscus
(E) solitary nucleus

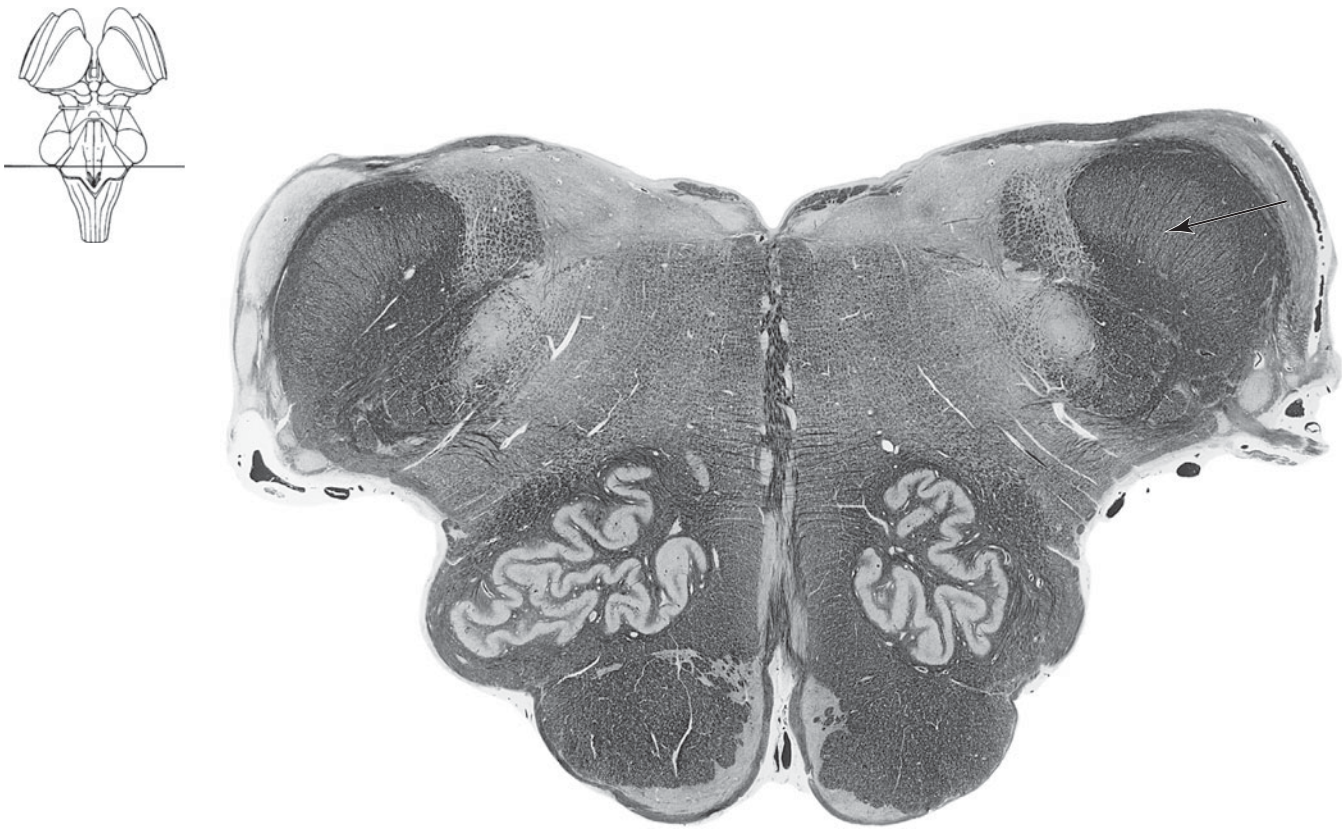

**FIG. 1-19.** (Reproduced with permission from Martin JH. *Neuroanatomy. Text and Atlas.* 3rd ed. New York: McGraw-Hill; 2003.)

# Answers and Explanations

**1. (D)** The olfactory pathway is the only sensory pathway that does not project to the thalamus. The olfactory nerve penetrates the cribriform plate of the ethmoid bone and enters the olfactory bulb to synapse with the second-order neurons: mitral and tufted cells. The axons of the second-order neurons course posteriorly as the olfactory tract in the orbital surfaces of the frontal lobe and project to the primary olfactory cortex in the temporal lobe. In the visual pathway, axons of the ganglion cells in the retina gather together at the optic disk to form the optic nerve. The two optic nerves come together at the optic chiasma, where a partial crossing of optic nerve fibers takes place. The crossed and uncrossed fibers from the optic nerves join caudal to the optic chiasma to form the optic tracts, which extend from the dorsolateral corners of the chiasma to the lateral geniculate bodies. These constitute a thalamic nucleus that provides a relay station for all the axons of the retinal ganglion cells subserving vision. The lateral geniculate nucleus is laminated into six layers. Not all parts of the retina are represented equally in it. The central area of the retina has larger representation than does the periphery of the retina. Axons of neurons of the lateral geniculate nucleus project to the visual cortex in the occipital lobe via the geniculocalcarine tract. Geniculocalcarine fibers project to the visual cortex.

The auditory pathway is described as a four-tiered neuronal network. The auditory cochlear nerve, extending from the organ of Corti to the cochlear nucleus, generates action potentials that travel in the afferent nerve fibers via the central components (axons) of bipolar neurons in the spiral ganglion to reach the cochlear nuclei in the pons. The second-order neurons of the auditory pathway are formed by fibers of cochlear nuclei crossing to the contralateral inferior colliculus. The latter contains the third-order neurons and serves as the central relay nucleus in the auditory pathway. The projections from the inferior colliculus terminate in the medial geniculate body, a thalamic auditory relay nucleus. The fourth-order neurons are formed by the geniculotemporal fibers that project to the primary auditory cortex. Vibration sensation is mediated by Merkel disk receptors and Meissner's corpuscules. Fibers mediating vibration terminate in the deeper layers of the dorsal horn. Second-order neurons from the dorsal horn ascend through the ipsilateral dorsolateral funiculus, terminating on neurons in the nuclei of the posterior dorsal column (nucleus gracilis and nucleus cuneatus) in the medulla oblongata. Axons of these nuclei cross the midline to form the medial lemniscus, which ascends to the thalamus (ventral posterolateral nucleus) and from there to the primary sensory cortex. Temperature sensation is mediated by the lateral spinothalamic tract, which projects into the ventral posterolateral nucleus of the thalamus. *(Parent, 748–754; Afifi, 53, 314, 319; Brazis, 133–138, 307–309)*

**2. (E)** The lateral geniculocalcarine tract connects the lateral geniculate nucleus to the visual cortex. The geniculocalcarine fibers from the upper halves of both retinas course directly backward around the lateral ventricle in the inferior part of the parietal cortex to reach the visual cortex. Geniculocalcarine fibers from the lower halves of both retinas course forward toward the tip of the temporal horn of the

lateral ventricle and then loop backward in the temporal lobe to reach the visual cortex. Because of the spread of geniculocalcarine fibers in the parietal and temporal lobes, a lesion involving the upper fibers located in the temporal lobe (as shown in Figure 1-1) produces a contralateral inferior quadrantic visual field defect. A lesion involving the lower fibers located in the parietal lobe produces a contralateral superior quadrantic visual field defect. *(Afifi, 314)*

3. **(D)** All the fibers forming the posterior funiculus are ascending fibers throughout the spinal cord and synapse on the posterior column nuclei (nucleus gracilis and nucleus cuneatus) in the medulla oblongata. Approximately 85% of ascending fibers in the posterior funiculus are primary afferents. These have cell bodies in the dorsal root ganglia and are activated by stimulation of mechanoreceptors but not nociceptors. These cells are called unimodal afferents. Approximately 15% of fibers in the posterior funiculus are nonprimary afferents. These have cell bodies in the dorsal root ganglia, establish synapses in laminae III to V in the posterior horns of the cervical and lumbar enlargement, and are activated by stimulation of both mechanoreceptors and nociceptors. They are called polymodal afferents. *(Afifi, 53)*

4. **(A)** In lesions of the posterior column, discrepancies in loss of vibration and position sense have been observed. A possible explanation of this is that different pathways are used for the transmission of the two modalities. In experimental animals, it has been shown that vibration sensation in forelimbs and hindlimbs transmits its impulses via the dorsal columns and the spinocervical thalamic tract. In contrast, propioceptive sensations from the forelimbs utilize the dorsal column, while those from the hindlimbs travel with the gracile tract to the level of the dorsal nucleus of Clarke. From there, these sensations leave the gracile tract, synapse in the nucleus dorsalis of Clarke, and travel with the dorsal spinocerebellar fibers to terminate on the nucleus of Z, a small collection of cells in the most rostral part of the nucleus gracilis of the medulla. *(Afifi, 54)*

5. **(A)** The long thoracic nerve arises from the motor roots of C5, C6, and C7. It courses downward through and in front of the medial scalenus muscle and further descends dorsal to the brachial plexus along the medial axillary wall to innervate the serratus anterior muscle. The suprascapular nerve innervates the supraspinatus and infraspinatus. The dorsal scapular nerve innervates the rhomboid and levator scapulae. *(Parent, 276; Staal, 19)*

6. **(E)** The axillary nerve originates from the posterior fascicle of the brachial plexus and carries fibers from C5 and C6. It is divided into superior and inferior branches. The superior branch travels with the circumflex artery around the humeral head neck to innervate the deltoid muscle. The inferior branch supplies the teres minor muscle. The axillary nerve sends a sensory branch, the lateral brachial cutaneous nerve, to the skin of the upper outer surface of the arm, mainly in the deltoid region. An axillary nerve lesion results in weakness of arm abduction against resistance in the horizontal position. The first 30 degrees of abduction of the upper arm from the trunk is performed by the supraspinatus muscle, which is innervated by the suprascapular nerve, not by the axillary nerve. There is also weakness in retracting the horizontal upper arm against resistance, with sensory loss in the skin area overlying the deltoid muscle. The axillary nerve is often involved in neuralgic amyotrophy; in about 10% of cases, it is affected in isolation. *(Parent, 275–277; Staal, 27–29; Brazis, 32–33)*

7. **(C)** The musculocutaneous nerve arises from the lateral cord of the brachial plexus and carries fibers from the roots of C5, C6, and C7. The nerve proceeds obliquely downward between the axillary artery and the median nerve. The nerve pierces the coracobrachialis muscle while giving off branches to it, and it descends further between the biceps and brachialis muscles to supply them both. The lateral cutaneous nerve of the forearm is the sensory continuation of the musculocutaneous nerve. It innervates the skin from the elbow to the wrist and covers the entire forearm from the dorsal to the ventral midline. The

coracobrachialis muscle is a forward elevator of the arm. The biceps is a forearm supinator, especially if the elbow is flexed at 90 degrees. Isolated lesions of the musculocutaneous nerve are rare. Such lesions would cause weakness of elbow flexion against resistance in a fully supinated hand, possible weakness in arm elevation, arm pain, and radial forearm paresthesia. *(Brazis, 34–35; Staal, 31–33)*

**8. (E)** The radial nerve arises from the posterior cord of the brachial plexus and comprises fibers from spinal levels C5 to C8. After descending posterior to the axillary artery, the nerve courses posterior to the humerus in the spiral groove. It is at this site that the nerve is most often damaged by compression. *(Staal, 35)*

**9. (D)** The dorsal scapular nerve is a pure motor nerve. It carries fibers from the C4 and C5 spinal nerves and, after piercing the medial scalenus muscle, courses downward behind the brachial plexus to innervate the levator scapulae. From there it courses along the medial border of the scapula to the rhomboid muscles. These elevate and adduct the medial border of the scapula, antagonizing the serratus anterior. Along with the levator scapulae, the rhomboid muscles rotate the scapula so that the inferior angle moves medially. These muscles are tested by having the patient press his or her elbow backward against resistance while the hand is on the hip. *(Staal, 17; Brazis, 29)*

**10. (A)** The upper trunk of the brachial plexus is formed by the anterior primary rami of the fifth and sixth cervical roots. They course downward between the scalenus medius and anterior muscles and unite to form the upper trunk. The latter traverses the supraclavicular fossa, accompanied by the middle and lower trunk. Lateral to the first rib and behind the axillary artery, the three trunks split into three anterior and three posterior divisions. The anterior divisions of the upper and middle trunks unite to form the lateral cord. The posterior divisions of the three trunks unite to form the posterior cord. Two branches arise from the proximal aspect of the upper trunk, the suprascapular nerve innervating the suprasinatus and infraspinatus muscles, and the subclavian nerve innervating the subclavian muscle. Prior to forming the brachial plexus trunks, the long thoracic nerve arises from the C5–C7 anterior primary rami to innervate the serratus anterior muscle, and the dorsal scapular nerve arises from the C4–C5 anterior primary rami to innervate the rhomboid and levator scapulae muscles. The teres minor muscles are innervated by the axillary nerve, which originates from the posterior cord and does not carry any contribution from the lateral cord. The innervation of the four other muscles listed in the question is carried by both the upper trunk and lateral cord. The pronator teres, flexor carpi radialis, and abductor pollicis brevis are innervated by the median nerve, which is formed in the axilla where the lateral cord joins with the medial cord of the brachial plexus. The biceps muscle is innervated by the musculocutaneous nerve, which arises from the lateral cord of the brachial plexus. *(Brazis, 75–76)*

**11. (D)** The extensor indicis proprius as well the other muscles innervated by the C8 radial nerve receive their innervation via the lower plexus, posterior division of the lower trunk, and posterior cord without any contribution from the medial cord. *(Brazis, 75–76)*

**12. (B)** The pronator teres is innervated by the C6–C7 median nerve. The lateral cord (derived from the upper and middle trunk of the brachial plexus) provides innervations to the pronator teres without any contribution from the posterior cord. *(Brazis, 75–76)*

**13. (D)** The sciatic nerve is a mixed nerve that carries fibers from L4 to S3 and leaves the pelvis through the sciatic foramen below the piriform muscle. The nerve then curves laterally and downward beneath the gluteus maximus muscle and runs on the dorsal side of the femoral bone to terminate at the proximal part of the popliteal fossa, where it divides into the tibial nerve medially and the peroneal nerve laterally. Within the sciatic nerve, as proximal as the gluteal region, the fibers of the tibial and peroneal nerves are arranged into two separate divisions: the medial and the lateral trunks.

The medial part of the nerve innervates the adductor magnus and the hamstring muscles except for the short head of the biceps femoris (it is the only thigh muscle supplied by the lateral peroneal division). The hamstring muscles are flexors of the knee joint and include the semimembranosus muscle, the semitendinosus muscle, and the short and long heads of the biceps femoris. *(Staal, 117–118)*

**14. (A)** The point of entrapment of the median nerve in carpal tunnel syndrome lies under the flexor retinaculum, which forms the roof of the carpal tunnel, whereas the carpal bones and their connective tissue components form the floor of the carpal tunnel. In Guyon's canal, the hamate and pisiform bones are sites of compression of the ulnar nerve at the wrist. Rarely, radial nerve compression occurs at the level of the styloid process, just proximal to the wrist. *(Staal, 56–66; Brazis, 38)*

**15. (B)** The femoral nerve supplies the sartorius muscle (a flexor and everter of the thigh) and the quadriceps (an extensor of the leg). The obturator nerve supplies the adductor muscles of the thigh. The genitofemoral nerve is predominantly a sensory nerve. It divides near the inguinal ligament into the external genital branch (responsible for the innervation of the cremaster muscle) and the medial femoral branch (responsible for the innervation of the skin of the upper thigh over the femoral triangle). The superior gluteal nerve innervates the gluteus medius and gluteus minimus. The inferior gluteal nerve innervates the gluteus maximus. *(Brazis, 51–56)*

**16. (A)** This is a brainstem section at the level of the medulla. The structure indicated by the arrow is the hypoglossal nucleus. The section shows a schematic diagram of the origin and intramedullary course of rootlets of the hypoglossal nerve. Except for its most rostral and caudal levels, the nucleus of the hypoglossal nerve extends throughout the medulla oblongata. It is divided into cell groups that correspond to the tongue muscles they supply. The root fibers of the nerve course in the medulla oblongata lateral to the medial leminiscus and emerge on the ventral surface of the medulla between the pyramid and inferior olive. *(Afifi, 87–88)*

**17. (D)** Vertical saccades are controlled by cortical pathways descending to the rostral interstitial nucleus of the medial longitudinal fasciculus at the junction between the midbrain and the thalamus. *(Kline and Bajandas, 50)*

**18. (E)** The abducens nucleus is the site of horizontal versional control. The nucleus of the abducens nerve contains two types of neurons: those that innervate the ipsilateral lateral rectus and those that project via the contralateral medial longitudinal fasciculus to the contralateral oculomotor nucleus. The parapontine reticular formation contains cells that project to the abducens nucleus and activate it. The parapontine reticular formation contains excitatory burst neurons that discharge just prior to a horizontal saccade to stimulate cells in the abducens nucleus. Once the eye reaches a new eccentric position at the end of the saccade, stimulation of the abducens nucleus by the parapontine reticular formation burst neurons is substituted by a tonic gaze-holding mechanism to maintain the eccentric position. This requires a neuronal network that integrates a velocity-coded signal into a position-coded signal. This is referred to as the neural integrator, which includes the horizontal gaze center, the medial vestibular nucleus, and the nucleus prepositus hypoglossi. *(Kline and Bajandas, 55)*

**19. (A)** The rostral interstitial nucleus of the medial longitudinal fasciculus contains excitatory burst neurons for vertical and torsional saccade. It projects bilaterally to the oculomotor nuclei in the case of upward gaze and mainly ipsilaterally in the case of downward gaze. The gaze-holding neural integrator for vertical gaze is located in the interstitial nucleus of Cajal. *(Kline and Bajandas, 52)*

**20. (E)** The trochlear nerve is purely a motor nerve and is the only cranial nerve to exit the brain dorsally. The trochlear nerve supplies one muscle: the superior oblique. The cell bodies that originate in the trochlear nerve are located in the ventral part of the brainstem in the

trochlear nucleus. The trochlear nucleus gives rise to fibers that cross to the other side of the brainstem just prior to exiting the pons. Thus each superior oblique muscle is supplied by nerve fibers from the trochlear nucleus of the opposite side. The nerve travels in the lateral wall of the cavernous sinus and then enters the orbit via the superior orbital fissure. It passes medially and diagonally across the levator palpebral superioris and superior rectus muscles to innervate the superior oblique. *(Parent, 531)*

**21.** **(A)** The perihypoglossal nuclei are nuclear masses in close proximity to the hypoglossal nerve. They receive input from the cerebral cortex, vestibular nuclei, accessory oculomotor nuclei, and paramedian pontine reticular formation. The output of these nuclei terminates in the cranial nuclei involved in extraocular movements: the oculomotor nerve, trochlear nerve, and abducens nerve. The output of the perihypoglossal nuclei also terminates in the thalamus and the cerebellum. *(Afifi and Bergman, 88)*

**22.** **(C)** The nucleus ambiguus is the ventral motor nucleus of the vagus. Axons of neurons in this nucleus convey special visceral efferent impulses to the branchiomeric muscles of the pharynx and larynx. It also contributes efferent fibers to the glossopharyngeal and accessory nerves. The dorsal motor nucleus of the vagus is located dorsolateral or lateral to the hypoglossal nucleus. It receives afferent fibers from the vestibular nuclei and conveys efferent preganglionic parasympathetic fibers responsible for general efferent impulses to the viscera in the thorax and abdomen. The nucleus of the spinal tract of the trigeminal nerve receives general somatic afferent fibers from the external ear. The nucleus solitarius receives special visceral afferent fibers that convey taste sensation from the region of the epiglottis. It also receives general visceral afferent fibers that convey pain sensation from the mucosa of the posterior third of the tongue. *(Afifi and Bergman, 90–91)*

**23.** **(B)** The nucleus solitarius, the dorsal motor nucleus of the vagus, and the caudal and rostral ventrolateral medulla comprise the brainstem nuclei involved in cardiovascular control. They receive direct projections from the sensorimotor cortex. The cortical input to these nuclei provides the basis for cortical influences on the baroreceptor reflex and sympathetic vasomotor mechanisms for the control of blood pressure. *(Afifi and Bergman, 92)*

**24.** **(C)** The rostral and lateral zone of the nucleus solitarius is concerned with taste sensation. It receives gustatory sensations via three cranial nerves: the facial nerve conveys taste sensation from the anterior two thirds of the tongue; the glossopharyngeal nerve conveys taste sensation from the posterior third of the tongue; and the vagus nerve conveys taste sensation from the epiglottis. *(Afifi and Bergman, 92)*

**25.** **(B)** The structure indicated by the arrow in Figure 1-3 is the pontine reticular nucleus. Damage to the pontine reticular nuclei in the tegmentum and corticospinal fibers in the basis pontis is associated with anosognosia for hemiplegia, in which patients are unware of their motor deficit. A similar syndrome occurs in damage to the nondominant parietal lobe. *(Afifi and Bergman, 105–106)*

**26.** **(B)** The afferent roots of the trigeminal nerve contains general somatic sensory fibers that convey pain, temperature, and touch sensation from the face and anterior aspect of the head. The neurons of origin of these fibers are situated in the semilunar ganglion (gasserian ganglion). The peripheral processes of neurons in the ganglion are distributed in the three divisions of the trigeminal nerve. The proprioceptive fibers from the deep structures of the face are peripheral processes of unipolar neurons in the mesencephalic nucleus of the trigeminal nerve that travel via afferent and efferent roots of the trigeminal nerve. The proprioceptive fibers in the mesencephalic nucleus convey pressure and and kinesthesia from the teeth, periodontium, hard palate, and joint capsules as well as impulses from stretch receptors in the muscles of mastication. The mesencephalic nucleus of the trigeminal nerve is involved in control of the bite force. The facial nerve conveys taste sensation from the anterior two third of the tongue. The motor nucleus of the trigeminal nerve is

involved in eliciting the jaw reflex. The facial motor nuclei are involved in eliciting the corneal reflex. Collaterals from the secondary ascending trigeminal tracts establish synapses with the facial motor nuclei on both sides, resulting in the bilateral blink reflex and the corneal reflex in response to unilateral corneal stimulation. *(Afifi and Bergman, 115–118)*

**27. (D)** Figure 1-4 is a schematic diagram of the ventral surface of the midbrain and pons.

The structure indicated by the arrow is the trochlear nerve. The nerve fascicles course posteroinferiorly around the aqueduct to decussate in the dorsal midbrain in the anterior medullary velum. After traveling on the undersurface of the tentorial edge, it pierces the dura and travels to the cavernous sinus to reach the superior orbital fissure and innervate the superior oblique muscle. *(Afifi and Bergman, 130; Brazis, Masdeu, and Biller, 185)*

**28. (A)** The mesencephalic nucleus of the trigeminal nerve is homologous in structure to the dorsal root ganglion but is uniquely placed within the central nervous system. It contains unipolar neurons with axons that convey proprioceptive impulses from the muscles of mastication and the periodontal membranes. *(Afifi and Bergman, 132)*

**29. (A)** Figure 1-5 is a schematic diagram of the midbrain at the level of the inferior colliculus. The structure indicated by the arrow is the rubrospinal tract. It conveys fibers from the red nucleus to the spinal cord and inferior olive. *(Afifi and Bergman, 132)*

**30. (B)** The locus ceruleus is located in the rostral pons and caudal mesencephalon. The neurons of the locus ceruleus provide noradrenergic innervations to most central nervous system regions. The substentia nigra has a neuronal population consisting of pigmented and nonpigmented neurons. The neurotransmitter in pigmented neurons is dopamine, whereas nonpigmented neurons are either cholinergic or GABAergic. The dorsal raphe nucleus sends serotonergic fibers to the substantia nigra, caudate, putamen, and neocortex. The red nucleus is a synaptic station in neural systems concerned with movement, linking the cerebral cortex, cerebellum, and spinal cord. The ventral tegmental nucleus is a part of a circuit concerned with emotion and behavior. *(Afifi and Bergman, 133–135, 138)*

**31. (E)** Figure 1-6 is a schematic diagram of the midbrain at the level of the superior colliculus. The structure indicated by the arrow in Figure 1-6 is the red nucleus. It is a prominent part of the tegmentum at the level of the superior colliculus, comprising a caudal magnocellular and a rostral parvocellular part. It is involved in motor coordination. *(Afifi and Bergman, 139)*

**32. (C)** Pupillary size is under the dual control of sympathetic and parasympathetic systems that innervate rings of radially arranged dilator and constrictor fibers, respectively. The resting size of the pupil depends on the intensity of light falling on the retina and the integrity of the parasympathetic nerves. A light stimulus is conveyed from the retina to the optic nerve, optic chiasm, and lateral geniculate body. Ten percent of the afferent fibers subserve the light reflex and are related, in the periaqueductal gray, to both Edinger–Westphal nuclei (which induce papillary constriction) and the consensual light reflex. The parasympathetic fibers are then carried by the third cranial nerve to the ciliary ganglion and to the pupillary constrictor fibers. The sympathetic system starts from the hypothalamus; its fibers pass to the cervicothoracic spinal cord at levels C8 and T1. The second-order neurons pass from the spinal cord to the superior cervical ganglion. The third-order neurons supply the pupillodilator fibers and the blood vessels of the eye, passing over the carotid artery. Any lesion affecting those afferent pathways that include the retina, optic chiasm, optic tract, and particularly the optic nerve will cause a Marcus Gunn pupil. When a light is shined in the normal eye, both pupils constrict (direct and consensual light reflexes). When the light is then swung to the symptomatic eye, less light reaches the oculomotor nucleus because of optic nerve damage. The oculomotor nucleus senses the less intense light and shuts off the parasympathetic response,

resulting in paradoxical pupillary dilatation. Adie's pupil is characterized by widely dilated pupil and a sluggish, prolonged pupillary contraction in reaction to light. It results from pathology of the ciliary ganglion within the orbit. *(Patten, 7–9; Afifi and Bergman, 143–144)*

**33. (D)** A waddling gait is seen with weak hip muscles, particularly the gluteus medius. This results in an excessive drop of the hip and trunk, tilting the pelvis to the side opposite to the foot placement. The hips oscillate up and down with every step, making the patient seem to waddle. Lesion to the anterior lobe of the cerebellum may cause discrete gait impairment. Severe loss of sensation in large muscle fibers may result in a steppage gait. This is characterized by excessive flexion of the hips and knees with every step. With severe sensory loss in the lower extremities, the heel tends to strike the ground heavily. Greater foot clearance is then used to avoid tripping on the toes or on irregularities of the floor or ground that are poorly felt. A steppage gait may be seen in Guillain–Barré syndrome and other demyelinating polyneuropathies. Acute vestibular lesions cause vestibular ataxia. This is characterized by instability and the patient's tendency to veer or even fall to the side of the lesion. Corticospinal tract lesions cause a spastic gait. *(Brazis, Masdeu, and Biller, 20–21)*

**34. (B)** After it passes between the two heads of the pronator teres, the median nerve gives off a purely motor anterior interosseous nerve that innervates the flexor pollicis longus, flexor digitorum profundus I and II, and pronator quadratus. *(Brazis, Masdeu, and Biller, 36)*

**35. (A)** The posterior interosseous nerve is a pure motor branch of the radial nerve. At some point, varying between 3 cm above and a similar distance below the humeroradial joint, the radial nerve divides into a deep motor branch, which is the posterior interosseous nerve, and a superficial sensory branch. The posterior interosseous nerve innervates the following muscles: the supinator, extensor carpi radialis brevis, extensor digitorum, extensor digiti minimi, extensor carpi ulnaris, abductor pollicis longus, extensors pollicis longus and brevis, and extensor indicis. *(Brazis, Masdeu, and Biller, 47; Staal, 35–36)*

**36. (A)** The tensor fascia lata is innervated by the superior gluteal nerve, which also innervates the gluteus medius and gluteus minimis. *(Staal, 113)*

**37. (C)** Although the deep peroneal nerve is mainly a motor nerve, it provides sensory innervation to the skin of the first interosseous space and the adjacent skin of the sides of the first and second toes. *(Brazis, Masdeu, and Biller, 59)*

**38. (C)** The medial wall of the cavernous sinus contains the abducens nerve, the internal carotid artery, and the sympathetic fibers of the carotid plexus. The lateral wall contains the oculomotor and trochlear nerves and the ophthalmic and maxillary divisions of the trigeminal nerve. *(Haines, 136)*

**39. (C)** The trigeminal nerve is a mixed nerve. It subserves the sensory innervation of the ipsilateral side of the face and the ipsilateral muscles of mastication (masseter, temporalis, and pterygoids). The sensory nucleus of the trigeminal nerve extends from the midbrain to the upper cervical cord: (a) The mesencephalic nucleus subserves proprioception and deep sensation from the tendons and muscles of mastication. (b) The main sensory nucleus (located in the pons) subserves light touch. (c) The spinal nucleus (which extends from the pons to the upper cervical cord and is divided into segments that correspond to concentric dermatomes around the mouth) subserves pain and temperature. The trigeminal nerve supplies sensation to the ipsilateral side of the face via three branches: the ophthalmic division (which innervates the frontal, lacrimal, and nasociliary areas), the maxillary division (which innervates the cheek and lower eyelid), and the mandibular division (which innervates the lower lip, tongue, and mandible except for the angle of the mandible). The motor nucleus lies medially to the main sensory nucleus and sends axons to the mandibular division of the trigeminal nerve. All divisions of the trigeminal nerve converge at the gasserian ganglion,

which lies in Meckel's cave of the temporal bone. *(Afifi and Bergman, 117–118)*

**40. (D)** The facial nerve leaves the pons and travels with the vestibulocochlear nerve through the internal auditory canal. *(Parent, 154–168)*

**41. (E)** The nervus intermedius is the sensory and parasympathetic division of the facial nerve. Its preganglionic parasympathetic fibers arise from the superior salivary nucleus and synapse in the pterygopalatine and submandibular nerves, which then send postganglionic fibers to submandibular, sublingual, lacrimal, palatal, and nasal glands. The sensory fibers of the nervus intermedius arrive at the nervus intermedius via the geniculate ganglion. They provide taste sensation to the anterior two thirds of the tongue. *(Afifi and Bergman, 112)*

**42. (A)** The patient described in this vignette has a pure motor deficit. The right pronator quadratus is weak because of paresis of forearm pronation. Also, there is paresis of the flexor digitorum profundus I and II and the flexor pollicis longus because of loss of flexion of the terminal phalanges of the second and third fingers and thumb, respectively. All of these muscles are innervated by an anterior interosseous nerve. The characteristic feature of a lesion of this nerve is the inability to make a circle with the thumb and index finger. *(Staal, 55–56)*

**43. (B)** The gray matter of the spinal cord is divided into the 10 laminae of Rexed, which form a cytoarchitectonic map of the spinal cord that correlates well with synaptic connections and neurophysiological data. Laminae I, II, III, and IV encompass most of the dorsal horn, which receives primary sensory fibers. Lamina I corresponds to the nucleus postmarginalis, lamina II corresponds to the substantia gelatinosa, and laminae III and IV correspond to the nucleus proprius dorsalis. All these nuclei integrate and modulate sensory information. They relay sensory information to higher centers like the cerebellum, thalamus, and brainstem. *(Afifi and Bergman, 49–50)*

**44. (B)** The striatum is the main receiving station for the basal ganglia. It receives massive projections from all areas of the cerebral cortex and from certain thalamic nuclei, the substantia nigra, and other brainstem nuclei. The term *neostriatum* refers to the caudate nucleus and putamen. The caudate nucleus, an elongated gray mass whose pear-shaped head is continuous with the putamen, lies adjacent to the inferior border of the anterior horn of the lateral ventricle. The slender end curves backward and downward as the tail; it enters the roof of the temporal horn of the lateral ventricle and tapers off at the level of the amygdala. The putamen is located lateral to the globus pallidus and medial to the external capsule. It is separated from the caudate nucleus by the internal capsule except rostrally, where the head of the caudate and the putamen are continuous around the anterior limb of the internal capsule. *(Afifi and Bergman, 180–181)*

**45. (C)** In the direct loop, cortical fibers project to the striatum, and striatal efferent neurons project to the internal globus pallidus and the substantia nigra pars reticulata. Efferents from the internal globus pallidus and the substantia nigra pars reticulata project to the dorsal thalamus, and the thalamic neurons project to specific areas of the cerebral cortex. Both the glutaminergic corticostriate projections and the thalamocortical projections are excitatory. However, the efferents from the striatum to the internal globus pallidus and the substantia nigra pars reticulata, as well as their projections to the thalamus, are all GABAergic inhibitory. The glutaminergic corticostriate fibers excite a select population of striatal efferent neurons that project to the internal globus pallidus and the substantia nigra pars reticulata. These striatal efferents, using GABA and substance P as a neurotransmitter, inhibit the spontaneous firing of the internal globus pallidus and substantia nigra pars reticulata efferents to the thalamus. These latter projections inhibit cortical relay neurons in the dorsal thalamus. Inhibition of these inhibitory neurons in the internal globus pallidus and substantia nigra pars reticulata leads to a disinhibition of the thalamocortical projections and an increase in cortical activity. *(Afifi and Bergman, 185–188; Brazis, Masdeu, and Biller, 421–424)*

**46.** **(A)** In the indirect loop, linking the cerebral cortex to the basal ganglia, cortical fibers project to the striatum, and striatal efferent neurons project to the external globus pallidus. Efferents from the external part of the globus pallidus project to the subthalamic nucleus. Neurons in the subthalamic nucleus project to both the internal globus pallidus and the substantia nigra pars reticulata. The internal globus pallidus and the substantia nigra pars reticulata project to the dorsal thalamus. The dorsal thalamus projects to the cerebral cortex. The glutaminergic corticostriate fibers excite a specific population of striatal efferent neurons that project to the external globus pallidus. These striatal efferent neurons are GABAergic, with enkephalin as a cotransmitter. They inhibit neurons on the external globus pallidus. The external globus pallidus's projection to the subthalamic nucleus has a high rate of spontaneous firing and is inhibitory. Neurons of the subthalamic nucleus are excitatory and glutaminergic; they project to both the internal globus pallidus and the substantia nigra pars reticulata. Because of the high spontaneous firing rate of the inhibitory neurons in the external globus pallidus, the excitatory effects of the subthalamic nucleus on neurons in the internal globus pallidus and substantia nigra pars reticulata are normally minimal. However, when the activity of the indirect loop increases, there is a disinhibition of the subthalamic nucleus. The increased rate of firing of the subthalamic nucleus's neurons in the internal globus pallidus and substantia nigra pars reticulata results in inhibition of the thalamic relay neurons. A corresponding decrease in the level of cortical activity occurs. *(Afifi and Bergman, 185–188; Brazis, Masdeu, and Biller, 421–424)*

**47.** **(A)** The cerebellum communicates with the brainstem through three pairs of massed projection fibers called cerebellar peduncles: the superior cerebellar peduncle, the middle cerebellar peduncle, and the inferior cerebellar peduncle. The superior cerebellar peduncle contains most of the cerebellar efferent fibers and all those arising from the dentate nucleus, the emboliform nucleus, and the globose nucleus. In addition, the superior cerebellar peduncle contains one cerebellar afferent pathway, the ventral spinocerebellar tract, which carries proprioceptive information to the cerebellum from the lower extremities and trunk. *(Burt, 352)*

**48.** **(B)** Cerebellar nuclei are the principal source of efferent fibers from the cerebellum projecting to the dorsal thalamus, vestibular nuclei, red nucleus, and other brainstem nuclei. The dentate nucleus receives projections from Purkinje cells in the cerebrocerebellum and collaterals from some of the pontocerebellar fibers. Fibers from the dentate nucleus enter the brachium conjunctivum in the superior cerebellar peduncle, cross at the level of the inferior colliculus, and terminate in the contralateral ventral nucleus of the thalamus. *(Burt, 352–354)*

**49.** **(B)** The cerebellar cortex contains three laminated cellular layers: the outermost molecular cell layer, a sheet of single large neurons, the Purkinje cell layer, and a deeper granular cell layer. These layers contain six types of neurons: basket, satellite, Purkinje, Golgi, granule cells, and the relatively rare Legato cells. Pyramidal cells are the most abundant cells of the cerebral cortex neuron types, are not found in the cerebellum, and are the most characteristic of the cerebral cortex. *(Afifi and Bergman, 203; Burt, 354)*

**50.** **(B)** The monoaminergic projections to the cerebellum originate from the pontine raphe nuclei, the locus ceruleus, and the hypothalamus. The raphe nuclei are the source of serotoninergic projections to both the granular and molecular layers. The locus ceruleus is the source of noradrenergic projection to the three layers of the cerebellar cortex. The dorsomedial, dorsal, and lateral areas of the hypothalamus are the sources of histaminergic projections to all three layers of the cerebellar cortex. *(Afifi and Bergman, 214–215)*

**51.** **(E)** The emboliform nucleus receives projections from the Purkinje cells in the spinocerebellum and collaterals from the fibers entering the restiform body and ventral spinocerebellar tract. Fibers from the emboliform nucleus enter

the brachium conjunctivum, decussate to the contralateral side, and terminate in both the contralateral ventral nucleus of the thalamus and the red nucleus. *(Burt, 352–354)*

**52. (A)** The learning of complex motor tasks requires modifying motor responses or sequences in order to adapt the responses to a new situation or changes in the surrounding conditions. A major component of this learning ability resides in the cerebellum and in the olivocerebellar climbing fiber system. Selective damage to this system results in loss of the ability to modify a motor response and the ability to maintain or store a modified response. *(Burt, 363)*

**53. (C)** The fastigial nucleus receives axons of the Purkinje cells in the vestibulocerebellum. It projects primarily to the lateral and inferior vestibular nuclei and to the pontine and medullary reticular formation. *(Burt, 352–354)*

**54. (A)** The tuberoinfundibular tract is an efferent hypothalamic pathway. It arises from the arcuate and periventricular nuclei. Axons from these neurons extend into the infundibular stalk of the neurohypophysis, where they end. *(Afifi and Bergman, 271)*

**55. (C)** Climbing fibers are axons of neurons originating from the contralateral inferior olivary nucleus that project to all areas of the cerebellar cortex. Climbing fibers are excitatory. Aspartate is the most likely transmitter for these fibers. Each single climbing fiber establishes 1,000 to 2,000 synaptic contacts with its Purkinje cell. When the climbing fibers fire, there is a massive synchronous depolarization of Purkinje cells, which activates $Ca^{2+}$ channels in the dendritic membrane. The major source of climbing fibers in the cerebellum is the inferior olive. Degeneration of the inferior olive (as seen in olivocerebellar atrophy) induces a drop in aspartate level in the cerebrospinal fluid. *(Afifi and Bergman, 211; Burt 359)*

**56. (A)** Purkinje cells are the largest cells in the central nervous system. Their cell bodies form a single cell layer. Their axons project primarily to the cerebellar nuclei, although a few exit the cerebellum and terminate directly in the vestibular nuclei. The Purkinje cell axon is the primary route for information leaving the cerebellar cortex. Each Purkinje cell axon courses through the granule cell layer and deep white matter to project onto deep cerebellar nuclei. However, some Purkinje cell axons from the vermis bypass the deep cerebellar nuclei to reach the lateral vestibular nucleus. Mossy fibers, climbing fibers, parallel fibers, and monoaminergic fibers are afferent projections to the cerebellum. Golgi cells are inhibitory interneurons in which the cell axons branch profusely in the granular layer and synapse with dendrites of a large number of granule cells, forming a negative feedback loop. *(Burt, 450–451)*

**57. (A)** The hypothalamus plays a major role in regulating eating behavior. The ventromedial nucleus is located in the tuberal region of the hypothalamus. Animal studies have demonstrated that bilateral lesions of the ventromedial nuclei of the hypothalamus cause hyperphagia, obesity, and savage behavior, whereas lesions of the lateral hypothalamus produce loss of appetite. The supraoptic nucleus belongs to the suprachiasmatic region and is located above the optic tract. With the paraventricular nucleus, the supraoptic nucleus is responsible for the secretion of vasopressin and oxytocin. Lesions of the paraventricular nucleus or the supraoptic nucleus cause diabetes insipidus. The anterior nucleus is located in the suprachiasmatic region. Stimulation of this nucleus may cause excessive water intake. The arcuate nucleus is located in the tuberal region. This nucleus contains dopamine, which is responsible for the control of prolactin and the secretion of growth hormone. The mammillary nucleus plays a role in memory. *(Afifi and Bergman, 274)*

**58. (A)** General somatic efferent fibers of the oculomotor nerve arise from the oculomotor nucleus, situated near the midline of the midbrain at the level of the superior colliculus. This nucleus is formed by subnuclei for each of the extraocular muscles. The superior rectus

muscle receives innervation from neurons in the contralateral subnucleus. The levator palpebral superioris muscle receives innervation from a medial subnucleus. The inferior rectus, medial rectus, and inferior oblique muscles receive innervation from ipsilateral subnuclei. *(Burt, 403–406)*

**59. (D)** General somatic efferents provide the motor innervation of somatic structures developed from the embryonic ectoderm and somatic mesoderm. The oculomotor nucleus provides general somatic efferent innervation to all extraocular muscles except the lateral rectus (which is innervated by the abducens nerve) and the superior oblique (which is innervated by the trochlear nerve). The hypoglossal nucleus provides general somatic efferents to the tongue musculature. The facial motor nucleus provides special visceral efferents to the muscles of facial expression and the stapedius muscle. *(Burt, 404)*

**60. (C)** The glossopharyngeal nerve provides parasympathetic innervation to the parotid gland via the otic ganglion. *(Afifi and Bergman, 91–92)*

**61. (B)** The trigeminal nerve has three sensory nuclei: the spinal nucleus, main sensory nucleus, and mesencephalic nucleus. The spinal nucleus of the trigeminal nerve is a long column of neurons extending from the point of entry of the trigeminal nerve to the upper cervical spinal cord. It is divided into three parts: the oral part, responsible for tactile sensation from the oral mucosa; the interpolar part, receiving afferents for dental pain; and the caudal part, receiving pain and temperature sensations from the face. Most of the small afferent fibers of the spinal tract of the trigeminal nerve terminate in the spinal nucleus. Most of the afferent large fibers that originate from the trigeminal ganglion end in the main sensory nucleus and are responsible for the transmission of discriminative touch. The mesencephalic nucleus is located at the rostral pons. It receives afferent fibers conveying kinesthesia and pressure from the teeth, periodontium, hard palate, joint capsules, and stretch receptors from the muscles of mastication. It sends efferent fibers to the cerebellum, thalamus, motor nuclei of the brainstem, and reticular formation. The motor nucleus of the trigeminal nerve provides somatic visceral efferents that innervate the muscles of mastication via the mandibular division and contains $\alpha$ and $\gamma$ motor neurons. *(Afifi and Bergman, 117–118)*

**62. (C)** Purkinje cells are found in the cerebellum. They constitute the sole output neurons of the cerebellar cortex. Their cell bodies are arranged in a single sheet at the border zone between the molecular and the granule cell layers. Their axons project primarily to cerebellar nuclei, although some axons from the vermis bypass the deep cerebellar nuclei to reach the vestibular nuclei directly. *(Afifi and Bergman, 203–204)*

**63. (D)** The cerebral neocortex has a laminar pattern of organization because of the distribution and size of neuronal cells and the horizontal pattern of incoming afferents. It is divided into six layers: Layer I, primarily a synaptic area, is the molecular layer. It is the most superficial layer of the cerebral cortex; its most characteristic cells are horizontal cells. Layer II, the external granular layer, is characterized by an abundance of small, densely packed neurons and a paucity of myelinated fibers. The dendrites of neurons in this layer project to layer I, while their axons project to deeper layers. Layer III, the external pyramidal layer, contains medium-to-large pyramidal cells and granule cells. Axons of most pyramidal cells descend through the cortex, forming cortical association fibers, both callosal and intrahemispheric. Layer IV, the internal granular layer, is the principal receiving station of the cerebral cortex. Layer V, the internal pyramidal layer, is the principal efferent layer of the cortex. This layer contains pyramidal cells that send their axons through the cortical white matter to the internal capsule and all subcortical sites except the thalamus, which receives fibers from layer VI. Layer VI, the fusiform layer, contains fusiform and pyramidal cells, which are the principal source of corticothalamic fibers and contribute to the intrahemispheric cortical association fibers. *(Afifi and Bergman, 230–232; Burt, 451–452)*

**64. (D)** Layer IV of the cerebral cortex, the internal granular layer, is the principal receiving station of the cortex. The input from the

modality-specific thalamic nuclei projects mainly onto neurons in lamina IV, with some projections on laminae III and IV. The nonspecific thalamocortical input originating from nonspecific thalamic nuclei projects diffusely on all laminae and establishes mostly axodendritic types of synapses. *(Afifi and Bergman, 230–232; Burt, 451–452)*

**65. (D)** There are at least six neurochemically distinct extrathalamic projection systems that reach the cerebrum monosynaptically, without a relay in the thalamus: three arise from the brainstem reticular formation, two from the hypothalamus, and one from the basal forebrain. The first system arises from the locus ceruleus of the pontine reticular formation, using norepinephrine. The second system arises from the midbrain raphe nuclei, using serotonin. The third system arises from the ventral midbrain, using dopamine. The fourth and fifth systems arise from two hypothalamic nuclei, using histamine and GABA, respectively, as neurotransmitters. From the nucleus basalis, located in the basal forebrain, arises a cholinergic extrathalamic modulatory system. The basal forebrain contains four populations of cholinergic neurons with projection to the cerebral cortex, with the nucleus basalis of Meynert as the principal source of cholinergic neurons. *(Burt, 459–463)*

**66. (B)** Damage to the right posterior parietal lobe causes neglect of the left side of the body. This neglect may have several dimensions: sensory, motor, cognitive, and attentional. In addition to the primary auditory function, the whole temporal cortex is involved in associative function. Temporal lobe damage may lead to difficulties in the performance of visually cued tasks requiring a high degree of visual discrimination. Temporal lobe lesions may also cause prosopagnosia, an inability to recognize familiar faces. This disorder is caused by impairment of some of the pathways responsible for visual processing. The patient is still able to recognize family and friends from the sound of their voices. Lesions of the prefrontal association cortex may cause problem-solving and emotional deficits. A problem-solving deficit is characterized by the inability of the patient to make an informed decision. The emotional deficit is characterized by bizarre and socially unacceptable behavior. The patient has a labile and unpredictable emotional status. *(Burt, 466–468)*

**67. (D)** The lateral geniculate body receives a dual arterial supply: from the anterior choroidal artery laterally and the lateral posterior choroidal artery medially. *(Brazis, Masdeu, and Biller, 140)*

**68. (D)** The orbicularis oculi controls eye closure and is innervated by the facial nerve. Eye opening is controlled by the levator of the lid, which is innervated by the oculomotor nerve. *(Brazis, Masdeu, and Biller, 287–290)*

**69. (D)** The nervus intermedius is the sensory and parasympathetic division of the facial nerve. It carries preganglionic parasympathetic fibers to the submaxillary ganglion and to the pterygopalatine ganglion. It receives sensory fibers from the geniculate ganglion. This ganglion receives fibers that carry taste sensation from the anterior two thirds of the tongue and afferents from the mucosae of the pharynx, nose, and palate. *(Afifi and Bergman, 112)*

**70. (D)** The intracranial portion of the facial nerve is supplied by the anteroinferior cerebellar artery. The intrapetrosal portion is supplied by the superficial branch of the middle meningeal artery and the stylomastoid branch of the posterior auricular artery. The extracranial part of the facial nerve is supplied by the stylomastoid, posterior auricular, superficial temporal, and transverse facial arteries. *(Brazis, Masdeu, and Biller, 290)*

**71. (C)** The first-order neurons of the auditory pathway have their cell bodies in the spinal ganglion of the cochlear nerve and enter the brainstem at the level of the ventral cochlear nuclei as the cochlear nerve. The second-order neurons arise from the ventral and dorsal cochlear nuclei and send several projections to the contralateral brainstem; these ascend as the lateral lemniscus. Fibers in the lateral lemniscus project on the nucleus of the lateral lemniscus

and then to the inferior colliculus. The inferior colliculus contains the third-order neurons of the auditory pathway. These neurons project to the medial geniculate body. Geniculotemporal fibers, the fourth-order neurons of the auditory pathway, project to the primary auditory cortex. *(Brazis, Masdeu, and Biller, 307–310)*

**72. (C)** The glossopharyngeal nerves travel through the jugular foramen with the vagus nerve and the bulbar fibers of the spinal accessory nerve. *(Burt, 420–423)*

**73. (A)** Glomus jugulare tumors or basal skull fractures may cause jugular foramen syndrome. The glossopharyngeal, vagus, and spinal accessory nerves may be injured in this syndrome. Clinical signs include ipsilateral trapezius and sternocleidomastoid weakness, dysphonia, dysphagia, depressed gag reflex, ipsilateral loss of taste in the ipsilateral posterior third of the tongue, ipsilateral vocal cord paresis, and anesthesia of the posterior third of the tongue. There is no tongue deviation, since the twelfth cranial nerve is not affected. *(Brazis, Masdeu, and Biller, 327)*

**74. (B)** Paramedian and circumferential vessels supply the midbrain. The paramedian vessels arise from the posterior cerebral arteries and include the thalamoperforating and peduncular arteries, which supply the medial peduncles and midbrain tegmentum. The circumferential arteries include the quadrigeminal arteries (which supply the superior and inferior colliculi), the superior cerebellar arteries (which supply the cerebral peduncles and brachium conjunctivum), and the posterior and anterior choroidal arteries. *(Brazis, Masdeu, and Biller, 361)*

**75. (C)** $Na^+$ and $K^+$ channel localization and clustering are essential for proper electrical signal generation and transmission in central nervous system's myelinated nerve fibers. In particular, $Na^+$ channels are clustered at high density at nodes of Ranvier, and Shaker-type $K^+$ channels are sequestered in juxtaparanodal zones, just beyond the paranodal axoglial junctions. There is strong evidence that Schwann cells initiate sodium channel clustering in the peripheral nervous system just after the latter become committed to myelination. In the peripheral nervous system, conduction is invariably blocked when the myelin is stripped from the entire internode, but it can be restored by only minimal glial ensheathment. This restoration of conduction is likely related to the early sodium channel clustering that accompanies initial steps in remyelination. As myelination proceeds, $Na^+$ channels are initially found in broad zones within gaps between neighboring oligodendroglial processes and then are condensed into focal clusters. This process appears to depend on the formation of axoglial junctions. It has been suggested that juxtaparanodal potassium channels may serve to inhibit repetitive activation of nodal sodium channels. Sodium channel expression is increased in demyelinated lesions in multiple sclerosis. *(Rasband and Shrager, 63–73)*

**76. (A)** The myelin sheaths of the central and peripheral nervous system contain distinct sets of proteins. In the peripheral nervous system, the noncompact myelin contains E-cadherin, myelin-associated glycoprotein (MAG), and connexin 32 (C×32). The compact myelin in the peripheral nervous system contains protein 0 (P0), peripheral myelin protein 22 (PMP22), and myelin basic protein (MBP). In the central nervous system, the compact myelin contains proteolipid protein (PLP), oligodendrocyte-specific protein (OSP), myelin-oligodendrocyte basic protein, and myelin basic protein. *(Arroyo and Scherer, 1–18)*

**77. (A)** Myelination in the central nervous system differs from that in the peripheral nervous system in several ways. Oligodendrocytes are responsible for myelination in the central nervous system, whereas Schwann cells are responsible for myelination in the peripheral nervous system. Both oligodendrocytes and Schwann cells ensheathe multiple axons; however, each Schwann cell is responsible for the myelination of only one axon. Each oligodendrocyte makes multiple myelin sheaths. The number varies from tract to tract and appears to relate to the caliber of the axons. Oligodendrocytes make fewer sheaths in tracts containing large

myelinated fibers; this is the result of axooligodendrocyte interactions rather than an intrinsic trait of the oligodendrocytes themselves. Oligodendrocytes do not have a basal lamina or microvilli, and their incisures do not have distinguishing molecular markers such as connexin 32 (C×32), myelin-associated glycoprotein (MAG), or E-cadherin. The molecular components of the central nervous system myelin sheaths partially overlap with those of the peripheral nervous system. Both contain high amounts of lipids, especially cholesterol and sphingolipids, including galactocerebroside and sulfatide. Similarly, in both the central nervous system and the peripheral nervous system, compact myelin contains myelin basic protein (MBP), and the adaxonal surface contains MAG. Like myelinating Schwann cells, oligodendrocytes also express C×32, but mainly on their cell bodies and proximal processes. Oligodendrocytes express two proteins that are not expressed by Schwann cells: myelin-oligodendrocyte glycoprotein (MOG) on their outer cell membrane and myelin-oligodendrocyte basic protein (MOBP) in the major dense line of compact myelin. *(Arroyo and Scherer, 1–18)*

**78.** **(A)** All glial cells express class I MHC, but only astrocytes and microglia express class II MHC. All glial cells express adhesion molecules and synthesize cytokines. Both astrocytes and microglial cells express costimulatory molecules (B7) and complement components. They may act as antigen-presenting cells. *(Antel, Birnbaum, and Hartung, 29–31)*

**79.** **(B)** The plasma membrane of a nerve controls ion transport, so that sodium and chloride are more concentrated outside the cell than inside it, whereas potassium and organic anions are relatively more concentrated inside the cell. The interior of the cell ends up with a relative excess of negative charges, so a voltage difference exists across the cell membrane. This voltage difference is called the resting potential; in a typical neuron it has a value of about −70 mV. *(Dumitru, 8)*

**80.** **(A)** Sensory axons are grouped on the basis of their diameters and myelin thickness into groups I, II, III, and IV. The thicker the diameter of the axon and its myelin, the faster the conduction velocity. Class I axons are large and heavily myelinated. Classes II and III are progressively smaller and less myelinated. Class IV axons are smallest and unmyelinated. Class I is divided into subclasses Ia and Ib; the faster Ia fibers supply muscle spindles and the slower Ib fibers supply Golgi tendon organs. *(Dumitru, 17)*

**81.** **(E)** Neurulation is brought about by morphological changes in the neuroblasts, the immature and dividing future neurons. Microfilaments in each cell form a circular bundle parallel to the future laminar surface, whereas microtubules extend along the length of the cell. Colchicine may stop neurulation by inhibiting microfilament-based contraction or by depolymerizing microtubules. *(Haines, 72)*

**82.** **(D)** Secondary neurulation induces the formation of the neural canal, which is open to the amniotic cavity both rostrally and caudally. In the rostral opening, the anterior neuropore closes at about 24 days; in the caudal opening, the posterior neuropore closes about 2 days later. *(Haines, 73–74)*

**83.** **(A)** Congenital malformations associated with defective neurulation are called dysraphic defects. There is an intimate relationship between the neural tissue and the surrounding bone, meninges, muscle, and skin. They are interdependent via inductive factors, so failure of neurulation also impairs the formation of these surrounding structures. Most dysraphic disorders occur at either the anterior or posterior neuropores. Failure of the anterior neuropore to close causes anencephaly. In this disorder, the brain is not formed, the surrounding meninges and skull may be absent, and there may be associated facial abnormalities. Failure in the closure of the posterior neuropore causes a range of malformations known collectively as myeloschisis. These defects always involve a failure of the vertebral arches at the affected levels to form completely and fuse to cover the spinal cord. This defect is called spina bifida. Spina bifida may be accompanied by a saccular structure that contains only meninges and

cerebrospinal fluid. This defect is called a meningocele. If the saccular structure contains meninges, cerebrospinal fluid, and spinal neural tissue, it is called a meningomyelocele. Myelodysplasia is a malformation of the neural tube during secondary neurulation, such as a tethered cord syndrome, in which the conus medullaris and filum terminale are abnormally fixed to a defective vertebral column. *(Haines, 72)*

**84. (B)** Prosencephalization is the process whereby the forebrain vesicle differentiates into diencephalon and telencephalon. Failure of this process results in a holoprosencephaly. *(Haines, 74)*

**85. (A)** The process of forebrain development into diencephalon and telencephalon is referred to as central induction and occurs mainly in the second month of gestation. The adult telencephalon derivatives include the cerebral cortex, the subcortical white matter (including the internal capsule), the olfactory bulb and tract, the basal ganglia, the amygdala, and the hippocampus. *(Haines, 74)*

**86. (E)** The diencephalon develops into the thalamic nuclei and associated structures. The ventricular system is an elaboration of the lumen of the cephalic portions of the neural tube. The cavities of the telencephalon become the lateral ventricles, the diencephalic cavity becomes the third ventricle, the rhombencephalic cavity becomes the fourth ventricle, and the mesencephalic cavity becomes the narrow cerebral aqueduct of Sylvius. The cerebral cortex and the olfactory bulb are derivatives of the telencephalon. *(Haines, 74)*

**87. (A)** Defects in the closure of the posterior neuropore cause a range of malformations known collectively as myeloschisis. The defect always involves a failure of the vertebral arch at the affected levels to form completely and fuse to cover the spinal cord. If the skin covering the defect is closed, the malformation is called spina bifida occulta. If the skin over the vertebral defect is not closed, leaving a a patent aperture, the malformation is called spina bifida aperta. *(Haines, 72–73)*

**88. (C)** Neuroblasts arise from the ventricular surface of the developing brain, which is the luminal surface of the neural tube. *(Haines, 81)*

**89. (A)** In the brainstem, the dorsal portion of the neural tube rotates dorsolaterally as the developing cerebellum invades it. The central canal of the mesencephalon invaginates into the fourth ventricle. This results in a lateral-to-medial orientation of the sensory area, which is the alar plate, versus the motor area of the developing brainstem, which is the basal plate. The basal plates in the brainstem give rise to cranial nerve motor nuclei, whereas the alar plates give rise to cranial nerve sensory nuclei. *(Haines, 81–82)*

**90. (A)** The mammillary body is located in the posterolateral part of the hypothalamus. The mammillary body receives afferents from the mediotemporal lobe through the fornix, from the midbrain tegmental nuclei through the mammillary peduncle, and from the septal nuclei through the medial forebrain bundle. *(Burt, 384–386)*

**91. (D)** The thalamus is the largest component of the diencephalon. It is divided by a band of myelinated fibers, the internal medullary lamina, into the rostrocaudal and the mediolateral group of nuclei. The anterior nucleus of the thalamus consists of a large principal nucleus and two smaller nuclei. The cells of this nucleus receive dense limbic-related projections from the mammillary nuclei via the mammillothalamic tract and the medial temporal lobe via the fornix. The output of this nucleus is primary directed to the cingulated gyrus through the anterior limb of the internal capsule. *(Haines, 233; Martin, 40)*

**92. (A)** The dorsomedial nucleus of the thalamus is formed by a dorsomedial magnocellular division, a dorsolateral parvicellular division, and a paralaminar division. It has a reciprocal connection with the prefrontal cortex via the anterior thalamic peduncle and with the frontal eye fields. It also receives inputs from the temporal neocortex, amygdaloid nucleus, substantia nigra pars reticulare, and adjacent thalamic

nuclei, particularly the lateral and intralaminar groups. The dorsomedial nucleus plays a role in control of eye movement, affective behavior, decision making and judgment, memory, and the integration of somatic and visceral activity. *(Haines, 233; Afifi and Bergman, 158–159)*

**93. (B)** The medial geniculate body carries auditory information from the brachium of the inferior colliculus and sends efferents to the transverse temporal gyrus of Heschl. The lateral geniculate body is a relay station for the visual pathway, which receives afferents from the retinal ganglion cells; these are the axons that form the optic tract and from which the axons that project to the calcarine cortex through the optic radiation originate. *(Brazis, Masdeu, and Biller, 399–401)*

**94. (B)** The process of infolding of the neural tube from the neural plate is called primary neurulation. Secondary neurulation occurs in the caudalmost portion of the neural tube, which will give rise to sacral and coccygeal levels of the cord. Congenital malformations associated with defective neurulation are called dysraphic defects. Most of them occur at the location of the anterior or posterior neuropore. Failure of the anterior neuropore to close results in anencephaly. In this defect, the brain is not formed and the surrounding meninges and skull may be absent. *(Haines, 72)*

**95. (A)** *Myelodysplasia* refers to malformations of the part of the neural tube formed by secondary neurulation. A common malformation of sacral and coccygeal levels of the cord is tethered cord syndrome, in which the conus medullaris and filum terminale are abnormally fixed to the defective vertebral column. The sustained traction damages the cord, with subsequent loss of sensations from the legs and feet and problems with bladder control. Congenital hydrocephalus is caused by a prenatal obstruction of the cerebral aqueduct. Patients with the Dandy–Walker malformation have enlarged ventricles, including cystic dilatation of the fourth ventricle accompanied by a variable degree of cerebellar vermis aplasia. Anencephaly is caused by failure of the anterior neuropore to close. Prosencephaly results from failure of the prosencephalon to undergo cleavage and differentiate into the diencephalic and telencephalic vesicles. *(Haines, 74–76)*

**96. (B)** Heterotopia is a defect in migration of immature neurons from the ventricular surface to the cerebral cortex. This defect causes mature neurons to appear in the intermediate zones. The degree of disruption varies from mild microscopic clusters of neurons in the white matter and deeper cortical layers to large macroscopic clusters of neurons that can be seen grossly and on neuroimaging. *(Haines, 84)*

**97. (D)** In addition to containing the glossopharyngeal nerve, the vagus nerve, and the spinal accessory nerve, the jugular foramen also serves as a conduit for other important structures. The jugular foramen may be subdivided into three compartments, each with its own contents: The anterior compartment transmits the inferior petrosal sinus. The intermediate compartment transmits the glossopharyngeal, vagus, and accessory nerves. The posterior compartment transmits the sigmoid sinus and some meningeal branches from the occipital and ascending pharyngeal arteries. *(Haines, 217–218)*

**98. (C)** The thalamic arteries arise from the posterior communicating arteries and the perimesencephalic segment of the posterior cerebral arteries. The polar arteries arise from the posterior communicating arteries and supply the reticular, ventral, and medial anterior nuclei. The posteromedian and posterolateral choroidal arteries as well as the thalamogeniculate and thalamomesencephalic arteries originate from the posterior cerebral artery and are responsible for the vascular supply of the thalamus. *(Afifi, 166)*

**99. (D)** The Papez circuit is a closed circuit starting and ending in the hippocampus. It is thought to play a role in emotional reactions. The circuit consists of outflow of impulses from the hippocampus, fornix, mammillary body, mammillothalamic tract, anterior and dorsomedial thalamic nuclei, cingulate gyrus, and cingulum. *(Haines, 505–506)*

**100.** **(A)** The ventral posterolateral and the ventral posteromedian nuclei of the thalamus receive somatosensory input from the contralateral side of the body. The medial lemniscus and the spinothalamic fibers terminate in a somatosensory manner (cervical fibers medial, sacral fibers lateral) within the ventral posterolateral nucleus of the thalamus, whereas the trigeminothalamic fibers from the spinal trigeminal nucleus and the principal trigeminal sensory nucleus terminate in the ventral posteromedian nucleus of the thalamus. Both the ventral posteromedian and the ventral posterolateral nuclei of the thalamus project to the somatosensory cortex of the parietal lobe. *(Haines, 234–235)*

**101.** **(D)** The preoptic nucleus of the thalamus is involved in the control of body temperature and the heat loss mechanism. Nuclei of the chiasmatic region are generally involved in regulating hormone release (preoptic, supraoptic, and periventricular nuclei), cardiovascular function (anterior), and circadian rhythms (suprachiasmatic). The ventromedial nucleus of the thalamus is regarded as the satiety center governing food intake. *(Haines, 238–239)*

**102.** **(A)** Brodmann area 6 is part of the frontal cortex in the human brain. The current best evidence in humans supports the view that the frontal eye field is primarily in Brodmann area 6. Situated just anterior to the primary motor cortex, it is composed of the premotor cortex and, medially the supplementary motor area. Brodmann area 6 projects nuclei in the midbrain and pons that, in turn, project into the oculomotor, trochlear, and abducens nuclei controlling eye movement. *(Haines, 248)*

**103.** **(D)** The anterior spinal artery supplies the medial lemniscus in the medulla; penetrating branches of the basilar artery supply in the pons. *(Haines, 269)*

**104.** **(B)** The ventral posterior nucleus is composed of the laterally located ventral posterolateral nucleus and the medially located ventral posteromedial nucleus. These two nuclei are separated from each other by fibers of the arcuate lamina. The ventral posterolateral nucleus receives ascending input from the medial lemniscus, whereas the ventral posteromedial nucleus receives input from the trigeminothalamic tract. The ventral posterolateral nucleus has two populations of identified neurons. The first population consists of large-diameter multipolar cells that give rise to axons traversing the posterior limb of internal capsule and terminate mainly in the primary and secondary somatosensory cortices. These thalamocortical cells and fibers send excitatory glutaminergic input to the cortex. The second population consists of inhibitory GABAergic local circuit interneurons. *(Haines, 270)*

**105.** **(A)** Most of the somatosensory information from craniofacial structures, including the oral and nasal cavities, is transmitted to the brainstem over the trigeminal nerve. The cell bodies of the trigeminal primary afferent neurons are located in the trigeminal semilunar (gasserian) ganglion and in the mesencephalic trigeminal nucleus. The central processes of trigeminal ganglion cells form the large sensory root of the trigeminal nerve as they enter the lateral aspect of the pons. Within the brainstem, central processes of most trigeminal ganglion cells bifurcate into ascending and descending branches before terminating on second-order neurons in the brainstem trigeminal sensory nuclei. *(Haines, 270)*

**106.** **(D)** The central target of nocieptive primary afferent fibers includes laminae I, II, and V of the posterior horn. Rexed lamina I, the posteromarginal nucleus, receives mainly input from Aδ fibers. Neurons in this nucleus project to other spinal cord laminae, the brainstem reticular formation, and the thalamus. Lamina V neurons receive both noxiouis and nonnoxious input and project to the medullary and mesencephalic reticular formation, the thalamus, and the hypothalamus. *(Haines, 286)*

**107.** **(B)** Information originating from nociceptors is conducted almost exclusively by sympathetic nerves. In contrast, input originating from physiological receptors travels primarily in parasympathetic nerves. Most sympathetic

afferent fibers are either unmyelinated or thinly myelinated and therefore are slowly conducting fibers. Cell bodies of origin of sympathetic fibers are located in the posterior root ganglia at about levels T1 to L2 The central processes of these fibers enter the spinal cord via the lateral division of the posterior root. They may ascend or descend one or two spinal levels in the posterolateral fasciculus before termining in laminae I and V and/or laminae VII and VIII. *(Haines, 304)*

**108.** **(B)** The posteroinferior cerebellar artery originates from the vertebral artery and supplies the posterolateral medulla, including the restiform body, the choroid plexus of the fourth ventricle, and the caudomedial regions of the inferior cerebellar surface, including the vermis. *(Haines, 435)*

**109.** **(C)** The afferent fibers to the cerebellar cortex are grouped into three types: the climbing fibers, the mossy fibers, and multilayered fibers. The cerebellar afferent axons that end as mossy fibers originate from cell bodies in the cerebellar nuclei and from other nuclei of the spinal cord and the brainstem. In the cerebellar granular layer, mossy fibers synapse with the granule cells to form the mossy fibers rosettes. Mossy fibers utilize gluconate as their neurotransmitter and are excitatory to the granule layer cells. *(Haines, 439–440)*

**110.** **(B)** The inferior olivary nuclei are the only source of cerebellar afferent axons that end as climbing fibers in the cerebellar cortex. Climbing fibers are afferent cerebellar fibers that terminate in the molecular layer to synapse with the dendritic trees of Purkinje cells. Each Purkinje cell is innervated by a single climbing fiber, but olivocerebellar axons may branch to serve several Purkinje cells. Climbing fibers use aspartate as a neurotransmitter and excite Purkinje cells and cerebellar nuclear neurons. *(Haines, 440)*

**111.** **(D)** The visceral motor component of the oculomotor nerve arises from the Edinger–Westphal nucleus. These preganglionic fibers terminate in the ciliary ganglion. Postganglionic axons innervate the sphincter muscle of the iris and the ciliary muscle. *(Haines, 480)*

**112.** **(E)** The preganglionic parasympathetic fibers of the facial nerve originate in the superior salivary nucleus. They exit the brainstem in the intermediate nerve. Some of these fibers course via the greater petrosal nerve to terminate in the pterygopalatine ganglion, which supplies the lacrimal gland and nasal and palatal mucous glands. Other preganglionic fibers travel via the chorda tympani to the submandibular ganglion, which innervates the submandibular and sublingual salivary glands. *(Haines, 480)*

**113.** **(A)** The anterior nuclear group of the thalamus consists of two nuclei: principal anterior and anterodorsal. The anterior nuclear group of the thalamus has reciprocal connections with the mammillary body and the cingulate gyrus. It also receives a significant input from the hippocampal formation of the cerebral cortex via the fornix. *(Afifi and Bergman, 158)*

**114.** **(B)** The dorsomedial nucleus of the thalamus develops in parallel with the prefrontal cortex and is reciprocally connected with it via the anterior thalamic peduncle and the frontal eye fields. It also receives input from the temporal neocortex, amygdaloid nucleus and substantia nigra pars reticulate, and adjacent thalamic nuclei particularly the lateral and intra-laminar groups. *(Afifi and Bergman, 158)*

**115.** **(A)** The medial geniculate nucleus is part of the auditory thalamus and represents the thalamic relay between the inferior colliculus and the auditory cortex. It is made up of a number of subnuclei that are distinguished by their neuronal morphology and density, their afferent and efferent connections, and the coding properties of their neurons. The auditory fibers reach the medial geniculate nucleus via the brachium of the inferior colliculus. The medial geniculate nucleus receives feedback from the primary auditory cortex in the temporal lobe. The efferent outflow from the medial geniculate nucleus forms the auditory radiation of the internal capsule to the

primary auditory cortex in the temporal lobe. *(Afifi and Bergman, 163)*

**116.** **(E)** Five types of cells are distributed in the three cortical layers of the cerebellum. Basket and stellate cells are located in the molecular layer, Purkinje cells are located in the Purkinje cell layer, and granule and Golgi cells are located in the granule cell layer. Of these five types, the Purkinje cell constitutes the principal neuron of the cerebellum, since it is the only cerebellar neuron that sends its axon outside the cerebellum. All the other cells are intrinsic neurons and establish connections within the cerebellum. Purkinje cells send inhibitory projections to the deep cerebellar nuclei and constitute the sole output of all motor coordination in the cerebellar cortex. *(Afifi and Bergman, 203–204)*

**117.** **(E)** This is a schematic diagram showing the four regions of the medial hypothalamus. The structure indicated by the arrow is the mammillary body. The mammillary bodies are two spherical masses protruding from the ventral surface of the hypothalamus caudal to the tuber cinereum and rostral to the interpeduncular fossa and the anterior perforated substance. The mammillary bodies consist of two groups of nuclei, medial and lateral. The medial nucleus is the main target of the fornix and the source of the mammillothalamic tract. *(Afifi and Bergman, 269–271)*

**118.** **(B)** Figure 1-8 is a ventral view of the brain showing components of the rhinencephalon. The structure indicated by the arrow is the olfactory bulb, the main relay station in the olfactory pathways. *(Afifi and Bergman, 281)*

**119.** **(A)** Figure 1-9 is a midsagittal view of the brain showing components of the limbic lobe. The structure indicated by the arrow is the cingulate gyrus. A gyrus in the medial part of the brain, it partially wraps around the corpus callosum and is limited above by the cingulate sulcus. It receives inputs from the anterior nucleus of the thalamus and the neocortex as well as from somatosensory areas of the cerebral cortex. It projects to the entorhinal cortex via the cingulum and functions as an integral part of the limbic system, which is involved with the formation and processing of emotion, learning, and memory. *(Afifi and Bergman, 283–284)*

**120.** **(E)** The internal carotid arteries arise at the bifurcation of the common carotid artery in the neck, ascend in front of the transverse processes of the upper three cervical vertebrae, and enter the base of the skull through the carotid canal. Within the cranium, the internal carotid artery lies in the cavernous sinus. It then pierces the dura to begin its subarachnoid course. The internal carotid artery give rise to the ophtalmic, anterior choroidal, anterior cerebral, middle cerebral, and posterior communicating branches. The ophthalmic artery is the first intracranial branch of the internal carotid as it courses through the cavernous sinus. The ophthalmic artery supplies the optic nerve and the central artery of the retina. *(Afifi and Bergman, 349)*

**121.** **(B)** The recurrent artery of Heubner arises from the anterior cerebral artery either proximal or distal to the anterior communicating artery. It supplies the anterior limb and genu of the internal capsule and parts of the head of the caudate, rostral putamen, and globus pallidus. *(Afifi and Bergman, 350)*

**122.** **(C)** Figure 1-10 shows the lateral surface of cerebral hemisphere and brainstem and a portion of the spinal cord. The structure indicated by the arrow is the central sulcus. It is a prominent landmark of the brain, separating the parietal lobe from the frontal lobe and the primary motor cortex from the primary somatosensory cortex. *(Martin, 14)*

**123.** **(E)** The foramina of Monro are channels that connect the paired lateral ventricles with the third ventricle at the midline of the brain. As channels, they allow cerebrospinal fluid produced in the lateral ventricles to reach the third ventricle and then the rest of the brain's ventricular system. The crescent-shaped interventricular foramina are located on the medial and inferior aspect of the lateral ventricles. Each

foramen is bounded by the fornix and thalamus. *(Martin, 19)*

**124. (D)** The structure indicated by the arrow in Figure 1-11 is the anterior spinal artery. As the blood vessel that supplies the anterior portion of the spinal cord, it arises from branches of the vertebral arteries and, descending in front of the medulla oblongata, unites with its fellow of the opposite side at the level of the foramen magnum. The single trunk thus formed descends on the front of the medulla spinalis and is reinforced by a succession of small branches that enter the vertebral canal through the intervertebral foramina. These branches are derived from the vertebral artery and the ascending cervical artery of the inferior thyroid artery in the neck; from the intercostal arteries in the thorax; and from the lumbar artery, iliolumbar artery, and lateral sacral arteries in the abdomen and pelvis. They unite, by means of ascending and descending branches, to form a single anterior median artery, which extend as far as the lower part of the medulla spinalis and continues as a slender twig on the filum terminale. *(Martin, 85–86; Afifi and Bergman, 67)*

**125. (E)** The structure indicated by the arrow in Figure 1-12 is the globus pallidus. It is a wedge-shaped nuclear mass located between the putamen and the internal capsule. It can be divided into two parts: the globus pallidus externa (GPe) and the globus pallidus interna (GPi). Both receive input from the caudate and putamen and both are in communication with the subthalamic nucleus. It is the GPi, however, that sends the major inhibitory output from the basal ganglia back to the thalamus. The GPi also sends a few projections to an area of the midbrain, presumably to assist in postural control. *(Martin, 91; Afifi and Bergman, 185)*

**126. (B)** The cerebrospinal fluid (CSF) is produced from arterial blood by the choroid plexuses of the lateral and fourth ventricles by a combined process of diffusion, pinocytosis, and active transfer. The choroid plexus consists of tufts of capillaries with thin fenestrated endothelial cells. These are covered by modified ependymal cells with bulbous microvilli. The total volume of CSF in the adult is about 140 mL. The volume of the ventricles is about 25 mL. CSF is produced at a rate of 0.2 to 0.7 mL per minute or 600 to 700 mL per day. The CSF is absorbed across the arachnoid villi into the venous circulation. Although the chorid plexus is the main source of CSF, approximately one third of the CSF is generated by extrachoroidal sources. The capillary–astrocyte complex in the blood–brain barrier (BBB) has been implicated as an active producer of brain interstitial fluid. CSF from this extrachoroidal source enters the ventricular system through the ependymal cells, the ciliated cuboidal epithelial cells that line the ventricles. Another likely source of CSF is the ependyma lining the ventricles. *(Martin, 98–99; Johanson, c2008)*

**127. (B)** Gustatory fibers innervating the taste buds enter the brainstem and collect in the solitary tract located in the dorsal medulla. The axon terminals leave the tract and synapse on neurons in the surrounding solitary nucleus, which is the first central nervous system relay for taste. *(Martin, 211)*

**128. (A)** The inferior salivary nucleus is a cluster of neurons controlling the parasympathetic input to the parotid gland. It is one of the components of the glossopharyngeal nerve. It contains parasympathetic preganglionic neurons whose axons course in the glossopharyngeal nerve and synapse on postganglionic neurons in the otic ganglion. Parasympathetic postganglionic neurons in the otic ganglion innervate the parotid gland, which secretes saliva. *(Martin, 269)*

**129. (C)** Clarke's nucleus and the accessory cuneate nucleus are the principal nuclei relaying somatosensory information to the spinocerebellum. Clarke's nucleus is a small section of gray matter located in lamina VII of the intermediate zone of the spinal cord, which is found ventral to the gracile and cuneate columns and is involved in unconscious proprioception. It is found at the level of the eighth cervical segment to approximately the second lumbar segment on the spinal cord and relays somatosensory information from the lower limbs and trunk. Clarke's nucleus is the origin

of the dorsal spinocerebellar tract, which ascends in the outermost portion of the ipsilateral lateral column to reach the cerebellum via the inferior cerebellar peduncle. *(Martin, 315–317)*

**130. (A)** The climbing fibers originate entirely from the inferior olivary nuclear complex. These fibers pass through the pons and enter the cerebellum, where they form synapses with the deep cerebellar nuclei and Purkinje cells. *(Martin, 312–313)*

**131. (A)** The lateral sulcus (also called the Sylvian fissure) is one of the most prominent structures of the human brain. It divides the frontal and parietal lobes above from the temporal lobe below. It occurs in both hemispheres of the brain but is longer in the left hemisphere. The lateral sulcus is one the earliest-developing sulci of the human brain. It first appears around the 14th gestational week. *(Martin, 411; Chi, 86–93)*

**132. (C)** The structure indicated by the arrow in Figure 1-14 is the left mammillary body. It is a small, round, paired cell group that protrudes into the interpeduncular fossa from the inferior aspect of the hypothalamus. It receives a major bundle of hippocampal fibers from the fornix and projects fibers to the anterior thalamic nuclei and into the tegmentum of the brainstem. *(Martin, 414)*

**133. (B)** The structure indicated by the arrow in Figure 1-15 is the oculomotor nerve. It arises from the anterior aspect of mesencephalon. On emerging from the brain, the nerve is invested with a sheath of pia mater. It passes between the superior and posterior cerebral arteries and then pierces the dura mater anterior and lateral to the posterior clinoid process, passing between the free and attached borders of the tentorium cerebelli. It runs along the lateral wall of the cavernous sinus and above the other orbital nerves, receiving in its course one or two filaments from the cavernous plexus of the sympathetic nervous system and a communicating branch from the ophthalmic division of the trigeminal nerve. It then divides into two branches, which enter the orbit through the superior orbital fissure, between the two heads of the lateral rectus. The superior branch of the oculomotor nerve supplies the superior rectus and levator palpebrae superioris. The inferior branch of the oculomotor nerve supplies the medial rectus muscle, the inferior rectus muscle, and inferior oblique. *(Martin, 416)*

**134. (C)** The structure indicated by the arrow in Figure 1-16 is the abducens nerve. It leaves the brainstem at the junction of the pons and the medulla, then entering the subarachnoid space when it emerges from the brainstem. It runs upward between the pons and the clivus and then pierces the dura mater to run between the dura and the skull. At the tip of the petrous temporal bone, it makes a sharp turn forward to enter the cavernous sinus. In the cavernous sinus, it runs alongside the internal carotid artery. It then enters the orbit through the superior orbital fissure and innervates the lateral rectus muscle of the eye. *(Martin, 418)*

**135. (E)** The structure indicated by the arrow in Figure 1-17 is the trochlear nerve. It emerges from the dorsal aspect of the brainstem at the level of the caudal mesencephalon, just below the inferior colliculus. It passes between the posterior cerebral artery and the superior cerebellar artery and then pierces the dura just under the free margin of the tentorium cerebelli, close to the crossing of the attached margin of the tentorium and within millimeters of the posterior clinoid process. It enters the cavernous sinus, where it is joined by the other two extraocular nerves (oculomotor and trochlear nerves), the internal carotid artery, and portions of the trigeminal nerve. Finally, it enters the orbit through the superior orbital fissure and innervates the superior oblique muscle. *(Martin, 420; Bisaria, 29–35)*

**136. (A)** The structure indicated by the arrow in Figure 1-18 is the pineal gland. It is reddish-gray in color, located just rostrodorsal to the superior colliculus and behind and beneath the stria medullaris, between the laterally positioned thalamic bodies. It is part of the epithalamus. *(Martin, 422)*

**137. (C)** The structure indicated by the arrow in Figure 1-19 is the inferior cerebellar peduncle. It carries many types of input and output fibers that are mainly concerned with integrating proprioceptive sensory input with motor vestibular functions, such as the maintenance of balance and posture. *(Martin, 442)*

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CHAPTER 2

# Localization Signs in Neurology
## Questions

**1.** Small irregular pupils fixed to light but reactive to accommodation are suggestive of

(A) Holmes–Adie pupil
(B) Argyll–Robertson pupil
(C) epidemic encephalitis
(D) Parinaud syndrome
(E) Marcus Gunn pupils

**2.** Postganglionic Horner syndrome may accompany

(A) ipsilateral internal artery dissection
(B) hypothalamic infarction
(C) midbrain infaction
(D) breast cancer
(E) lung cancer

**3.** A unilateral large, poorly reactive pupil is caused by

(A) botulism
(B) traumatic carotid dissection
(C) third nerve palsy
(D) an acute pontine lesion
(E) delirium

**4.** Opsoclonus usually indicates a lesion of the

(A) cerebellum
(B) visual cortex
(C) retina
(D) optic nerve
(E) lateral geniculate body

**5.** A 45-year-old right-handed woman with a history of mitral valve stenosis developed a pattern of acute pressured speech and the inability to follow simple commands. Her speech was profuse and filled with paraphasic errors. She was unable to repeat sentences or name objects correctly. The most likely location of a brain lesion associated with her condition is the

(A) left frontal lobe
(B) left superior temporal gyrus
(C) left inferior frontal gyrus
(D) bilateral medial occipital gyrus
(E) left cerebellar gyrus

**6.** A pure lesion of the dominant angular gyrus causes

(A) Broca aphasia
(B) Wernicke aphasia
(C) alexia without agraphia
(D) alexia with agraphia
(E) anosognosia

**7.** Alexia without agraphia is caused by damage to the

(A) combined medial dominant occipital region and contralateral splenium of the corpus callosum
(B) dominant angular gyrus
(C) nondominant angular gyrus
(D) bilateral lateral geniculate body
(E) bilateral occipital cortex

**8.** Repetition is preserved in

(A) conduction aphasia
(B) Broca aphasia
(C) Wernicke aphasia
(D) global aphasia
(E) transcortical sensory aphasia

**9.** Gerstmann syndrome is characterized by

(A) damage to the nondominant occipital cortex
(B) dysarthria
(C) dressing apraxia
(D) visual anosognosia
(E) finger agnosia

**10.** Optic ataxia is

(A) characterized by failure to shift gaze on command
(B) defined by a disturbance of reaching a target under visual control
(C) caused by cerebellar damage
(D) usually accompanied by an optic nerve lesion
(E) a part of Gerstmann syndrome

**11.** Anton syndrome (denial of blindness) results from a

(A) bilateral lateral occipital lesion
(B) bilateral mesial occipital lesion
(C) hippocampal lesion
(D) lesion of the cingulate gyrus
(E) callosal lesion

**12.** Impaired ipsilateral scanning may result from a

(A) lateral occipital lesion
(B) mesial occipital lesion
(C) lesion of the mesial frontal lobe
(D) lesion of the cingulate gyrus
(E) nondominant parietal lesion

**13.** Bilateral medial temporal damage may cause

(A) sensory aphasia
(B) alexia with agraphia
(C) alexia without agraphia
(D) tameness
(E) anosognosia

**14.** The alien hand sign is seen in lesions of the

(A) occipital cortex
(B) medial temporal lobe
(C) hippocampus
(D) cingulate gyrus
(E) parietal cortex

**15.** Blunted affect associated with impotence and the inability to plan and execute multistepped processes results from damage to the

(A) orbitofrontal area
(B) cingulate gyrus
(C) hippocampus
(D) parietal cortex
(E) corpus callosum

**16.** Lack of kinesthetic transfer associated with double hemianopia results from a damage to the

(A) orbitofrontal area
(B) cingulate gyrus
(C) hippocampus
(D) precentral gyrus
(E) corpus callosum

**17.** Hemiballismus is caused by a lesion located in the

(A) ipsilateral cerebellum
(B) contralateral caudate nucleus
(C) contralateral subthalamic nucleus
(D) ipsilateral globus pallidus
(E) ipsilateral substantia nigra

**18.** A unilateral lesion of the anteroventral portion of the caudate nucleus causes contralateral

(A) tremor
(B) dystonia
(C) parkinsonism
(D) choreoathetosis
(E) hemiballismus

**19.** A sudden bilateral paramedian thalamic lesion may cause

(A) visual hallucinations
(B) akinetic mutism
(C) hyperphagia
(D) hypersexual behavior
(E) amnesia

**20.** Prolonged latency of visually evoked saccadic eye movements results from

(A) a lesion of the pulvenar
(B) a lesion of the lateral geniculate body
(C) optic radiation
(D) a lesion of the hypothalamus
(E) a lesion of the anterior nucleus of the thalamus

**21.** Cheyne–Stokes respiration implies

(A) medullary dysfunction
(B) abnormal reduction of ventilatory response to $CO_2$
(C) a lower pontine lesion
(D) midbrain lesion
(E) forebrain damage

**22.** Apneustic breathing is most likely related to

(A) lower pontine tegmental dysfunction
(B) damage to the basis pontis
(C) medullary dysfunction
(D) hypothalamic damage
(E) forebrain damage

**23.** Medullary dysfunction may cause

(A) cluster breathing
(B) ataxic breathing
(C) apraxia for deep breathing
(D) apneustic breathing
(E) Cheyne–Stokes respiration

**24.** Bilateral small (pinpoint) pupils in a comatose patient are suggestive of

(A) midbrain dysfunction
(B) third nerve dysfunction
(C) diencephalic dysfunction
(D) tectal dysfunction
(E) pontine dysfunction

**25.** Damage to shaded area (indicated by the broken arrow) in Figure 2-1 results in

(A) loss of pain and temperature in the contralateral face
(B) contralateral ataxia
(C) vertigo
(D) homolateral half of the tongue paralysis
(E) diplopia response

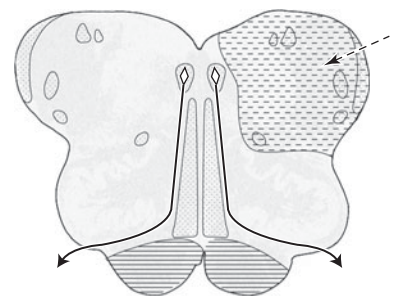

**FIG. 2-1.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

**26.** Damage to the shaded area indicated by the broken arrow in Figure 2-2 can cause

(A) homolateral paralysis of half of the tongue
(B) vertigo
(C) hiccups
(D) ipsilateral ataxia
(E) ipsilateral Horner syndrome

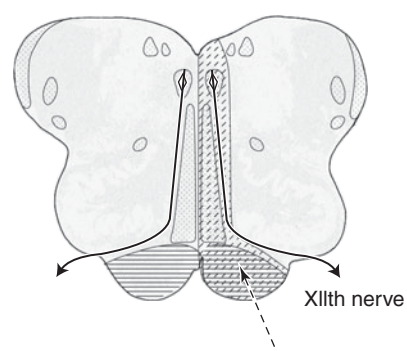


**FIG. 2-2.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

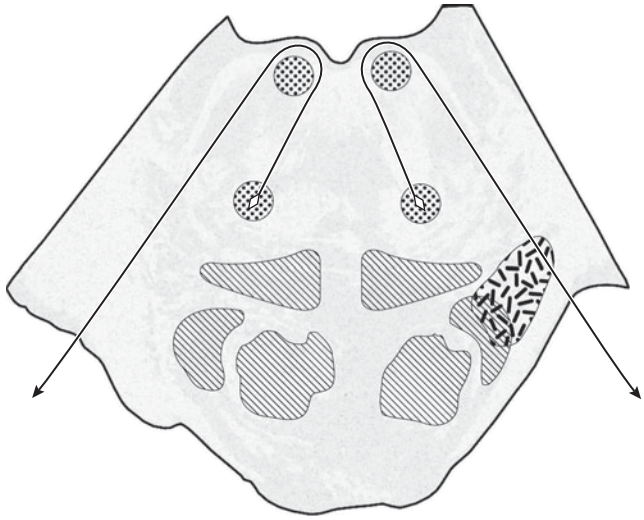

**FIG. 2-3.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

**27.** Which of the following clinical manifestations is newly developed by a 56-year-old man patient when his central nervous system damage extends from the dashed area in Figure 2-3 to the dashed area in Figure 2-4?

(A) Contralateral limb paralysis
(B) Ipsilateral paralysis of facial muscles
(C) Ipsilateral paralysis of ocular abduction
(D) Vertigo
(E) Dysphagia

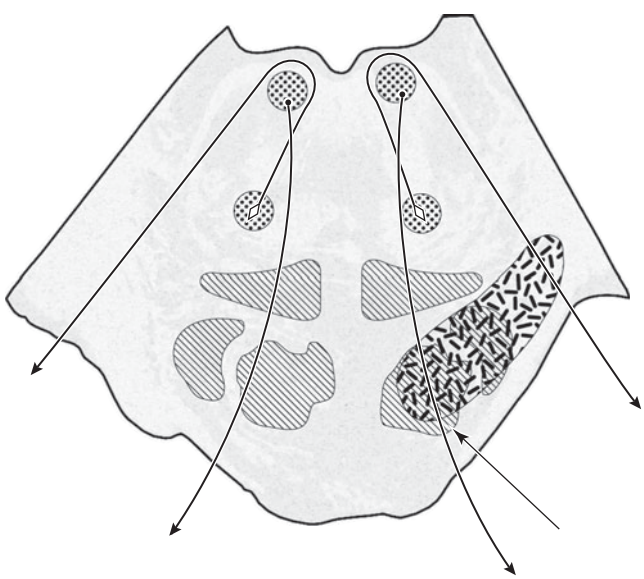

**FIG. 2-4.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

**28.** What is the earliest sign of damage to the area of the brain indicated by arrow A in Figure 2-5?

(A) Deep coma
(B) Moderate anisocoria
(C) External ophthalmoplegia
(D) Fully dilated pupil nonreactive to light
(E) Decorticate posturing

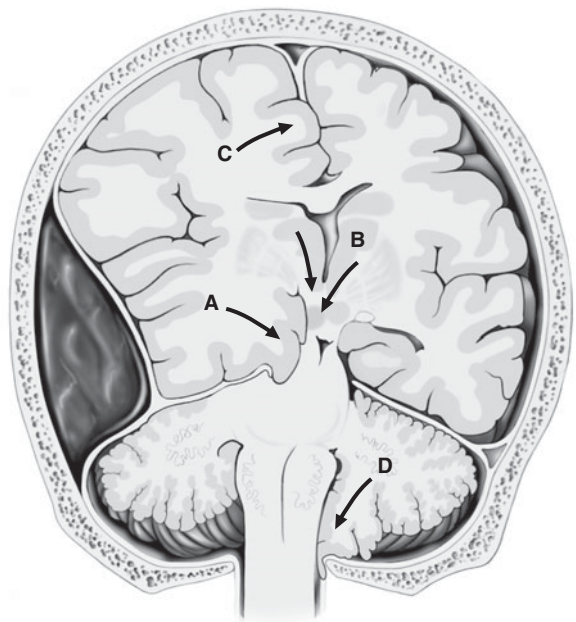


**FIG. 2-5.** (Reproduced with permission from Hauser SL, Josephson SA, English JD, Engstrom JW (eds). *Harrison's Neurology in Clinical Medicine.* New York: McGraw-Hill; 2006.)

**29.** What is the earliest sign of damage to the area of the brain indicated by arrow B in Figure 2-5?

(A) Eupneic breathing with deep sighs and yawns
(B) Stupor
(C) Decorticate posturing
(D) Hypothermia
(E) Cheyne–Stokes respiration

**30**. In a 72-year-old comatose man with a large frontal lobe hemorrhage, the occurrence of ataxic breathing with a drop in blood pressure and irregular heart rate indicate that the patient has moved to the

(A) early diencephalic stage
(B) late diencephalic stage

(C) midbrain stage
(D) lower pontine stage
(E) medullary stage

**31.** Pupillary examination of 37-year-old comatose woman reveals pupils in midposition, unresponsive to light with hippus. These findings are suggestive of central nervous system damage located in the

(A) midbrain tectum
(B) diencephalon
(C) midbrain tegmentum
(D) pons
(E) medulla

**32.** The occurrence of a long inspiratory pause, after which the air is retained for several seconds and then released in a comatose patient, indicates damage located in the

(A) medulla
(B) pons
(C) cerebellum
(D) midbrain
(E) diencephalon

**33.** A lesion affecting the dashed area in Figure 2-6 causes

(A) diplopia
(B) dysphagia
(C) dysarthria
(D) ipsilateral weakness of mastication
(E) ipsilateral limb weakness

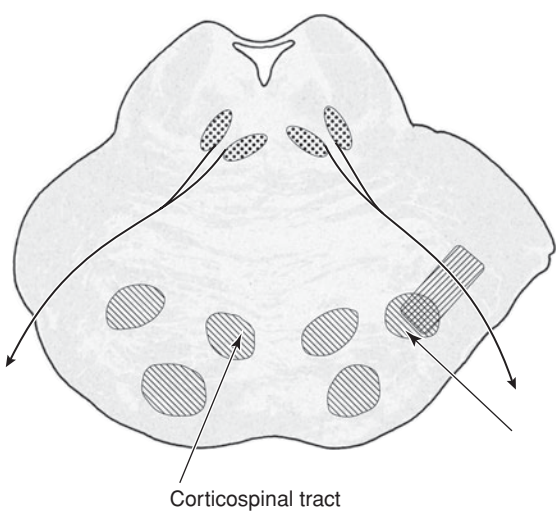


**FIG. 2-6.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

**34.** A lesion affecting the dashed area in Figure 2-7 causes

(A) ipsilateral loss of facial sensation
(B) dysphagia
(C) dysarthria
(D) ipsilateral weakness of mastication
(E) ipsilateral facial muscle weakness

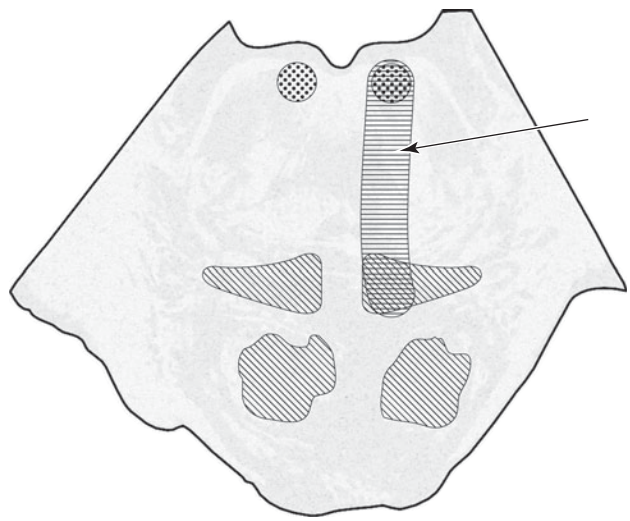

**FIG. 2-7.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

**35.** A lesion affecting the dashed area indicated by arrow A in Figure 2-8 causes

(A) ipsilateral loss of facial sensation
(B) dysphagia
(C) dysarthria
(D) ipsilateral dilated nonresponsive pupil
(E) ipsilateral tremor response

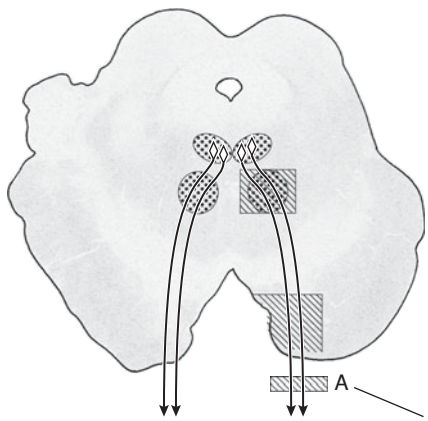


**FIG. 2-8.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

**36.** A lesion affecting the dashed area indicated by arrow B in Figure 2-9 causes

(A) ipsilateral loss of facial sensation
(B) contralateral limb weakness
(C) dysarthria
(D) contralateral dilated nonresponsive pupil
(E) ipsilateral tremor

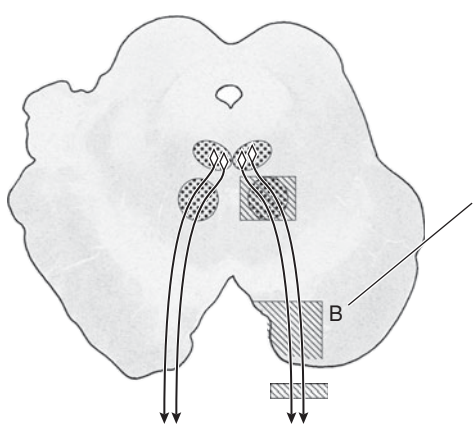


**FIG. 2-9.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

**37.** A lesion affecting the dashed area indicated by arrow C in Figure 2-10 causes

(A) ipsilateral loss of facial sensation
(B) contralateral tremor
(C) dysarthria
(D) ipsilateral weakness of mastication
(E) ipsilateral tremor

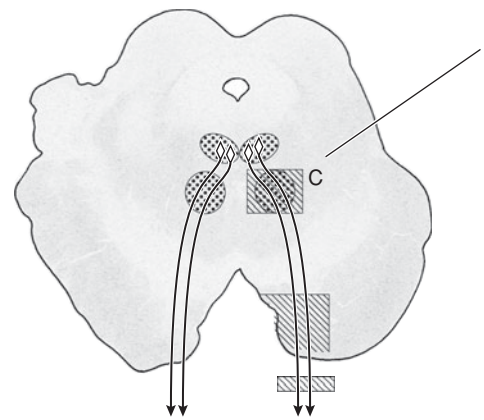


**FIG. 2-10.** (Reproduced with permission from Afifi AK, Bergman RA. *Functional Neuroanatomy: Text and Atlas.* 2nd ed. New York: McGraw-Hill; 2005.)

**38.** A pretectal lesion causes

(A) upward gaze paralysis
(B) ipsilateral tremor
(C) ipsilateral weakness of mastication
(D) ipsilateral loss of facial sensation
(E) dysarthria

**39.** Infarction of the anteromedial branches of the posterior cerebral artery causes

(A) ipsilateral ataxia
(B) ipsilateral oculomotor nerve palsy
(C) ipsilateral tremor
(D) hallucinations
(E) contralateral lid retraction

**40.** A 75-year-old woman developed hallucinations of animals and people sharing her room. This patient may have brain damage located in the

(A) midbrain
(B) medulla
(C) frontal cortex

(D) parietal cortex
(E) hypothalamus

**41.** Pain radiating into the arm and shoulder with weakness of shoulder abduction is suggestive of a

(A) first thoracic root lesion (T1)
(B) fifth cervical root lesion (C5)
(C) sixth cervical root lesion (C6)
(D) seventh cervical root lesion (C7)
(E) eighth cervical root lesion (C8)

**42.** Weakness of elbow flexion in the fully supine and half-pronated positions associated with deep aching pain spreading down the lateral forearm to the thumb and index finger, affecting both the palmar and dorsal aspects of the hand, is suggestive of a

(A) first thoracic root lesion (T1)
(B) fifth cervical root lesion (C5)
(C) sixth cervical root lesion (C6)
(D) seventh cervical root lesion (C7)
(E) eighth cervical root lesion (C8)

**43.** Weakness of shoulder adduction, elbow extension, and flexion and extension of the wrist with pain in the forearm, radiating into the middle, index, and ring fingers, is suggestive of a

(A) first thoracic root lesion (T1)
(B) fifth cervical root lesion (C5)
(C) sixth cervical root lesion (C6)
(D) seventh cervical root lesion (C7)
(E) eighth cervical root lesion (C8)

**44.** Weakness of the long extensor and flexor muscles of the hand with pain in the olecranon, radiating into the little and ring fingers, is suggestive of a

(A) first thoracic root lesion (T1)
(B) fifth cervical root lesion (C5)
(C) sixth cervical root lesion (C6)
(D) seventh cervical root lesion (C7)
(E) eighth cervical root lesion (C8)

**45.** Weakness of all intrinsic hand muscles with pain in the shoulder joint, axilla, and medial side of the upper arm down to the olecranon is suggestive of a

(A) first thoracic root lesion (T1)
(B) fifth cervical root lesion (C5)
(C) sixth cervical root lesion (C6)
(D) seventh cervical root lesion (C7)
(E) eighth cervical root lesion (C8)

**46.** Proximal forearm pain exacerbated by elbow extension with muscle wasting in the ventral arm, weakness of elbow flexion, and loss of the biceps reflex is suggestive of

(A) a radial nerve lesion at the spiral groove
(B) ulnar nerve entrapment at the wrist
(C) a musculocutaneous nerve lesion
(D) a median nerve lesion in the upper arm
(E) an axillary nerve lesion

**47.** "Saturday night palsy" is suggestive of

(A) a radial nerve lesion at the spiral groove
(B) ulnar nerve entrapment at the wrist
(C) a musculocutaneous nerve lesion
(D) a median nerve lesion in the upper arm
(E) an axillary nerve lesion

**48.** Pain in the little finger and medial half of the ring finger with weakness of all intrinsic hand muscles except for thumb abduction is suggestive of

(A) a radial nerve lesion at the spiral groove
(B) ulnar nerve entrapment at the wrist
(C) a musculocutaneous nerve lesion
(D) a median nerve lesion in the upper arm
(E) an axillary nerve lesion

**49.** Pain from the thumb to the middle finger and forearm with weakness of wrist flexion, thumb abduction, and the inability to form an O with the thumb and index fingers (pinch sign) is suggestive of

(A) a radial nerve lesion at the spiral groove
(B) ulnar nerve entrapment at the wrist
(C) a musculocutaneous nerve lesion
(D) a median nerve lesion in the upper arm
(E) an axillary nerve lesion

**50.** A 65-year-old woman developed a pain located diagonally across the thigh, with weakness on hip flexion, knee extension, and thigh adduction. The most likely anatomic location of the damage is in the

(A) lumbar plexus
(B) sacral plexus
(C) obturator nerve
(D) femoral nerve
(E) tibial nerve

**51.** A 23-year-old pregnant woman developed pain in the medial right thigh and weakness of thigh adduction. The most likely anatomic location of the damage is in the

(A) lumbar plexus
(B) sacral plexus
(C) obturator nerve
(D) femoral nerve
(E) tibial nerve

**52.** A 50-year-old man developed a progressive loss of sensation to all modalities in the sole and lateral border of the foot with weakness on plantarflexion and inversion of the foot. The most likely anatomic location of the damage is the

(A) lumbar plexus
(B) sacral plexus
(C) obturator nerve
(D) femoral nerve
(E) tibial nerve

**53.** After an intramuscular injection in his left buttock, a 56-year-old man developed a left flail foot, weakness of left knee flexion, decreased left Achilles reflex, and loss of sensation in the lateral left leg and dorsum of the foot. The most likely anatomic location of the damage is in the

(A) femoral nerve
(B) sacral plexus
(C) obturator nerve
(D) sciatic nerve
(E) tibial nerve

**54.** A 22-year-old female began, late in her pregnancy, to complain of tingling and burning sensations from her left lateral thigh spreading to the popliteal fossa. The most likely anatomic location of the damage is in the

(A) lateral femoral cutaneous nerve
(B) sacral plexus
(C) obturator nerve
(D) sciatic nerve
(E) tibial nerve

**55.** A 66-year-old woman with a past medical history of breast cancer developed loss of sensation in her left posterior thigh, lateral calf, and dorsum of the foot, including all the toes. Motor examination demonstrated weakness of left hip extension, left thigh abduction, and all left foot movements. The most likely anatomic location of the damage is in the

(A) lateral femoral cutaneous nerve
(B) sacral plexus
(C) obturator nerve
(D) sciatic nerve
(E) lumbar plexus

**56.** A 71-year-old man on warfarin for severe cardiomyopathy developed, after a fall on his back, severe pain in his anterior left thigh and medial leg down to his ankle. Neurological assessment was significant for the absence of left knee jerk and weakness of knee extension. The most likely anatomic location of the damage is in the

(A) femoral nerve
(B) sacral plexus
(C) obturator nerve
(D) sciatic nerve
(E) lumbar plexus

**57.** A 78-year-old woman developed loss of sensation in the dorsum of her foot and a dull ache in the anterolateral leg after a left knee arthroplasty. Neurological examination demonstrated weakness on dorsiflexion and eversion of her left foot. The most likely anatomic location of the damage is in the

(A) femoral nerve
(B) peroneal nerve

(C) obturator nerve
(D) sciatic nerve
(E) tibial nerve

**58.** A 22-year-old woman developed pain in her perineum and clitoris as well as fecal incontinence. The most likely anatomic location of the damage is in the

(A) femoral nerve
(B) sacral plexus
(C) obturator nerve
(D) sciatic nerve
(E) pudendal nerve

**59.** $B_{12}$ deficiency is associated with

(A) cecocentral scotoma
(B) binasal hemianopia
(C) optic neuritis
(D) optic nerve compression at the junction with the optic chiasm
(E) compression of the optic chiasm

**60.** Hydrocephalus is associated with

(A) cecocentral scotoma
(B) binasal hemianopia
(C) optic neuritis
(D) optic nerve compression at the junction with the optic chiasm
(E) compression of the optic chiasm

**61.** A 23-year-old male treated with ethambutol for tuberculosis may develop

(A) cecocentral scotoma
(B) binasal hemianopia
(C) optic neuropathy
(D) optic nerve compression at the junction with the optic chiasm
(E) compression of the optic chiasm

**62.** Ipsilateral central scotoma with contralateral temporal visual field defect may be associated with

(A) cecocentral scotoma
(B) binasal hemianopia
(C) optic neuritis
(D) optic nerve compression at the junction with the optic chiasm
(E) compression of the optic chiasm

**63.** Bitemporal hemianopia may be associated with

(A) cecocentral scotoma
(B) binasal hemianopia
(C) optic neuritis
(D) optic nerve compression at the junction with the optic chiasm
(E) compression of the optic chiasm

**64.** Cortical blindness is associated with

(A) Anton syndrome
(B) binasal hemianopia
(C) optic neuritis
(D) infarction of the anterior visual cortex
(E) compression of the optic chiasm

**65.** Hemianopia with macular sparing is associated with

(A) Anton syndrome
(B) binasal hemianopia
(C) optic neuritis
(D) infarction of the anterior visual cortex
(E) compression of the optic chiasm

**66.** Which of the following is true about Bell's phenomenon in Bell's palsy?

(A) Eyeball deviation occurs up and slightly outward on the affected side when the patient attempts to close both eyes.
(B) Eyeball deviation occurs down and slightly inward on the affected side when the patient attempts to close both eyes.
(C) Eyeball deviation occurs down and slightly inward on the normal side when the patient attempts to close both eyes.
(D) Eyeball deviation occurs up and slightly inward on the normal side when the patient attempts to close both eyes.
(E) Eyeball deviation is not a physiologic Bell's phenomenon and is seen only in peripheral facial nerve disease.

**67.** Tolosa–Hunt syndrome

(A) is characterized by recurrent unilateral facial pain
(B) is characterized by transient facial nerve palsy
(C) is caused by herpesvirus infection
(D) is characterized by a sensitivity to corticosteroids
(E) has a female predominance

**68.** A 28-year-old right-handed volleyball player has noticed, for the previous 3 weeks, mild right arm weakness on elevation, especially when shaving or combing his hair. The weakness is accompanied by a dull ache in the shoulder. On neurological examination, there was winging of the right scapula when the patient was asked to push against the wall with both arms. The lesion is most likely located in the

(A) C7-C8 cervical root
(B) long thoracic nerve
(C) suprascapular nerve
(D) dorsal scapular nerve
(E) trapezius muscle

**69**. A 45-year-old right-handed porter used to keep his arms outstretched and forearms in maximum supination when carrying heavy bags on his back. He consulted a neurologist because of weakness on extension of his right elbow, wrist, and fingers with slightly decreased sensation to all modalities in his lateral arm and posterior forearm and the web between the index finger and thumb. The lesion is most likely located in the

(A) radial nerve at the upper arm
(B) radial nerve at the axilla
(C) musculocutaneous nerve
(D) axillary nerve
(E) long thoracic nerve

**70.** A 56-year-old alcoholic man awoke in the morning after a heavy alcoholic binge complaining of inability to extend his right wrist and fingers, including the thumb. Neurological examination demonstrated weakness of wrist and metacarpophalangeal extension. Right arm extension was normal. Elbow flexion was weak, with the thumb pointing to the ceiling. The lesion is most likely located in the

(A) radial nerve at the upper arm
(B) radial nerve at the axilla
(C) musculocutaneous nerve
(D) axillary nerve
(E) long thoracic nerve

**71.** A 60-year-old man described progressive difficulty in extending his right little finger. This symptom progressed over several weeks to total inability to extend the fingers and thumb. Neurological examination demonstrated dropped fingers without wrist drop. The lesion is most likely located in the

(A) radial nerve at the upper arm
(B) radial nerve at the axilla
(C) radial nerve at the forearm
(D) radial nerve at the wrist
(E) axillary nerve

**72.** After he had been handcuffed by a police officer, a 30-year-old man developed a shooting pain on the radial side of his right wrist and paresthesias radiating into the thumb and index finger. The lesion is most likely located in the

(A) radial nerve at the upper arm
(B) radial nerve at the axilla
(C) radial nerve at the forearm
(D) radial nerve at the wrist
(E) axillary nerve

**73**. A 40-year-old woman, recently diagnosed with non-Hodgkin's lymphoma, noticed difficulty in holding a glass with her right hand and numbness of the palmar side of the thumb, index, and middle fingers of her right hand. Neurological examination of the right hand demonstrated weak pronation and abduction of the wrist against resistance, weak flexion of the proximal and distal interphalangeal joints against resistance of the second and third fingers, and inability to form an O with the thumb

and index finger. The lesion is most likely located in the

(A) median nerve at the upper arm
(B) median nerve at the elbow
(C) median nerve at the wrist
(D) ulnar nerve at the elbow
(E) ulnar nerve at the wrist

**74.** A 60-year-old African-American man, a few days after reduction of a dislocated left elbow, developed dull pain in his left forearm over several days. The pain spread to his index finger and thumb. Neurological examination demonstrated normal sensation and wrist flexion. There was weakness in pronation of the forearm when the elbow was flexed but not when it was extended. The lesion is most likely located in the

(A) median nerve at the upper arm
(B) anterior interosseous nerve
(C) posterior interosseous nerve
(D) ulnar nerve at the elbow
(E) ulnar nerve at the wrist

**75.** For the previous 4 months, a 45-year-old woman with a history of rheumatoid arthritis had noticed an intermittent sensation of pins and needles in both hands. The pain worsens upon awakening from sleep. She has also noticed clumsiness with fine finger movements. Neurological examination demonstrated abnormal pinprick sensation on the palmar surface of both hands, with hypesthesia in the distal aspect of the first three digits bilaterally. There was mild thenar atrophy, weakness of thumb abduction, and weakness on opposing the thumb against the little finger. The lesion is most likely located in the

(A) median nerve at the wrist
(B) anterior interosseous nerve
(C) posterior interosseous nerve
(D) ulnar nerve at the elbow
(E) ulnar nerve at the wrist

**76.** A 40-year-old woman noticed a pins-and-needles sensation in her right ring and little fingers. After a few weeks, she noticed atrophy of her nails in the two last fingers as her hand became claw-like. Neurological examination demonstrated weakness on right wrist abduction and adduction, decreased pinprick sensation in the palmar surface of the right hand, and diminished dorsal sensation of the little finger and medial aspect of the ring finger. There was weakness on flexion of the little finger. The lesion is most likely located in the

(A) median nerve at the wrist
(B) anterior interosseous nerve
(C) posterior interosseous nerve
(D) ulnar nerve at the elbow
(E) ulnar nerve at the wrist

**77.** A 37-year-old man developed a history of right hand weakness, mostly in the ring and little fingers, over the preceding 6 weeks. Neurological examination demonstrated weakness on thumb adduction, little finger abduction, and flexion. There was mild hypothenar muscle atrophy. The right palmaris brevis was spared on clinical examination. Sensory examination of the right hand was normal. The lesion is most likely located in the

(A) median nerve at the wrist
(B) anterior interosseous nerve
(C) posterior interosseous nerve
(D) ulnar nerve at the elbow
(E) ulnar nerve at the wrist

**78.** A 45-year-old woman had recently been started on warfarin for atrial fibrillation. She developed severe pain in her anterior right thigh and difficulty walking and rising from a chair. Neurological examination demonstrated weakness on right thigh and hip flexion as well as weakness on extension of the leg against resistance. The most likely diagnosis is

(A) right lower extremity embolism
(B) obturator nerve neuropathy
(C) femoral nerve neuropathy
(D) sciatic nerve neuropathy
(E) tibial nerve neuropathy

**79.** Lesions of the papillomacular bundle cause which of the following visual field defects?

(A) Paracentral scotoma
(B) Wedge-shaped temporal scotoma
(C) Comma-shaped extension of the blind spot
(D) Bjerrum arcuate scotoma
(E) Nasal step of Ronne

**80.** Optic tract lesions result in

(A) congruous hemianopia
(B) unilateral atrophy of the retinal nerve fiber
(C) normal pupillary reflex
(D) Wernicke pupil
(E) decreased visual acuity

**81.** A left homonymous superior quadranopsia ("pie in the sky") visual field defect is caused by a lesion of the

(A) left geniculate body
(B) left optic tract
(C) right parietal lobe
(D) left parietal lobe
(E) right anterior temporal lobe

**82.** A 50-year-old woman with a history of pituitary adenoma developed pain and paresthesias in the right periorbital area. The neurological examination demonstrated right ophthalmoplegia with loss of sensation in the distribution of the ophthalmic branch of the trigeminal nerve. This is suggestive of

(A) Millard–Gubler syndrome (lesion of the ventrocaudal pons)
(B) Foville syndrome (lesion of the dorsal pons)
(C) Raymond–Cestan syndrome (lesion of the ventromedial pons)
(D) subarachnoid syndrome of the abducens cranial nerve
(E) cavernous sinus syndrome

**83.** Following an otitis media, a 36-year-old man developed diplopia, left facial pain, and weakness in closing the left eye. Neurological examination demonstrated a left abducens and facial nerve palsy associated with left sensorineural deafness. This is suggestive of

(A) Millard–Gubler syndrome (lesion of the ventrocaudal pons)
(B) Foville syndrome (lesion of the dorsal pons)
(C) Raymond–Cestan syndrome (lesion of the ventromedial pons)
(D) subarachnoid syndrome of the abducens cranial nerve
(E) Gradenigo syndrome (lesion of the apex of the temporal bone)

**84.** A 70-year-old woman with a history of hypertension experienced a sudden onset of left-sided weakness with facial involvement. Neurological examination demonstrated right abducens nerve paresis, right facial paresis, and left hemiplegia. This is suggestive of

(A) Millard–Gubler syndrome (lesion of the ventrocaudal pons)
(B) Foville syndrome (lesion of the dorsal pons)
(C) Raymond–Cestan syndrome (lesion of the ventromedial pons)
(D) subarachnoid syndrome of the abducens cranial nerve
(E) Gradenigo syndrome (lesion of the apex of the temporal bone)

**85.** A 20-year-old woman with a history of pseudotumor cerebri developed an acute headache and blurred vision. Neurological examination demonstrated bilateral papilledema and abducens nerve palsy. This is suggestive of

(A) Millard–Gubler syndrome (lesion of the ventrocaudal pons)
(B) Foville syndrome (lesion of the dorsal pons)
(C) Raymond–Cestan syndrome (lesion of the ventromedial pons)
(D) subarachnoid syndrome of the abducens cranial nerve
(E) Gradenigo syndrome (lesion of the apex of the temporal bone)

**86.** A 75-year-old woman with a history of hypertension consulted a neurologist because of acute left-sided weakness. Neurological examination demonstrated horizontal conjugate gaze palsy with right trigeminal, facial, and cochleovestibular nerve palsies and right Horner syndrome. This is suggestive of

(A) Millard–Gubler syndrome (lesion of the ventrocaudal pons)
(B) Foville syndrome (lesion of the dorsal pons)
(C) Raymond–Cestan syndrome (lesion of the ventromedial pons)
(D) subarachnoid syndrome of the abducens cranial nerve
(E) Gradenigo syndrome (lesion of the apex of the temporal bone)

**87.** A 26-year-old male was brought to the Emergency Room because of a car accident with head trauma. Physical examination demonstrated mastoid ecchymosis, otorrhea, hemotympanum and left trigeminal, abducens, and facial nerve palsy. This is suggestive of

(A) Millard-Gubler syndrome (lesion of the ventrocaudal pons)
(B) Cavernous sinus syndrome
(C) Raymond-Cestan syndrome (lesion of the ventro medial pons)
(D) Petrous bone fracture
(E) Gradenigo syndrome (lesion of the apex of the temporal bone)

**88.** A 70-year-old man with a history of diabetes developed a left hemiparesis with right abducens nerve palsy. This is suggestive of

(A) Millard–Gubler syndrome (lesion of the ventrocaudal pons)
(B) cavernous sinus syndrome
(C) Raymond–Cestan syndrome (lesion of the ventromedial pons)
(D) petrous bone fracture
(E) Gradenigo syndrome (lesion of the apex of the temporal bone)

**89.** Which of the following is most suggestive of a lesion in the nucleus of the oculomotor nerve?

(A) Ipsilateral superior rectus palsy
(B) Bilateral ptosis
(C) Contralateral inferior oblique paresis
(D) Contralateral ptosis
(E) Contralateral medial rectus palsy

**90.** A 52-year-old woman with a history of migraine and hypertension developed a left ptosis. Neurological examination demonstrated left oculomotor nerve palsy without pupillary abnormality. The symptoms improved over the next 2 months. A follow-up visit in the third month showed an Argyll–Robertson pupil on the left side during convergence. The most likely cause of the pupillary abnormality is

(A) recurrence of left oculomotor palsy
(B) ischemic mononeuropathy of the oculomotor nerve
(C) primary aberrant regeneration of the oculomotor nerve
(D) secondary aberrant regeneration of the oculomotor nerve
(E) migraine

**91.** A 40-year-old man developed a new onset of diplopia. Neurological examination demonstrated eye misalignment on vertical gaze (the right eye higher than the left eye). This worsened on left gaze deviation and when the head was tilted to the right. Which of the following ocular muscles was affected?

(A) Right superior oblique
(B) Left superior oblique
(C) Right inferior rectus
(D) Left inferior rectus
(E) Right inferior oblique

**92.** A lesion at which of the following spinal cord segments causes inversion of the brachioradialis reflex?

(A) C8
(B) C4
(C) C7
(D) C6
(E) T1

**93.** A 35-year-old man developed progressive lower extremity weakness and gait ataxia over 6 months. Neurological examination demonstrated bilateral lower extremity spasticity, increased deep tendon reflexes throughout, and bilateral Babinski signs. Sensory examination showed no sensory level but loss of proprioception and vibratory sensation in both legs with preservation of temperature and pinprick sensations. These findings are suggestive of

(A) Brown–Séquard syndrome
(B) syringomyelia
(C) $B_{12}$ deficiency
(D) occlusion of the anterior spinal artery
(E) amyotrophic lateral sclerosis

**94**. A 50-year-old man had chronic lancinating leg pain, urinary incontinence, and gait ataxia progressing over 3 months. Neurological examination demonstrated impaired vibratory and joint position sense in the lower extremities, decreased tactile localization, and presence of the Romberg sign. Examination of the feet showed chronic trophic changes. These findings are suggestive of

(A) syringomyelia
(B) $B_{12}$ deficiency
(C) occlusion of the anterior spinal artery
(D) amyotrophic lateral sclerosis
(E) tabes dorsalis

**95.** A 30-year-old man consulted the neurologist because of generalized weakness and muscle atrophy in the right hand and foot. These symptoms had been progressing over the previous 2 years and were associated with painful cramps. Neurological examination demonstrated explosive dysarthria, generalized spasticity, increased deep tendon reflexes throughout, and bilateral Babinski signs. There was prominent muscle atrophy in the right hand and both feet, with fasciculations. Sensory examination was normal. Bladder and rectal sphincters were not affected. These findings are suggestive of

(A) syringomyelia
(B) $B_{12}$ deficiency
(C) occlusion of the anterior spinal artery
(D) amyotrophic lateral sclerosis
(E) tabes dorsalis

**96.** A 45-year-old woman developed thermoanesthesia in a cape-like distribution involving both upper extremities, with preservation of light touch sensation and proprioception. These findings are suggestive of

(A) syringomyelia
(B) $B_{12}$ deficiency
(C) occlusion of the anterior spinal artery
(D) amyotrophic lateral sclerosis
(E) tabes dorsalis

**97**. A 40-year-old man developed a sudden onset of back pain, followed by flaccid areflexic paraplegia with urinary incontinence. Neurological examination showed loss of sensation to pain and temperature at the T4 level with preservation of vibration and proprioception. These findings are suggestive of

(A) syringomyelia
(B) $B_{12}$ deficiency
(C) occlusion of the anterior spinal artery
(D) amyotrophic lateral sclerosis
(E) tabes dorsalis

**98.** Following back trauma, a 60-year-old woman developed weakness of the right lower extremity and urinary incontinence. Neurological examination demonstrated spastic monoplegia of the right lower extremity, loss of vibration sense, proprioception in the right side below the T6 level, and loss of pain and temperature sensation on the left side below the T6 level. These findings are suggestive of

(A) Brown–Séquard syndrome
(B) syringomyelia
(C) $B_{12}$ deficiency
(D) occlusion of the anterior spinal artery
(E) amyotrophic lateral sclerosis

**99.** Funnel vision is seen in

(A) glaucoma
(B) hysteria
(C) malingering

(D) pituitary tumor
(E) a lesion of the lateral geniculate body

**100.** A retrochiasmatic lesion of which of the following may cause a strictly unilateral visual field defect?

(A) The anteriormost aspect of the calcarine cortex
(B) The lateral geniculate body
(C) The optic radiation
(D) The medial occiput
(E) The optic tract

**101.** Ipsilateral facial nerve palsy with normal auditory and taste function is caused by

(A) a fascicular lesion of the facial nerve
(B) a lesion of the facial nerve in the meatal canal
(C) a lesion of the geniculate ganglion
(D) a lesion of the facial nerve between the departure of the nerve to the stapedius and the departure of the chorda tympani
(E) a lesion of the facial nerve at the stylomastoid foramen

**102.** Foville syndrome (lesion of the dorsal pons) is associated with

(A) a fascicular lesion of the facial nerve
(B) a lesion of the facial nerve in the meatal canal
(C) a lesion of the geniculate ganglion
(D) a lesion of the facial nerve between the departure of the nerve to the stapedius and the departure of the chorda tympani
(E) a lesion of the facial nerve at the stylomastoid foramen

**103.** Ramsay Hunt syndrome is associated with

(A) a fascicular lesion of the facial nerve
(B) a lesion of the facial nerve in the meatal canal
(C) a lesion of the geniculate ganglion
(D) a lesion of the facial nerve between the departure of the nerve to the stapedius and the departure of the chorda tympani
(E) a lesion of the facial nerve at the stylomastoid foramen

**104.** Ipsilateral facial palsy with loss of taste in the anterior two thirds of the tongue and normal hearing is associated with

(A) a fascicular lesion of the facial nerve
(B) a lesion of the facial nerve distal to the meatal canal and proximal to the nerve to the stapedius
(C) a lesion of the facial nerve in the meatal canal
(D) a lesion of the facial nerve between the departure of the nerve to the stapedius and the departure of the chorda tympani
(E) a lesion of the facial nerve at the stylomastoid foramen

**105.** Ipsilateral facial palsy, loss of taste sensation in the anterior two thirds of the tongue, and hyperacusis are associated with

(A) a fascicular lesion of the facial nerve
(B) a lesion of the facial nerve distal to the meatal canal and proximal to the nerve to the stapedius
(C) a lesion of the facial nerve esion in the meatal canal
(D) a lesion of the facial nerve between the departure of the nerve to the stapedius and the departure of the chorda tympani
(E) a lesion of the facial nerve at the stylomastoid foramen

**106.** Ipsilateral facial palsy with deafness and loss of taste in the anterior two thirds of the tongue are associated with

(A) a fascicular lesion of the facial nerve
(B) a lesion of the facial nerve distal to the meatal canal and proximal to the nerve to the stapedius
(C) a lesion of the facial nerve in the meatal canal
(D) a lesion of the facial nerve between the departure of the nerve to the stapedius and the departure of the chorda tympani
(E) a lesion of the facial nerve at the stylomastoid foramen

**107.** Millard–Gubler syndrome (lesion of the ventrocaudal pons) is associated with

(A) a fascicular lesion of the facial nerve
(B) a lesion of the facial nerve distal to the meatal canal and proximal to the nerve to the stapedius
(C) a lesion of the facial nerve in the meatal canal
(D) a lesion of the facial nerve between the departure of the nerve to the stapedius and the departure of the chorda tympani
(E) a lesion of the facial nerve at the stylomastoid foramen

**108.** A 70-year-old man with a history of atrial fibrillation developed a sudden onset of vertigo, nausea, vomiting, diplopia, and dysarthria. He also had pain in the right face and left arm and leg. Neurological examination demonstrated right Horner syndrome and decreased temperature sensation in the painful areas. The right palate and vocal cord were paralyzed. The right arm and leg were ataxic. These findings are suggestive of

(A) medial medullary syndrome
(B) Wallenberg syndrome (lateral medullary syndrome)
(C) locked-in syndrome
(D) Foville syndrome (lesion of the dorsal pontine tegmentum)
(E) Millard–Gubler syndrome (lesion of the ventrocaudal pons)

**109.** A 50-year-old woman with a history of diabetes developed left-sided weakness and dysarthria. Neurological examination demonstrated tongue deviation to the right side, left hemiplegia, and loss of vibratory and position sensation in the left arm and leg with preservation of temperature and pain sensation. These findings are suggestive of

(A) medial medullary syndrome
(B) Wallenberg syndrome (lateral medullary syndrome)
(C) locked-in syndrome
(D) Foville syndrome (lesion of the dorsal pontine tegmentum)
(E) Millard–Gubler syndrome (lesion of the ventrocaudal pons)

**110.** The neurological assessment of a 65-year-old comatose patient demonstrated right facial weakness, left gaze deviation, left hemiplegia, and left Babinski sign. These findings are associated with

(A) medial medullary syndrome
(B) Wallenberg syndrome (lateral medullary syndrome)
(C) locked-in syndrome
(D) Foville syndrome (lesion of the dorsal pontine tegmentum)
(E) Millard–Gubler syndrome (lesion of the ventrocaudal pons)

**111.** A 65-year-old woman with a history of diabetes and hypertension developed severe headache, followed by a dysarthria that progressed to total aphonia and generalized weakness. Neurological examination found an awake and alert patient with quadriparesis and ophthalmoplegia bilaterally with sparing of vertical eye movement and blinking. These findings are suggestive of

(A) medial medullary syndrome
(B) Wallenberg syndrome (lateral medullary syndrome)
(C) locked-in syndrome
(D) Foville syndrome (lesion of the dorsal pontine tegmentum)
(E) Millard–Gubler syndrome (lesion of the ventrocaudal pons)

**112.** A 30-year-old man with a history of cocaine abuse developed a sudden onset of ataxia and left-sided weakness. Neurological examination demonstrated right arm ataxia, left hemiparesis, and loss of temperature and pain sensation in the left arm. These findings are associated with

(A) Marie–Foix syndrome (lateral pontine lesion)
(B) Weber syndrome (lesion of the medial cerebral peduncle)

(C) Benedict syndrome (lesion of the mesencephalic tegmentum)
(D) Sylvian aqueduct syndrome
(E) Millard–Gubler syndrome (lesion of the ventrocaudal pons)

**113.** A 40-year-old woman with a history of diabetes developed a sudden onset of diplopia and left-sided tremor. Neurological examination demonstrated right ophthalmoplegia and left intention tremor. These findings are associated with

(A) Marie–Foix syndrome (lateral pontine lesion)
(B) Weber syndrome (lesion of the medial cerebral peduncle)
(C) Benedict syndrome (lesion of the mesencephalic tegmentum)
(D) Sylvian aqueduct syndrome
(E) Millard–Gubler syndrome (lesion of the ventrocaudal pons)

**114.** An 80-year-old man with a history of hypertension consulted the neurologist because of a new onset of double vision and left-sided weakness. Examination demonstrated right oculomotor paresis with a dilated pupil and left hemiplegia. These findings are associated with

(A) Marie–Foix syndrome (lateral pontine lesion)
(B) Weber syndrome (lesion of the medial cerebral peduncle)
(C) Benedict syndrome (lesion of the mesencephalic tegmentum)
(D) Sylvian aqueduct syndrome
(E) Millard–Gubler syndrome (lesion of the ventrocaudal pons)

**115.** A 20-year-old man consulted the neurologist because of his chronic headache and blurred vision. Neurological examination demonstrated paralysis of upward gaze and convergence retraction nystagmus on upward gaze. Magnetic resonance imaging (MRI) of the head showed a pineal tumor with hydrocephalus. These findings are associated with

(A) Marie–Foix syndrome (lateral pontine lesion)
(B) Weber syndrome (lesion of the medial cerebral peduncle)
(C) Benedict syndrome (lesion of the mesencephalic tegmentum)
(D) Sylvian aqueduct syndrome
(E) Millard–Gubler syndrome (lesion of the ventrocaudal pons)

**116.** A 5-year-old boy was brought to the neurology clinic because of the insidious onset of a staggering gait. Neurological examination demonstrated axial ataxia without limb ataxia and spontaneous nystagmus. MRI of the head showed a cerebellar mass suggesting medulloblastoma. These findings are suggestive of

(A) rostral vermis syndrome
(B) caudal vermis syndrome
(C) posteroinferior cerebellar artery occlusion syndrome
(D) anteroinferior cerebellar artery occlusion syndrome
(E) superior cerebellar artery occlusion syndrome

**117.** A 70-year-old diabetic woman developed a sudden onset of dizziness, nausea, vomiting, right-sided ataxia, and right hearing loss. Cranial nerve examination revealed sensorineural deafness on the right, peripheral facial palsy, and loss of facial pain and temperature sensation. The rest of the neurological examination demonstrated sensory loss to pain and temperature in the left trunk, arm, and leg and right Horner syndrome. These findings are suggestive of

(A) rostral vermis syndrome
(B) caudal vermis syndrome
(C) posteroinferior cerebellar artery occlusion syndrome
(D) anteroinferior cerebellar artery occlusion syndrome
(E) superior cerebellar artery occlusion syndrome

**118.** A 50-year-old man with a history of ethanol abuse consulted the neurologist because of progressive exacerbation of gait ataxia and slurred speech. Neurological examination demonstrated mild dysarthria, axial ataxia with minimal ataxia on the heel-to-shin maneuver, and normal arm coordination. These findings are suggestive of

(A) rostral vermis syndrome
(B) caudal vermis syndrome
(C) posteroinferior cerebellar artery occlusion syndrome
(D) anteroinferior cerebellar artery occlusion syndrome
(E) superior cerebellar artery occlusion syndrome

**119.** A 60-year-old man with a history of hypertension developed a sudden onset of vertigo and gait disturbance. Neurological examination demonstrated right Horner syndrome with horizontal nystagmus, left sensorineural deafness, right limb ataxia, and intention tremor. Sensory examination was significant for left-sided pain and temperature loss. These findings are suggestive of

(A) rostral vermis syndrome
(B) caudal vermis syndrome
(C) posteroinferior cerebellar artery occlusion syndrome
(D) anteroinferior cerebellar artery occlusion syndrome
(E) superior cerebellar artery occlusion syndrome

**120.** A 75-year-old woman with a history of hypertension and atrial fibrillation developed acute vertigo, headache, dysarthria, and gait disturbance. Neurological examination was significant for left limb ataxia, facial loss of temperature sensation, vocal cord palsy, Horner syndrome, and temperature and pain loss in the right trunk, arm, and leg. These findings are suggestive of

(A) rostral vermis syndrome
(B) caudal vermis syndrome
(C) posteroinferior cerebellar artery occlusion syndrome
(D) anteroinferior cerebellar artery occlusion syndrome
(E) superior cerebellar artery occlusion syndrome

**121.** The most common location of neurogenic gastrointestinal ulceration after an acute hypothalamic lesion is the

(A) upper esophagus
(B) lower esophagus
(C) fundus of the stomach
(D) ileum
(E) colon

**122.** The lesion most consistently associated with memory disturbance in patients with Wernicke–Korsakoff syndrome has been found in the

(A) mammillary bodies
(B) pulvinar
(C) medial dorsal nucleus of the thalamus
(D) fornix
(E) ventromedial region of the hypothalamus

**123.** Hemiballismus occurs with damage to the

(A) internal capsule
(B) subthalamic nucleus
(C) pituitary gland
(D) substantia nigra
(E) hypothalamus

**124.** Sensory inattention occurs most commonly with a lesion of the

(A) inferior parietal lobe
(B) thalamus
(C) mesencephalic reticular formation
(D) dorsolateral frontal lobe
(E) cingulate gyrus

**125.** Lesion of the septal region may induce

(A) sensory aprosodia
(B) indifference to pain
(C) blunt affect
(D) rage reaction
(E) depression

**126.** An orbitofrontal lesion may cause

(A) sensory aprosodia
(B) indifference to pain
(C) blunt affect
(D) rage reaction
(E) impulsive behavior

**127.** Apathy with indifference and psychomotor retardation is associated with lesions of the

(A) septal region
(B) orbitofrontal lesion
(C) frontal convexity
(D) medial frontal cortex
(E) cingulate lesion

**128**. Mutism with gait disturbance is associated with lesions located in the

(A) cingulate
(B) medial frontal lobe
(C) lateral frontal lobe
(D) parietal lobe
(E) temporal lobe

**129.** Sensory aprosodia is associated with

(A) right orbitofrontal lesions
(B) right parietotemporal lesions
(C) bilateral anterior temporal lesions
(D) bilateral anterior cingulate lesions
(E) left dorsofrontal lesions

**130.** Bland affect is associated with

(A) right orbitofrontal lesions
(B) right parietotemporal lesions
(C) bilateral anterior temporal lesions
(D) bilateral anterior cingulate lesions
(E) left dorsofrontal lesions

**131.** Indifference to pain may occur with

(A) right orbitofrontal lesions
(B) right parietotemporal lesions
(C) bilateral anterior temporal lesions
(D) bilateral anterior cingulate lesions
(E) left dorsofrontal lesions

**132.** Anger and hostility may occur with

(A) right orbitofrontal lesions
(B) right parietotemporal lesions
(C) bilateral anterior temporal lesions
(D) bilateral anterior cingulate lesions
(E) left dorsofrontal lesions

**133.** Paranoid behavior may occur with

(A) bilateral anterior temporal lesions
(B) bilateral anterior cingulate lesions
(C) left dorsofrontal lesions
(D) left temporal lobe lesions
(E) right temporal lesions

**134.** Which of the following hallucination types is associated with damage to the neocortex of the temporal lobe?

(A) Nocturnal bright-colored figures with a cartoon-like appearance
(B) Predominantly black-and-white–colored linear zigzags
(C) Predominantly multicolored patterns
(D) Pleasant dream-like visual hallucinations
(E) Déjà vécu illusions (illusions of previous experiences)

**135.** Which of the following hallucination types is associated with occipital seizures?

(A) Nocturnal bright-colored figures with a cartoon-like appearance
(B) Predominantly black-and-white–colored linear zigzags
(C) Predominantly multicolored patterns
(D) Pleasant dream-like visual hallucinations
(E) Déjà vécu illusions

**136.** Which of the following hallucination types is associated with midbrain lesions?

(A) Nocturnal bright-colored figures with a cartoon-like appearance
(B) Predominantly black-and-white–colored linear zigzags
(C) Predominantly multicolored patterns
(D) Pleasant dream-like visual hallucinations
(E) Déjà vécu illusions

**137.** Which of the following hallucination types is associated with the Charles Bonnet syndrome?

(A) Nocturnal bright-colored figures with a cartoon-like appearance
(B) Predominantly black-and-white–colored linear zigzags
(C) Predominantly multicolored patterns
(D) Pleasant dream-like visual hallucinations
(E) Déjà vécu illusions

**138.** Which of the following hallucination types is associated with migraine?

(A) Nocturnal bright-colored figures with a cartoon-like appearance
(B) Predominantly black-and-white–colored linear zigzags
(C) Predominantly multicolored patterns
(D) Pleasant dream-like visual hallucinations
(E) Déjà vécu illusions

**139.** Which of the following is characteristic of Balint syndrome?

(A) Gaze apraxia
(B) Denial of blindness
(C) Agraphia
(D) Color agnosia
(E) Finger agnosia

**140.** A 67-year-old man with a history of diabetes and hypertension suddenly developed a severe headache and blurred vision on the left. Neurological examination demonstrated a left homonymous hemianopia, normal response to threat, normal optokinetic nystagmus, and normal drawing and copying. Imaging studies showed an acute ischemic stroke. This is most likely a

(A) right occipitoparietal lesion
(B) right temporoparietal lesion
(C) bilateral occipital lesion
(D) bilateral lesion of the inferior banks of the calcarine fissure
(E) bilateral lesion of the superior banks of the calcarine fissure

**141.** Which of the following is characteristic of the frontal alien limb syndrome of the hand?

(A) Occurrence exclusively in the nondominant hand
(B) Caused by hemispheric disconnection
(C) Involving the compulsive manipulation of tools
(D) Intermanual conflict
(E) Apraxia

**142.** Limb-kinetic apraxia is caused by a lesion in the

(A) perirolandic cortex
(B) mesial frontal cortex
(C) supplementary motor cortex
(D) parietal cortex
(E) corpus callosum

**143.** Somatosensory disturbance is associated with damage located in the

(A) mesial occipital lobe
(B) lateral occipital lobe
(C) bilateral anterior tip of the temporal lobe
(D) lateroinferior aspect of the nondominant temporal lobe
(E) parietal postcentral gyrus

**144.** Impaired saccade with pure agraphia is associated with

(A) a lesion of the parietal postcentral gyrus
(B) a lesion of the mesial parietal lobe
(C) a lateral parietal lesion in the dominant hemisphere
(D) a mesiofrontal lesion
(E) alateral frontal premotor lesion

**145.** Lack of kinesthetic transfer is associated with

(A) a lesion of the parietal postcentral gyrus
(B) a lesion of the mesial parietal lobe
(C) a lateral parietal lesion in the dominant hemisphere
(D) a callosal frontal lesion
(E) a lateral frontal premotor lesion

**146.** Visual field defect with visual field agnosia and hallucination is associated with a lesion located in the

(A) mesial occipital lobe
(B) lateral occipital lobe
(C) bilateral anterior tip of the temporal lobe
(D) lateroinferior aspect of the nondominant temporal lobe
(E) parietal postcentral gyrus

**147.** Amnesia with storage impairment of geometric pattern is associated with a lesion located in the

(A) mesial occipital lobe
(B) lateral occipital lobe
(C) bilateral anterior tip of the temporal lobe
(D) lateroinferior aspect of the nondominant temporal lobe
(E) parietal postcentral gyrus

**148.** Blunt affect with impaired association of social nuance is associated with a

(A) lateral parietal lesion in the dominant hemisphere
(B) mesiofrontal lesion
(C) lateral frontal premotor lesion
(D) orbitofrontal lesion
(E) callosal frontal lesion

**149.** Alexia with agraphia, impaired ipsilateral scanning, and nystagmus are associated with a lesion located in the

(A) mesial occipital lobe
(B) lateral occipital lobe
(C) bilateral anterior tip of the temporal lobe
(D) lateroinferior aspect of the nondominant temporal lobe
(E) parietal postcentral gyrus

**150.** Klüver–Bucy syndrome is associated with a lesion located in the

(A) mesial occipital lobe
(B) lateral occipital lobe
(C) bilateral anterior tip of the temporal lobe
(D) lateroinferior aspect of the nondominant temporal lobe
(E) parietal postcentral gyrus

**151.** Transcortical sensory aphasia is associated with

(A) a lesion of the parietal postcentral gyrus
(B) a lesion of the mesial parietal lobe
(C) lateral parietal lesion in the dominant hemisphere
(D) a callosal frontal lesion
(E) a lateral frontal premotor lesion

**152.** Akinesia with perseveration and alien hand syndrome is associated with

(A) a lesion of the parietal postcentral gyrus
(B) a lesion of the mesial parietal lobe
(C) a lateral parietal lesion in the dominant hemisphere
(D) a callosal frontal lesion
(E) a mesiofrontal lesion

**153.** Alexia with agraphia, finger agnosia, and acalculia is associated with

(A) a lesion of the parietal postcentral gyrus lesion
(B) a lesion of the mesial parietal lobe
(C) a lateral parietal lesion in the dominant hemisphere
(D) a callosal frontal lesion
(E) a mesiofrontal lesion

**154.** A 74-year-old man developed loss of sensation to all modalities in the right mandible and lower external ear after a right endarterectomy. Motor examination showed weakness of right lateral and anterior head flexion and rotation as well as weakness on external rotation of the scapula. These findings are associated with

(A) Erb–Duchenne palsy
(B) Dejerine–Klumpke palsy
(C) a lesion of the cervical plexus
(D) thoracic outlet syndrome
(E) lumbar plexopathy

**155.** A 33-year-old woman with a history of cervical cancer developed an insidious onset of lower back pain and right proximal thigh and buttock pain. Sensory examination demonstrated loss of sensation in the lateral right leg and dorsum of the foot. Motor examination demonstrated a flail right foot; weakness of right knee flexion as well as abduction and internal rotation of the right thigh; and paresis of hip extension. These findings are suggestive of

(A) Dejerine–Klumpke palsy
(B) a lesion of the cervical plexus
(C) thoracic outlet syndrome
(D) lumbar plexopathy
(E) sacral plexopathy

**156.** A 40-year-old woman consulted the neurologist because of recurrent coldness and cyanosis of the left upper extremity with pain at the ulnar border of the right hand. Examination of the right hand demonstrated thenar wasting. These findings are suggestive of

(A) Erb–Duchenne palsy
(B) Dejerine–Klumpke palsy
(C) a lesion of the cervical plexus
(D) thoracic outlet syndrome
(E) lumbar plexopathy

**157.** A 22-year-old football player consulted the neurologist because of an acute transient episode of intense burning and weakness in his left upper extremity following a sudden depression of his left shoulder during a football game. A few weeks later, neurological examination showed weakness of internal rotation and adduction of the left limb. The forearm was held in extension and pronation because of elbow flexion weakness. These findings are suggestive of

(A) Erb–Duchenne palsy
(B) Dejerine–Klumpke palsy
(C) a lesion of the cervical plexus
(D) thoracic outlet syndrome
(E) lumbar plexopathy

**158.** A 52-year-old man with a history of colorectal cancer consulted the neurologist because of a new onset of back and right-lower-extremity pain. Neurological assessment demonstrated sensory loss to pinprick over the lateral and medial right thigh and weakness of hip flexion, leg extension, and thigh adduction. These findings are suggestive of

(A) Erb–Duchenne palsy
(B) Dejerine–Klumpke palsy
(C) a lesion of the cervical plexus
(D) thoracic outlet syndrome
(E) lumbar plexopathy

**159.** A 65-year-old man with a history of thoracotomy for a left lung cancer consulted the neurologist because he developed paresthesias of the left medial arm and forearm and a claw deformity of the left hand. These findings are suggestive of

(A) Erb–Duchenne palsy
(B) Dejerine–Klumpke palsy
(C) a lesion of the cervical plexus
(D) thoracic outlet syndrome
(E) lumbar plexopathy

# Answers and Explanations

**1.** **(B)** Argyll–Robertson pupil is classically seen in patients with neurosyphilis. The lesion is thought to be in the rostral midbrain, injuring the supranuclear inhibitory fibers that affect the visceral oculomotor nuclei. The pupils are usually affected bilaterally and are irregularly miotic with variable iris atrophy. There is a decrease or absence of the pupillary light reaction with conservation of the near response in the presence of normal visual acuity.

Holmes–Adie or tonic pupil syndrome is a condition of unknown cause related to degeneration of nerve cells in the ciliary ganglion. The degeneration of short ciliary nerves, with subsequent collateral sprouting, results in a predominance of accommodation elements in the innervation of the iris. It is more frequent in females and can be unilateral at first. Typically, the patient presents with blurred near vision, loss of knee and ankle jerks, and impaired sweating. The pupil is round and widely dilated; it reacts poorly to light but better to accommodation. The minimal reaction to accommodation or to light is probably related to partial reinnervation of parasympathetic fibers and slow inhibition of sympathetic fibers. The diagnosis is confirmed by pupillary reaction to pilocarpine drops. Pilocarpine is rapidly hydrolyzed by acetylcholine esterase and has no effect on the normal pupil. In Holmes–Adie syndrome, the denervated pupil with enzyme depletion allows the pilolоconstrictor effect to occur.

Epidemic encephalitis lethargica causes loss of convergence with parkinsonism. The patient's pupils react to light but not to accommodation.

Parinaud syndrome results from a lesion in the dorsal rostral midbrain that interferes with the decussating light reflex fibers in the periaqueductal area. The syndrome is characterized by dilated, fixed pupils to light; loss of upward gaze; defective convergence; skew deviation; light near dissociation (reaction to accommodation but not to light); and lid retraction.

Any lesion affecting the afferent pathways—the retina, optic chiasm, optic tract, and particularly the optic nerve—will cause Marcus Gunn pupil. When the abnormal eye is stimulated by light, it will slowly and briefly constrict and may start to dilate while it is still illuminated. This is also illustrated in the swinging flashlight test: the abnormal eye dilates instead of constricting when the light is rapidly alternated from one eye to another, whereas the normal eye constricts and stays small. *(Brazis, Masdeu, and Biller, 197–205; Thompson and Miller, 961–1040)*

**2.** **(A)** Pupillary size is under the dual control of sympathetic and parasympathetic systems that innervate rings of radially arranged dilator and constrictor fibers, respectively. The sympathetic system starts from the hypothalamus; its fibers descend in the brainstem and lateral column of the spinal cord to exit at the cervical (C8) and thoracic (T1-T2) levels as a second-order neurons. These neurons pass from the spinal cord to the superior cervical ganglion and exit as third-order neurons, which supply the pupillodilator fibers and blood vessels of the eye, passing over the carotid artery. Horner syndrome may result from a lesion anywhere along the three neural pathways of the sympathetic nervous sytem. It is characterized by the triad of miosis, ptosis, and anhidrosis of the the forehead. Patients with central or first-order Horner syndrome can usually be identified by the presence

of associated hypothalamic, brainstem, or spinal cord signs or symptoms. The syndrome occurs more commonly with vascular damage to the brainstem, as with midbrain infarction and spinal artery thrombosis. It may also be seen with hypothalamic infarction, hemorrhage, or tumor. The second-order neuron Horner syndrome may include neck or arm pain, anhidrosis involving the face and neck, brachial plexopathy, vocal cord paralysis, or phrenic nerve palsy. Neoplasms located in the head, neck, brachial plexus, lung, or breast may also cause a second-order Horner syndrome. In postganglionic (third-order) Horner syndrome, the patient may have ipsilateral pain and other symptoms suggestive of cluster migraine headaches. Postganglionic Horner syndrome may be caused by ipsilateral cartotid dissection, Cavernous sinus lesions, neoplasms, otitis media, and inflammatory or infectious lesions. *(Brazis, Masdeu, and Biller, 199–201)*

3. **(C)** A unilateral large, poorly reactive pupil may occur in third-nerve palsy, contusion of the eye, focal seizure, and during accidental exposure to aerosolized anticholenergic drugs. Botulism as well as delirium may cause bilateral mydriasis with normal reaction to light. A unilateral small reactive pupil may occur as a part of Horner syndrome in traumatic carotid dissection. An acute pontine lesion may cause reactive, bilateral pinpoint pupils. *(Brazis, Masdeu, and Biller, 204)*

4. **(A)** Opsoclonus consists of rapid, involuntary, multivectorial, unpredictable, conjugate fast eye movements without intersaccadic intervals. It indicates brainstem (especially mesencephalic) or cerebellar disease. It persists during eye closure and during sleep and is thought to be due to dysfunction of omnipause neurons that normally exert tonic inhibition on burst neurons. *(Brazis, Masdeu, and Biller, 218)*

5. **(B)** The patient described in the vignette developed an acute onset of speech dysfunction. An acute embolic stroke could be the cause of her condition because of her past medical history of mitral stenosis. Although her speech fluency was relatively preserved, her comprehension, naming, and repetition abilities were affected. The most likely diagnosis of this patient is Wernicke aphasia. In most right-handed patients and more than two thirds of left handers, the left superior temporal gyrus and the neighboring inferior parietal lobule play the greatest role in processing language-related auditory stimuli. Lesion centered in the posterior two thirds of the superior temporal gyrus affecting the auditory association cortex (area 22 of Brodmann, or Wernicke area) tend to cause the greatest impairment in the comprehension of auditory language. Patients with Wernicke aphasia are unable to repeat sentences, assemble phonemes, and name things correctly. However, their speech is fluent (effortless, melodic, well woven, and produced at a normal or even faster rate). *(Brazis, Masdeu, and Biller, 484–485)*

6. **(D)** Alexia with agraphia is usually associated with a pure lesion of the dominant angular gyrus if the patient does not have Wernicke aphasia. In addition to the reading and writing disturbance, affected patients usually have acalculia, finger agnosia, right-left disorientation, and difficulty with spelling words and understanding spelled-out words. *(Brazis, Masdeu, and Biller, 482)*

7. **(A)** In alexia without agraphia, the affected patient is able to write on dictation but not able to read. This difficulty results from damage to the pathways conveying visual input from both hemispheres to the dominant angular gyrus, which itself remains intact but disconnected from visual regions. This phenomenon usually occurs with combined lesions of the dominant medial occipital region and the fibers that reach the angular gyrus from the nondominant occipitotemporal cortex. These fibers are often damaged in the splenium of the corpus callosum. *(Brazis, Masdeu, and Biller, 482)*

8. **(E)** Transcortical sensory aphasia is seen in patients who have poor comprehension but retain fluent grammatical speech. They can repeat words well but are unable to understand their meaning, whether the words are spoken or written. Except for spared repetition,

transcortical sensory aphasia is an analogue of Wernicke aphasia. It is most often due to lesions in the posterior middle temporal gyrus, angular gyrus, white matter of the temporal isthmus, or posterior periventricular area. *(Brazis, Masdeu, and Biller, 487–488)*

**9.** **(E)** Gerstmann syndrome is characterized by the association of finger agnosia, right–left disorientation, agraphia, and acalculia. It may be seen in damage to the angular and supramarginal gyri of the dominant hemisphere. Such damage can also involve the subangular white matter, affecting the forceps of the splenium of the corpus callosum. *(Brazis, Masdeu, and Biller, 492)*

**10.** **(B)** Optic ataxia is a part of Balint syndrome, which follows a bilateral parietooccipital lesion in the convexity of the hemispheres and is characterized by (a) failure to shift gaze on command and difficulty in redirecting attention voluntarily; (b) optic ataxia, a disturbance of reaching a target under visual control, manifested by a clumsiness of object-bound movements of the hand performed under visual guidance; and (c) reduced visual attention, affecting mainly the peripheral visual fields and resulting in constriction of the fields to tunnel vision. *(Brazis, Masdeu, and Biller, 481)*

**11.** **(B)** Patients with acute bilateral and extensive medial occipital lesions that render them blind may deny any difficulty with seeing and may confabulate about what they see. *(Brazis, Masdeu, and Biller, 482)*

**12.** **(A)** Damage to the lateral occipital cortex may result in alexia with agraphia, visual allesthesia, palinopsia, impaired ipsilateral scanning, and impaired optokinetic nystagmus. *(Brazis, Masdeu, and Biller, 506)*

**13.** **(D)** Bilateral medial temporal lobe damage may cause Klüver–Bucy syndrome. The amygdala has been particularly implicated in the pathogenesis of this syndrome. Affected patients may develop (a) abnormal docility, characterized by the exhibition of diminished fear responses or unusually low levels of aggression—a phenomenon that has been termed "placidity" or "tameness"; (b) abnormal dietary changes, as with eating inappropriate things and/or overeating (e.g., bulimia); (c) hyperorality; (d) hypersexuality; (e) hypermetamorphosis; and (f) visual agnosia. *(Brazis, Masdeu, and Biller, 506)*

**14.** **(D)** The alien limb sign includes failure to recognize ownership of one's limb when visual cues are removed, a feeling that a body part is foreign, personification of the affected body part, and autonomous activity of the limb that is perceived as being beyond voluntary control. This sign is seen with damage to the corpus callosum, mesial frontal lobe, or cingulate gyrus or with combined infarction of the posterior corpus callosum and thalamus. *(Brazis, Masdeu, and Biller, 507)*

**15.** **(A)** The orbitofrontal cortex is interlinked with limbic and reticular areas and is activated with the emotions of anger or fear; some of its neurons respond selectively to aversive stimuli. Damage to the orbitofrontal area may cause blunted affect, impaired appreciation of social nuances, impaired goal-directed behavior, impotence, facetiousness, and environmental dependency syndrome. *(Brazis, Masdeu, and Biller, 503–508)*

**16.** **(E)** The corpus callosum is a structure of the mammalian brain in the longitudinal fissure that connects the left and right cerebral hemispheres. It also facilitates communication between the two hemispheres. Much of the interhemispheric communication in the brain is conducted across the corpus callosum. Damage to the corpus callosum may specifically affect tasks that require coordination between the left and right hemispheres. Such damage also causes lack of kinesthetic transfer with inability to mimic position of the contralateral hand, left-hand apraxia, left-hand agraphia, right-hand constructional apraxia, and intermanual conflict. Other signs of damage to the corpus callosum include perplexity, double hemianopia, and left hemiparalexia. *(Brazis, Masdeu, and Biller, 508)*

**17.** **(C)** Hemiballismus results from damage to the contralateral subthalamic nucleus. *(Brazis, Masdeu, and Biller, 424)*

**18.** **(D)** Choreoathetosis results from damage to the contralateral anteroventral portion of the caudate nucleus. *(Brazis, Masdeu, and Biller, 508)*

**19.** **(B)** Sudden bilateral paramedian thalamic lesions may cause a decreased level of alertness ranging from somnolence to coma. Akinetic mutism may follow bilateral paramedian lesions. It is characterized by absolute mutism and complete immobility except for the eyes, which are kept open and move in all directions. The patient appears awake and maintains a sleep–wake cycle without the ability to communicate. Akinetic mutism has also been described with injury of the mesencephalic reticular formation. *(Brazis, Masdeu, and Biller, 407; Afifi, 153)*

**20.** **(A)** Lesion of the pulvenar may result in a decrease in the critical flicker frequency and neglect of visual objects at the periphery of the contralateral visual field, prolonged latency of visual evoked saccadic eye movements, and paucity of spontaneous eye movements directed toward the contralateral hemifield. *(Brazis, Masdeu, and Biller, 412)*

**21.** **(E)** This is a pattern of periodic breathing in which phases of hyperpnea regularly alternate with apnea. The breathing waxes from breath to breath in a smooth crescendo and then, once a peak is reached, wanes in an equally smooth decrescendo. The hyperpneic phase usually lasts longer than the apneic phase. Cheyne–Stokes respiration implies bilateral dysfunction of neurological structures usually lying deep in the cerebral hemispheres or diencephalon. Cheyne–Stokes respiration is the outcome of a combination of an abnormally increased ventilatory response to $CO_2$ stimulation, causing hyperpnea, and an abnormally decreased forebrain ventilatory stimulus, permitting posthyperventilation apnea. Patients with bilateral hemispheric lesions overbreathe when stimulated by $CO_2$, a phenomenon reminiscent of other facilitated neurological responses to stimulation. As a result of the overbreathing, the blood's $CO_2$ content drops below the level where it stimulates the respiratory centers and, in the presence of brain dysfunction, breathing stops. During apnea, $CO_2$ reaccumulates until it exceeds the respiratory threshold, and the cycle repeats itself. *(Brazis, Masdeu, and Biller, 560)*

**22.** **(A)** Apneustic respiration is an abnormal pattern of breathing characterized by deep, gasping inspiration with a pause at full inspiration followed by a brief, insufficient release. It is seen in dysfunction of the lower pontine tegmentum. *(Plum, 35)*

**23.** **(B)** Ataxic breathing has a completely irregular pattern in which both deep and shallow breaths occur randomly. Irregular pauses appear haphazardly, and there is no predicting the future respiratory rhythm from the pattern of past breaths. Physiologically, ataxic breathing represents primary functional disruption of the medullary neuronal populations that normally generate the respiratory rhythm. *(Plum, 38)*

**24.** **(E)** Pontine lesions in the tegmentum interrupt descending sympathetic pathways and produce bilaterally small pupils. Pinpoint pupils generally mean pontine hemorrhage and are believed to result from parasympathetic irritation in combination with sympathetic interruption. *(Plum, 44–45)*

**25.** **(C)** Figure 2-1 is a schematic diagram of the structures involved in lateral medullary syndrome: spinal nucleus of the trigeminal nerve and its tract, adjacent spinothalamic tract, nucleus ambiguus or its axons, restiform body, vestibuilar nuclei, descending sympathetic fibers from the hypothalamus, and olivocerebellar fibers. The neurological signs and symptoms resulting from the shaded area in Figure 2-1 include the following: loss of pain and temperature sensation in the ipsilateral face and contralateral half of the body, ataxia, vertigo, loss of gag reflex and difficulty with swallowing, ipsilateral Horner syndrome, vomiting, nausea, nystagmus, hiccups, and ocular lateropulsion. *(Afifi, 99)*

**26.** **(A)** Figure 2-2 is a schematic diagram of the structures involved in medial medullary syndrome: medial lemniscus, rootlets of the hypoglossal nerve or its nucleus within the

medulla and pyramid. The neurological signs and symptoms resulting from the shaded area in Figure 2-2 include paralysis of the homolateral half of the tongue, contralateral upper motor neuron syndrome, and contralateral loss of kinesthesia and discrimination touch. *(Afifi, 99)*

**27. (C)** Figure 2-3 is a schematic diagram of the structures involved in the caudal pontine syndrome (Millard–Gubler): the corticospinal tract and facial nerve. The manifestations of this syndrome include ipsilateral facial paralysis of the peripheral type and contralateral hemiplegia of the upper motor neuron type. Frequently, the lesion may extend medially and rostrally to include the rootlets of the sixth nerve, as illustrated in Figure 2-4. In addition to the manifestations of the Millard–Gubler syndrome, the affected patient may develop ipsilateral paralysis of ocular abduction. *(Afifi, 124)*

**28. (B)** In uncal herniation, the innermost part of the temporal lobe, the uncus, can be squeezed so much that it goes by the tentorium and puts pressure on the brainstem, most notably the midbrain. As illustrated in Figure 2-5, an expanding lesion (which could be located in the lateral middle fossa or temporal lobe) commonly pushes the medial edge of the uncus and hippocampal gyrus toward the midline and over the free lateral edge of the tentorium. Because the diencephalon may be not the first structure encroached upon, impaired consciousness is not consistently an early sign of impending uncal herniation, and the state of alertness in different subjects may vary from near wakefulness through stupor to coma. The uncus can squeeze the third cranial nerve, which controls parasympathetic input to the eye on the side of the affected nerve. This interrupts parasympathetic neural transmission, causing the pupil of the affected eye to dilate and fail to constrict as it should in response to light. Thus, the earliest consistent sign of uncal herniation is the unilaterally dilated pupil. Moderate anisocoria with a sluggish light reaction of the dilated pupil can somtimes last for several hours before other signs appear. Pupillary dilation often precedes a later finding of oculomotor nerve compression, which is deviation of the eye to a "down and out" position due to loss of innervation to all ocular motility muscles except for the lateral rectus (innervated by the abducens cranial nerve) and the superior oblique (innervated by the trochlear cranial nerve). *(Plum, 109)*

**29. (A)** Unlike temporal masses, frontal, parietal, or occipital masses first compress the diencephalon, which, as the supratentorial pressure increases, shifts downward and buckles over the midbrain. Subsequently, flattening of the midbrain and pons in the rostrocaudal direction causes elongation and rupture of the paramedian perforating arteries feeding these structures, resulting in infarction and hemorrhage in the tegmentum of the midbrain first and pons afterward. The first evidence that a supratentorial mass is beginning to impair the diencephalon is usually a change in alertness or behavior. Initially, subjects with such lesions find it difficult to concentrate and tend to lose the orderly details of recent events. Respiration in the early diencephalic stage of the central syndrome is commonly interrupted by deep sighs, yawns, and occasional pauses. As such patients sink into deeper somnolence, many have periodic breathing of the Cheyne–Stokes type. *(Plum, 103–104)*

**30. (E)** In the medullary stage of central herniation, ataxic breathing occurs and soon gives way to apnea. The blood pressure drops and the pulse becomes irregular. *(Brazis, Masdeu, and Biller, 574)*

**31. (A)** Pretectal or tectal midbrain lesions affecting the posterior commissure abolish the light reflex, but the pupils, which are midsized or large, may show spontaneous oscillation in size (hippus) and become larger when the neck is pinched (ciliospinal reflex). Tegmental lesions that involve the third-nerve nucleus may cause irregular constriction of the sphincter of the iris, with a resultant pear-shaped pupil or displacement of the pupil to one side (corectopia). *(Brazis, Masdeu, and Biller, 563)*

**32. (B)** Apneustic breathing is characterized by a long inspiratory pause, after which the air is retained for several seconds and then released.

This abnormality appears with lesions of the lateral tegmentum of the lower half of the pons. *(Brazis, Masdeu, and Biller, 561)*

**33. (D)** Figure 2-6 is a schematic diagram showing structures involved in the rostral basal pontine syndrome: the trigeminal nerve and the corticospinal tract. A basal pontine lesion at the level of the trigeminal nerve results in ipsilateral paralysis of the masticatory muscles (masseter, temporalis, medial and lateral pterygoid muscles), ipsilateral loss of facial sensation, and contralateral limb paralysis. *(Afifi, 125)*

**34. (E)** Figure 2-7 is a schematic diagram showing structures involved in the medial tegmental syndrome: the nucleus and the rootlets of the abducens nerve, the genu of the facial nerve, and the medial lemniscus. The manifestations of the lesion therefore include ipsilateral abducens nerve paralysis with lateral gaze palsy, ipsilateral facial nerve paralysis of peripheral type, and contralateral loss of kinesthesia and discriminative touch. *(Afifi, 125)*

**35. (D)** The dashed area indicated by arrow A in Figure 2-8 includes rootlets of the oculomotor nerve. Damage to the oculomotor nerve causes a dilated unresponsive pupil, drooping of the eyelid, and deviation of eye downward and outward. *(Afifi, 152)*

**36. (B)** The dashed area indicated by arrow B in Figure 2-8 includes rootlets of the oculomotor nerve and the underlying cerebral peduncle. Damage to the dashed area causes Weber syndrome, which is characterized by ipsilateral oculomotor paralysis (dilated unresponsive pupil, drooping of the eyelid, and deviation of eye downward and outward) and contralateral upper motor neuron paralysis that includes the lower face. *(Afifi, 151–152)*

**37. (B)** The dashed area indicated by arrow C in Figure 2-8 includes rootlets of the oculomotor nerve within the tegmentum of the mesencephalon and the underlying red nucleus. Lesions of the dashed area cause the syndrome of Benedikt. It is characterized by ipsilateral oculomotor nerve paralysis (dilated unresponsive pupil, drooping of the eyelid, and deviation of eye downward and outward) and contralateral tremor. *(Afifi, 151)*

**38. (A)** A pretectal lesion causes Parinaud syndrome. Patients with this syndrome present with upward gaze paralysis, pupillary abnormalities (large pupil, light–near dissociation), lid retraction, and convergence retraction nystagmus on upward gaze. *(Afifi, 152)*

**39. (B)** Infarction in the anteriomedial branches of the posterior cerebral artery is the cause of Claude syndrome in the majority of patients. It is characterized by ipsilateral oculomotor nerve palsy, contralateral tremor, and ataxia. *(Afifi, 152)*

**40. (A)** The patient described in this vignette suffers from peduncular hallucinosis syndrome. It is characterized by nonthreatening hallucinations, often formed nonstereotypically, that are colored and vivid; they usually occur in somnolent patients with presumed lesions of the tegmentum and cerebral peduncle. Peduncular hallucinosis has been reported in vascular and infective lesions of the thalamus, pars reticulata of substantia nigra, midbrain, pons, and basal diencephalon as well as by compression of the midbrain. Transient peduncular hallucinations due to extrinsic compression of the midbrain by cystic craniopharyngioma have also been reported. Such hallucinations have also been reported following the excision of a posterior fossa medulloblastoma. *(Afifi, 153; Kumar, 183–185; Kumar, 500–503)*

**41. (B)** A C5 root lesion induces neck, shoulder, and anterior upper arm pain. Muscle weakness occurs predominantly but variably in the following muscles: the supraspinatus and deltoid, resulting in weakness of shoulder abduction, and the rhomboid, serratus anterior, infraspinatus, biceps, and brachioradialis. Biceps and brachioradialis reflexes may be depressed. *(Brazis, Masdeu, and Biller, 93; Patten, 288–291)*

**42. (C)** A C6 root lesion is often caused by compression from disk herniation at the C5-C6 vertebral level. It results in pain in the lateral arm and dorsal forearm. Paresthesia and hypesthesia

occur in the lateral forearm, lateral hand, and first and second digits. Muscle weakness occurs in the biceps, pronator teres, and brachioradialis, inducing weakness of elbow flexion in both the fully supine position and half-pronated positions. The extensor carpi radialis longus, flexor carpi radialis brevis, supinator, and serratus anterior are also affected by C6 root damage. The biceps and brachioradialis reflexes may be depressed. *(Brazis, Masdeu, and Biller, 93; Patten, 288–291)*

**43. (D)** In monoradiculopathy, C7 is the most commonly affected level of the cervical roots, followed by the C6 nerve root. In C7 radiculopathy, pain is located in the dorsal forearm and middle and ring fingers. Paresis occurs variably in the pectoralis major and latissimus dorsi (inducing weakness of shoulder adduction), the triceps (inducing weakness of elbow extension), and the flexor carpi radialis, extensor carpi radialis longus, extensor carpi radialis brevis, and extensor digitorum (inducing weakness of wrist extension). The triceps reflex may be affected. *(Brazis, Masdeu, and Biller, 93; Patten, 288–291)*

**44. (E)** A C8 nerve root lesion causes pain in the medial arm, the forearm, and the fifth digit. Paresis occurs predominantly in the long forearm extensors and flexors of the fingers. *(Brazis, Masdeu, and Biller, 94; Patten, 288–291)*

**45. (A)** A T1 nerve root lesion causes a deep aching sensation in the shoulder joint, axilla, and medial side of the upper arm down to the olecranon. There is a loss of intrinsic hand muscles, including the abductor pollicis brevis muscle, which differentiates T1 nerve root lesions from ulnar nerve lesions (in ulnar nerve lesions, all intrinsic muscles of the hand are affected except the abductor pollicis brevis). *(Brazis, Masdeu, and Biller, 94; Patten, 288–291)*

**46. (C)** The musculocutaneous nerve arises from the lateral cord of the brachial plexus, opposite the lower border of the pectoralis minor, its fibers being derived from the fifth, sixth, and seventh cervical nerves. It penetrates the coracobrachialis muscle and passes obliquely between the biceps brachii and the brachialis, to the lateral side of the arm; a little above the elbow, it pierces the deep fascia lateral to the tendon of the biceps brachii and is continued into the forearm as the lateral antebrachial cutaneous nerve. In its course through the arm it innervates the coracobrachialis, biceps brachii, and the greater part of the brachialis. Musculocutaneous dysfunction causes atrophy of the biceps and brachialis, resulting in wasting of the ventral aspect of the upper arm and absence of the biceps reflex. *(Brazis, Masdeu, and Biller, 34; Patten, 292–296)*

**47. (A)** The radial nerve originates from the posterior cord of the brachial plexus with roots from C5, C6, C7, C8, and T1. The radial nerve and its branches supply the dorsal muscles, such as the triceps brachii, the extrinsic extensors of the wrist and hands, and cutaneous nerve supply to most of the back of the hand. It divides into a deep branch (which becomes the posterior interosseous nerve) and continues as the superficial branch, which goes on to innervate the dorsum (back) of the hand. "Saturday night palsy" corresponds to compression of the radial nerve within the spiral groove of the humerus. Clinical signs may include paralysis of extension of the wrist and elbow flexion and weakness of supination. Elbow extension is preserved because the radial nerve branches to the triceps muscle originate proximal to the spiral groove. *(Brazis, Masdeu, and Biller, 45–48; Patten, 292–296)*

**48. (B)** The ulnar nerve comes from the medial cord of the brachial plexus and runs inferior on the posterior and medial (posteromedial) aspects of the humerus down the arm, going behind the medial epicondyle and through the cubital tunnel at the elbow. At the forearm, it enters the anterior compartment of the forearm through the two heads of flexor carpi ulnaris and runs alongside the ulna. There it supplies 1½ muscles (the flexor carpi ulnaris and medial half of flexor digitorum profundus). After it travels down the ulna, the ulnar nerve enters the palm of the hand and passes superficial to the flexor retinaculum via the ulnar canal to give off the superficial and deep

branches of the ulnar nerve. The deep branch of the ulnar nerve supplies the hypothenar muscles (opponens digiti minimi, abductor digiti minimi, flexor digiti minimi brevis), adductor pollicis, the third and fourth lumbrical muscles, and the dorsal and palmar interossei. The superficial branch of the ulnar nerve supplies the palmaris brevis. An ulnar nerve lesion at the wrist may cause paralysis of all intrinsic hand muscles except the abductor pollicis brevis, which is innervated by the median nerve. Since the ulnar nerve lesion is proximal to the origin of the superficial terminal cutaneous branch of the ulnar nerve, there is sensory loss on the distal part and the palmar surfaces of the fifth and medial half of the fourth fingers. *(Brazis, Masdeu, and Biller, 40–44; Patten, 292–296)*

**49.** **(D)** A median nerve lesion at the upper arm may cause pain in the thumb, index, and middle fingers that spreads up from the forearm to the elbow. Motor signs may include paresis of forearm pronation, radial wrist flexion, distal flexion of the thumb, palmar abduction, opposition of the thumb, and flexion of the second and, to a lesser extent, third fingers. Weakness of the pinch sign results from paresis of the flexor digitorum profundus of the index finger and of the flexor pollicis longus. *(Brazis, Masdeu, and Biller, 35–40; Patten, 292–296)*

**50.** **(A)** The lumbar plexus is formed by the loops of communication between the anterior divisions of the first three and the greater part of the fourth lumbar nerves; the first lumbar often receives a branch from the last thoracic nerve. The first lumbar nerve, frequently supplemented by a twig from the last thoracic, splits into upper and lower branches; the upper and larger branch divides into the iliohypogastric and ilioinguinal nerves; the lower and smaller branch unites with a branch of the second lumbar to form the genitofemoral nerve. The remainder of the second lumbar nerve and the third and fourth lumbar nerves split into ventral and dorsal divisions. The ventral division of the second lumbar nerve unites with the ventral divisions of the third and fourth lumbar nerves to form the obturator nerve. The dorsal divisions of the second and third nerves divide into two branches, a smaller branch from each uniting to form the lateral femoral cutaneous nerve and a larger branch from each joining with the dorsal division of the fourth nerve to form the femoral nerve. The accessory obturator, when it exists, is formed by the union of two small branches given off from the third and fourth nerves. A lumbar plexus lesion causes pain across the thigh. Sensation may be lost in the inguinal region and over the genitalia innervated by the iliohypogastric, ilioinguinal, and genitofemoral nerves. The sensation of the anterior and medial parts of the thigh may be affected. Motor signs include paresis and atrophy of muscles innervated by the femoral and obturator nerves. Thus, there is weakness of thigh flexion because of paresis of the iliopsoas, leg extension because of paresis of the quadriceps, thigh eversion because of paresis of the sartorius, and thigh adduction because of paresis of the adductor muscles. The patellar and cremasteric reflexes may be decreased or absent. *(Brazis, Masdeu, and Biller, 81–84; Patten, 299–314)*

**51.** **(C)** The obturator nerve arises from the ventral divisions of the second, third, and fourth lumbar nerves; the branch from the third is the largest, while that from the second is often very small. It descends through the fibers of the psoas major and emerges from its medial border near the brim of the pelvis; it then passes behind the common iliac vessels, on the lateral side of the hypogastric vessels and ureter, and runs along the lateral wall of the lesser pelvis, above and in front of the obturator vessels, to the upper part of the obturator foramen. Here it enters the thigh through the obturator canal and divides into anterior and posterior branches, which are separated at first by some of the fibers of the obturator externus and lower down by the adductor brevis. The obturator nerve is responsible for the sensory innervation of the skin of the medial aspect of the thigh. It is also responsible for the motor innervation of the adductor muscles of the lower extremity (external obturator, adductor longus, adductor brevis, adductor magnus, gracilis). The patient in this vignette developed

sensory and motor disturbance in the territory of the obturator nerve: disturbance of sensation in the medial aspect of the thigh and weakness of the adductor muscles. Pregnancy may cause compression of the obturator nerve in the obturator canal. *(Brazis, Masdeu, and Biller, 53–55; Patten, 299–314)*

**52. (E)** The tibial nerve is a branch of the sciatic nerve. It passes through the popliteal fossa and below the arch of soleus. In the popliteal fossa, the nerve gives off branches to the gastrocnemius, popliteus, soleus, and plantaris muscles, an articular branch to the knee joint, and a cutaneous branch that becomes the sural nerve. The sural nerve is joined by fibers from the common peroneal nerve and runs down the calf to supply the lateral side of the foot. Below the soleus muscle, the nerve lies close to the tibia and supplies the tibialis posterior, the flexor digitorum longus, and the flexor hallucis longus. The nerve passes into the foot running posterior to the medial malleolus. Here it is bound down by the flexor retinaculum in company with the posterior tibial artery. In the foot, the nerve divides into medial and lateral plantar branches. The medial plantar nerve supplies the abductor hallucis, the flexor digitorum brevis, the flexor hallucis brevis, and the first lumbrical. Cutaneous distribution of the medial plantar nerve is to the medial sole and medial 3½ toes, including the nail beds on the dorsum (like the median nerve in the hand). The lateral plantar nerve supplies the quadratus plantae, flexor digiti minimi, adductor hallucis, interossei, three lumbricals, and abductor digiti minimi. Cutaneous innervation is to the lateral sole and lateral 1½ toes. The patient described in the vignette has sensory loss in the territory of the tibial nerve. Weakness of plantarflexion and inversion of the foot is caused by weakness of the gastrocnemius and the tibialis posterior muscles (both are innervated by the tibial nerve). *(Brazis, Masdeu, and Biller, 57; Patten, 299–314)*

**53. (D)** The sciatic nerve is the longest and widest single nerve in the body. It supplies nearly the whole of the skin of the leg, the muscles of the back of the thigh, and those of the leg and foot. The nerve enters the lower limb by exiting the pelvis through the greater sciatic foramen, below the Piriformis muscle. It descends midway in the greater trochanter of the femur and the tuberosity of the ischium, and along the back of the thigh to about its lower third, where it divides into two large branches, the tibial and common peroneal nerves. The nerve gives off articular and muscular branches. The articular branches (rami articulares) arise from the upper part of the nerve and supply the hip-joint, perforating the posterior part of its capsule. The muscular branches (rami musculares) are distributed to the following muscles of the lower limb: Biceps femoris, Semitendinosus, Semimembranosus, and Adductor magnus. The nerve to the short head of the Biceps femoris comes from the common peroneal part of the sciatic, while the other muscular branches arise from the tibial portion, as may be seen in those cases where there is a high division of the sciatic nerve. The muscular branch eventually gives off the tibial nerve and common peroneal nerve, which innervates the muscles of the (lower) leg. The tibial nerve goes on to innervate all muscles of the foot except the extensor digitorum brevis (peroneal nerve). The patient described in this vigentte has a flail foot because of paralysis of flexors and extensors of the left foot, and knee flexion weakness due to paresis of the hamstring muscles. A single lesion in the sciatic nerve would result in these and in loss of sensation in the lateral leg. Decreased Achilles reflex can occur in sciatic lesions because the tibial nerve subserves this reflex. Sciatic nerve injury may be caused by fracture dislocation of the hip, pelvic cancer surgery, infection, and buttock intramuscular injection, as illustrated in this case. *(Brazis, Masdeu, and Biller, 57–64; Patten, 299–314)*

**54. (A)** The lateral cutaneous nerve of the thigh is a nerve of the lumbar plexus. It arises from the dorsal divisions of the second and third lumbar nerves. It emerges from the lateral border of the psoas major at about its middle and crosses the iliacus muscle obliquely, toward the anterosuperior iliac spine. It then passes under the inguinal ligament and over the sartorius muscle into the thigh, where it divides into anterior and posterior branches. The anterior branch

becomes superficial about 10 cm below the inguinal ligament and divides into branches that are distributed to the skin of the anterior and lateral parts of the thigh as far as the knee. The posterior branch pierces the fascia lata and subdivides into filaments that pass backward across the lateral and posterior surfaces of the thigh, supplying the skin from the level of the greater trochanter to the middle of the thigh. The patient described in this vignette has a sensory disturbance located in the region of the lateral femoral cutaneous nerve. Entrapment of this nerve is also known as meralgia paresthetica. Entrapment usually occurs at the inguinal ligament. The peak incidence for this condition is in middle age. The entrapment may be from intrapelvic, extrapelvic, or mechanical causes. Intrapelvic causes would include pregnancy, abdominal tumors, uterine fibroids, diverticulitis, and appendicitis. Examples of extrapelvic causes include trauma to the region of the anterosuperior iliac spine (e.g., a seatbelt from a motor vehicle accident), tight garments, belts, girdles, or stretch from obesity and ascites. Mechanical factors include prolonged sitting or standing and pelvic tilt from leg-length discrepancy. Symptoms include anterior and lateral thigh burning, tingling, and/or numbness that increase with standing, walking, or hip extension. Symptoms may also increase with lying prone. Symptoms are usually unilateral but may be bilateral in rare cases. The symptoms usually improve with sitting unless compressive forces, such as tight belts or garments, remain. Physical examination findings may be completely normal. Findings may include hyperesthesia over the lateral thigh (usually in a smaller area than the symptoms). Pain can be produced by pressure medial to the anterosuperior iliac spine . A positive Tinel sign may be present over the anterosuperior iliac spine or inguinal ligament. *(Brazis, Masdeu, and Biller, 55–56; Patten, 299–314)*

**55. (B)** The patient described in this vignette developed loss of sensation in the territory of the left posterior femoral cutaneous and sciatic nerves. There is weakness of all movement of the foot. This includes foot plantarflexion (due to weakness of the gastrocnemius and soleus), toe dorsiflexion and plantarflexion, foot eversion and inversion (due to weakness of the peronei and tibialis anterior and the posterior calf muscles, respectively). All of these muscles are in the sciatic distribution. Paresis of hip extension results from weakness of the gluteus maximus, innervated by the inferior gluteal nerve. Paresis of abduction and internal rotation of the thigh results from weakness of the gluteus medius and minimus, innervated by the superior gluteal nerve. Thus the patient described in this vignette has symptoms and signs in the distribution of the sciatic nerve, superior gluteal nerve, and inferior gluteal nerve. Compression of the left sacral plexus by metastasis from the breast may explain the patient's clinical picture. *(Brazis, Masdeu, and Biller, 81–83; Patten, 299–314)*

**56. (A)** The femoral nerve, the largest branch of the lumbar plexus, arises from the dorsal divisions of the second, third, and fourth lumbar nerves. It descends through the fibers of the psoas major, emerging from the muscle at the lower part of its lateral border, and passes down between it and the iliacus, behind the iliac fascia; it then runs beneath the inguinal ligament into the thigh, and splits into anterior and posterior divisions. Under the inguinal ligament, it is separated from the femoral artery by a portion of the psoas major. Within the abdomen, the femoral nerve gives off small branches to the iliacus and a branch that is distributed upon the upper part of the femoral artery; the latter branch may arise in the thigh. In the thigh, the anterior division of the femoral nerve gives off anterior cutaneous and muscular branches. The muscular branches supply the pectineus and sartorius muscles. The posterior division of the femoral nerve gives off the saphenous nerve and muscular and articular branches.The muscular branches supply the four parts of the quadriceps femoris. The patient reported in this vignette developed weakness of left knee extension, presumably by quadriceps weakness, and pain in the anterior thigh and medial leg caused by injury to the medial cutaneous nerve of the thigh and the saphenous nerves (both are branches of the femoral nerve). These symptoms suggest left

femoral nerve dysfunction. As the patient in this case has a history of falling and of warfarin use, a retroperitoneal hematoma with femoral nerve compression is the most likely etiology. However, retroperitoneal hematoma is more commonly associated with diffuse weakness because multiple portions of the lumbosacral plexus are involved. *(Brazis, Masdeu, and Biller, 51–53; Patten, 299–314)*

**57. (B)** The common peroneal nerve is derived from the dorsal branches of the fourth and fifth lumbar and the first and second sacral nerves. It descends obliquely along the lateral side of the popliteal fossa to the head of the fibula, close to the medial margin of the biceps femoris muscle. It lies between the tendon of the biceps femoris and lateral head of the gastrocnemius muscle, winds around the neck of the fibula between the peroneus longus and the bone, and divides beneath the muscle into the superficial and deep peroneal nerves. Previous to its division it gives off articular and lateral sural cutaneous nerves. The deep fibular nerve supplies muscular branches to the tibialis anterior, extensor digitorum longus, fibularis (peroneus) tertius, and extensor hallucis longus (propius). The patient described in the vignette developed weakness of foot dorsiflexion and eversion associated to a sensory loss suggestive of left peroneal neuropathy. *(Brazis, Masdeu, and Biller, 57–62; Patten, 299–314)*

**58. (E)** The pudendal nerve originates in the sacral plexus; it derives its fibers from the ventral rami of the second, third, and fourth sacral nerves (S2, S3, and S4). It passes between the piriformis and coccygeus muscles and leaves the pelvis through the lower part of the greater sciatic foramen. It crosses the spine of the ischium and reenters the pelvis through the lesser sciatic foramen. The pudendal nerve gives off the inferior rectal nerves. It soon divides into two terminal branches: the perineal nerve, and the dorsal nerve of the penis (in males) or the dorsal nerve of the clitoris (in females). The patient described in the vignette has clinical manifestations suggesting pudendal nerve damage. Pudendal neuropathy can cause rectal, perineal, or genital pain. The symptoms may include stabbing, twisting, or burning pain, pins and needles, numbness, or hypersensitivity. Usually, the symptoms are made worse by sitting and better by either standing or lying down. *(Brazis, Masdeu, and Biller, 56–57; Patten, 299–314)*

**59. (A)** $B_{12}$ deficiency and ethanol abuse may cause toxic optic neuropathy. Peripheral vision is usually spared, since the pattern of loss typically involves a central or cecocentral scotoma, a visual field defect at or surrounding the point of fixation. $B_{12}$ deficiency may affect mitochondrial oxidative phosphorylation, causing an acquired mitochondrial optic neuropathy. Vision loss in $B_{12}$ deficiency is bilateral, symmetric, painless, gradual, and progressive. Dyschromatopsia, a change in color vision, is often the first symptom. Some patients notice that certain colors, particularly red, are less bright or vivid; others have a general loss of color perception. Loss of visual acuity may start with a blur or haze at the point of fixation followed by a progressive decline. The degree of vision loss can extend to total blindness, but a loss beyond 20/400 is rare. *(Kline, 159)*

**60. (B)** Bilateral compression of the lateral optic chiasm is rare. It may be caused by the intracavernous part of an arteriosclerotic carotid artery pushing the chiasm against the opposite carotid artery. It may also be caused by dilatation of the third ventricle secondary to chronic aqueductal stenosis. The chiasm is splayed laterally by the dilated third ventricle and damaged by the pulsatile carotid arteries pressing against its lateral edge. Bilateral compression of the lateral chiasm may cause binasal hemianopia. However, binasal hemianopia is most often caused by retinal or optic nerve disease. Intracranial causes may include skull fracture, neurosyphilis, chiasmal arachnoiditis, and neoplasms. *(Kline, 227)*

**61. (C)** The drug ethambutol is commonly associated with toxic optic neuropathy. The optic neuropathy that occurs is dose-dependent and duration-related. Loss of vision does not tend to occur until the patient has been on the drug for at least 2 months, but there are rare reports of early onset of severe bilateral visual loss

even with appropriate dosing. Symptoms generally appear between 4 months to a year after the initiation of treatment. This onset may be sooner if the patient has concurrent renal disease, because this will result in reduced excretion of the drug and therefore elevated serum levels. The clinical presentation may include a central visual deficit. Some patients may complain of such a deficit and often claim that if they could see around it, their vision would be normal. The clinical presentation may also include dyschromatopsia. Therefore, appropriate color vision testing is of particular importance in screening patients on this drug. *(Kline, 157)*

**62. (D)** At the chiasm, fibers from the inferior part of the nasal retina are ventral in the chiasm and loop into the proximal part of the contralateral optic nerve before turning back to join uncrossed inferotemporal fibers in the optic tract. Compression of the junction between the optic nerve and optic chiasm may cause an ipsilateral central scotoma with a contralateral superior temporal visual defect. *(Brazis, Masdeu, and Biller, 162–163)*

**63. (E)** Bitemporal hemianopsia is a type of partial blindness where vision is missing in the outer half of both the right and left visual fields. It is usually associated with lesions of the optic chiasm. Bitemporal hemianopia most commonly occurs as a result of tumors located at the midoptic chiasm, such as pituitary adenomas and craniopharyngiomas. *(Brazis, Masdeu, and Biller, 162–163)*

**64. (A)** Anton's blindness is a rare symptom of brain damage occurring in the occipital lobe. The affected patients tend to dismiss their failure to see through confabulation. This condition is mostly seen following an acute extensive and medial occipital stroke. *(Brazis, Masdeu, and Biller, 482–483)*

**65. (D)** The anterior visual cortex is supplied by the posterior cerebral artery. Infarction of this area causes a macula-sparing hemianopia because the macular cortex has a dual vascular supply from the middle and posterior cerebral arteries. *(Brazis, Masdeu, and Biller, 162–163)*

**66. (A)** With eyelid closure, reflex innervation of the extraocular muscles results in an upward and slightly outward rotation of the globe. This reflex eye movement is Bell's phenomenon, a physiological mechanism that protects the cornea from exposure and ulceration. In patients who have reduced or absent Bell's phenomenon, a tarsorrhaphy or placement of a gold weight in the upper eyelid is sometimes needed to protect the affected eye. *(Brazis, Masdeu, and Biller, 245)*

**67. (D)** The Tolosa–Hunt syndrome, a painful ophthalmoplegia, is characterized by steady, unremitting retro- and supraorbital pain in the trigeminal nerve's ophthalmic distribution in association with paresis of the oculomotor, trochlear, and abducens nerves as well as a diminished corneal reflex. Sensory loss and pain in the mandibular trigeminal distribution may also occur. Less frequently, the optic nerve and oculosympathetic fibers may be affected. Symptoms may persist for weeks to months. Both sexes are equally affected. The sedimentation rate may be elevated. Pathologically, a low-grade, noninfectious granulomatous process adjacent to the cavernous sinus or within the superior orbital fissure has been identified. The granulomas consist of lymphocytes and plasma cells. The Tolosa–Hunt syndrome typically responds dramatically to systemic corticosteroids, although symptoms may recur months to years later. Spontaneous remissions have also been reported. *(Goetz and Pappert, 167)*

**68. (B)** The patient described in the vignette has weakness on right arm elevation associated with winging of the scapula. These signs point toward weakness of the serratus anterior muscle. This muscle fixes and stabilizes the scapula against the chest wall. It is tested by observing for scapular winging (the vertebral border of the scapula stands away from the thorax, forming a wing, while the patient pushes the extended arm against a fixed object). The serratus anterior muscle is innervated by the long thoracic nerve, which may be affected by a variety of athletic activities, like volleyball, for example. A C7 cervical root

lesion may cause weakness of the serratus anterior muscle, but in combination with weakness of the extensors of the arm, wrist, or fingers. Volleyball players are also prone to suprascapular nerve injuries. However, a lesion of the suprascapular nerve results in weakness of arm abduction and external rotation without scapular winging. A dorsal scapular nerve lesion causes weakness of the rhomboid and levator scapulae muscles, resulting in weakness of elevation and adduction of the medial border of the shoulder blade. Weakness of the trapezius muscle may cause winging of the scapula on abduction of the arm; the shoulder is lower on the affected side because there is weakness on elevation and retraction. *(Brazis, Masdeu, and Biller, 29; Staal, 19–21)*

**69. (B)** The radial nerve derives from the posterior cord of the brachial plexus and comprises fibers from spinal levels C5 to C8. In the axilla, the nerve gives rise to the posterior cutaneous nerve of the arm, which supplies the skin over the posterior aspect of the arm as far down as the olecranon. A secondary sensory branch, the posterior cutaneous nerve of the forearm, innervates the skin on the distal extensor aspect of the arm and the extensor aspect of the forearm up to the wrist. Within or proximal to the spiral groove, the radial nerve supplies the triceps and the anconeus; both are forearm extensors. At the level of the lateral condyle of the humerus, the radial nerve gives off branches to the brachialis muscle (an elbow flexor that is also innervated by the musculocutaneous nerve), the brachioradialis muscle (a forearm flexor midway between pronation and supination), and the extensor carpi radialis longus (radial extensor of the hand). The radial nerve then bifurcates into superficial and deep branches. The superficial branch emerges in the distal forearm and supplies the skin of the medial aspect of the back of the hand and the dorsum of the first four fingers. The deep branch is a purely motor nerve and is referred to as the posterior interosseous nerve. It supplies the supinator muscle (a forearm supinator), the extensor carpi radialis brevis (a radial extensor of the hand), the extensor digitorum (an extensor of the metacarpophalangeal joint of the second through the fifth fingers), the extensor digiti minimi (an extensor of the metacarpophalangeal joint of the fifth finger), the extensor carpi ulnaris (an ulnar extensor of the hand), the abductor pollicis longus (an abductor of the metacarpal of the thumb), the extensor pollicis longus and brevis (extensors of the thumb), and the extensor indicis (an extensor of the second finger). A lesion of the radial nerve at the axilla causes weakness of elbow extension, loss of the triceps reflex (triceps muscle), wrist drop, finger drop, and sensory loss on the entire extensor surface of the arm, the forearm, the web between the index finger and the thumb, and the radial side of the dorsum of the hand. There is also weakness of forearm flexion and a depressed radial reflex (brachioradialis muscle). *(Brazis, Masdeu, and Biller, 45–49; Staal, 35–48)*

**70. (A)** An extensive description of the anatomy and the course of the radial nerve was reported in the answer to question 69. A lesion of the radial nerve in the upper arm causes the same symptoms as those seen in radial nerve lesions at the axilla with sparing of the triceps and the posterior cutaneous nerve of the skin of the arm. A radial nerve lesion in the upper arm may by seen in alcohol-induced sleep, where acute retrohumeral nerve compression occurs. The tingling and pain that normally wake normal individuals do not occur in the inebriated. *(Brazis, Masdeu, and Biller, 45–49; Staal, 35–48)*

**71. (C)** A lesion of the radial nerve at the forearm will spare the triceps, brachioradialis, and extensor carpi radialis muscles. Typically, the patient has finger but not wrist drop. There is a radial deviation of the extended hand when the patient is asked to make a fist, illustrating the weakness of the extensor carpi ulnaris compared with the extensor carpi radialis muscles. *(Brazis, Masdeu, and Biller, 45–49; Staal, 35–48)*

**72. (D)** The patient described in this question has purely sensory symptoms that correspond to a

wrist compression of the dorsal digital nerve. *(Brazis, Masdeu, and Biller, 21–26; Staal, 35–48)*

**73.** **(A)** The median nerve carries fibers from C5 to T1 roots. It is a mixed nerve formed in the axilla by the joining of the lateral cord of the brachial plexus with the medial cord. The nerve descends on the medial side of the arm and enters the forearm between the two heads of the pronator teres to supply the pronator teres (C6-C7), the flexor carpi radialis (C6-C7) (a radial flexor of the hand), the palmaris longus (C7-T1) (a flexor of the wrist), and the flexor digitorum superficialis (C7-T1) (a flexor of the middle phalange of the second to the fifth fingers). After it passes between the two heads of the pronator teres, it gives off the anterior interosseous nerve. It then courses deep to the flexor retinaculum at the wrist to reach the hand. The palmar cutaneous branch takes off to the flexor retinaculum either subcutaneously or through the superficial ligament fibers to supply the skin over the thenar eminence and the proximal palm on the radial aspect of the hand. The purely motor anterior interosseous nerve innervates the flexor pollicis longus (a flexor of the terminal phalanx of the thumb), the flexor digitorum profundus I and II (a flexor of the terminal phalanges of the second and third digits), and the pronator quadratus (a forearm pronator). At the distal end of the carpal tunnel, the median nerve divides into its terminal branches. The motor branches innervate the first and second lumbricals (which are flexors of the proximal phalanges and extensors of the two distal phalanges of the second and third fingers), the thenar muscles (which include the abductor pollicis brevis, an abductor of the thumb, the opponens pollicis, and the superficial head of the flexor pollicis brevis). Soft tissue tumors, such as lymphomas, may cause a compression of the median nerve in the upper arm. Signs of a lesion at this level include sensory loss in the territory of the palmar cutaneous and palmar digital branches, atrophy of the thenar eminence muscles, paresis of forearm pronation, radial wrist flexion, distal flexion of the thumb, palmar abduction, opposition of the thumb, and flexion of the second and, to a lesser extent, third fingers. *(Brazis, Masdeu, and Biller, 36–37; Staal, 52–60)*

**74.** **(B)** Dislocation of the elbow may expose the patient to injury of the median nerve in its anterior interosseous branch. The purely motor anterior interosseous nerve innervates the flexor pollicis longus (a flexor of the terminal phalanx of the thumb), the flexor digitorum profundus I and II (a flexor of the terminal phalanges of the second and third digit), and the pronator quadratus (a forearm pronator). Neurological signs in this case are purely motor. They include the inability of the patient to form a small circle by pinching the end of the phalanx of the thumb and index finger together, resulting from a weakness of the flexor digitorum profundus of the index finger and the flexor pollicis longus, and weakness of forearm pronation on flexion because of weakness of the pronator quadratus muscle. Elbow pronation on extension is conserved because of the integrity of the pronator teres. *(Brazis, Masdeu, and Biller, 36–37; Staal, 52–60)*

**75.** **(A)** The patient described in this question has the clinical features of carpal tunnel syndrome. There is sensory loss in the palmar aspect of the hand, weakness, and atrophy of the abductor pollicis brevis and opponens pollicis. Carpal tunnel syndrome occurs when the median nerve, which runs from the forearm into the hand, becomes pressed or squeezed at the wrist. The carpal tunnel—a narrow, rigid passageway of ligament and bones at the base of the hand—houses the median nerve and tendons. Sometimes thickening from irritated tendons or other swelling narrows the tunnel and causes the median nerve to be compressed. The result may be pain, weakness, or numbness in the hand and wrist, radiating up the arm. Symptoms usually start gradually, with frequent burning, tingling, or itching numbness in the palm of the hand and the fingers, especially the thumb and the index and middle fingers. The symptoms often first appear in one or both hands during the night, since many patients sleep with flexed wrists. A patient with carpal tunnel syndrome may wake up feeling the need to "shake out" the hand or wrist. As symptoms worsen, the patient might feel tingling during the day. Decreased grip strength may make it difficult to form a fist, grasp small

objects, or perform other manual tasks. *(Brazis, Masdeu, and Biller, 36–37; Staal, 52–60)*

**76. (D)** The ulnar nerve carries fibers from C7 to T1 roots. Immediately distal to the elbow joint, the ulnar nerve innervates the flexor carpi ulnaris, an ulnar flexor of the wrist, and the flexor digitorum profundus, a flexor of the terminal phalanges of the fourth and fifth fingers. In the middle of the forearm, the ulnar nerve gives off the palmar cutaneous branch, which supplies the skin over the hypothenar eminence. It then gives off a dorsal cutaneous branch, which supplies the dorsal aspects of the hand and of the fifth and fourth fingers. In the hand, it gives off the superficial terminal branch, a sensory branch to the skin of the distal part of the ulnar aspect of the palm and the palmar aspect of the fifth finger and half of the fourth finger. It then passes between the pisiform and hamate bones to give off superficial terminal branches, which are mainly sensory and deep motor terminal branches. The superficial terminal branch innervates the palmaris brevis muscle. The deep branch innervates the abductor digiti minimi (an abductor of the fifth finger), the opponens digiti minimi, the flexor digiti minimi (a flexor of the fifth finger), and the lumbricals III and IV (flexors of the metacarpophalangeal joints and extensors of the proximal interphalangeal joints). The deep muscle branch also innervates the interosseous muscles (flexors of the metacarpophalangeal joints and extensors of the proximal interphalangeal joints; the dorsal interosseous muscles are finger abductors, whereas the palmar interosseous muscles are finger adductors) and the adductor pollicis. The patient described in this question has a claw-like hand, which is characteristic of ulnar nerve injury. It is caused by the unopposed action of long finger extensors from the paralyzed interossei and ulnar lumbrical muscles. Weakness of hand adduction and flexion associated with weakness of flexion of the little finger in the distal interphalangeal joint suggests involvement of the flexor carpi ulnaris and the flexor digitorum III and IV, respectively. These findings localize the lesion of the ulnar nerve at the elbow in the cubital tunnel. *(Brazis, Masdeu, and Biller, 40–45; Staal, 79–80)*

**77. (E)** The patient presented in this vignette has a pure motor deficit with weakness of right hand muscles innervated by the ulnar nerve except the palmaris brevis muscle. Entrapment of the ulnar nerve may occur distal to Guyon's canal, between the distal border of the pisiform bone and the point where the superficially running ulnar nerve rounds the hook of the hamate bone before traversing the palm to innervate the interosseous, lumbrical, and adductor pollicus muscles. The superficial terminal branch goes off within the canal; accordingly, the palmaris brevis muscle functions normally and there is no sensory loss. Thus, if the pamaris brevis muscle is preserved whereas all other hand muscles innervated by the ulnar nerve are affected and sensation is normal, the site of compression lies distal to the fibers going to the palmaris brevis muscle and just proximal to where the deep terminal fibers divide into branches to the interossei and the hypothenar muscles. *(Brazis, Masdeu, and Biller, 40–45; Staal, 80)*

**78. (C)** The patient described in this vignette shows weakness of the right quadriceps and psoas muscles, both of which are innervated by the femoral nerve. In the context of recent anticoagulation, compression of the femoral nerve by a hematoma of the psoas muscle is the most likely diagnosis. *(Staal, 104–107)*

**79. (A)** Retinal nerve fibers enter the optic disk via the disk's temporal aspect, the temporal aspect of its superior and inferior poles, and its nasal aspect. The papillomacular bundle is formed by macular fibers that enter the disk's temporal aspect. A lesion in these fibers may cause a central scotoma (a defect covering central fixation), a centrocecal scotoma (a central scotoma connected to the blind spot), or a paracentral scotoma. The arcuate bundle is formed by fibers from the retina temporal to the disk that enter its superior or inferior poles. A lesion of the arcuate fibers may cause a Bjerrum arcuate scotoma, Seidel scotoma (a defect in the proximal portion of the nerve fibers that causes a comma-shaped extension of the blind spot), or nasal step of Ronne scotoma respecting the horizontal meridian. A defect in the nasal nerve's fiber bundle results in a wedge-shaped

temporal scotoma arising from the blind spot. *(Kline and Bajandas, 6–7)*

**80. (D)** An optic tract lesion causes a contralateral hemianopia. The defect is incongruous (not identical in shape, location, and size in both eyes), since the lesion is located anterior to the occipital lobe, and nerve fibers of corresponding points do not lie adjacent to one another. An optic tract syndrome also includes bilateral nerve fiber atrophy and relative afferent defect on the side opposite the lesion. Wernicke pupil consists of absence of pupillary reaction to light stimulation of a blind retina, while stimulation of an intact retina causes a normal pupillary response. *(Kline and Bajandas, 10–13)*

**81. (E)** Ipsilateral inferotemporal fibers and contralateral inferonasal fibers course anteriorly from the lateral geniculate body into the temporal lobe, forming Meyer's loop. A right anterior temporal lobe lesion tends to produce left midperipheral and peripheral "pie in the sky" homonymous superior quadrantanopia. *(Kline and Bajandas, 13–14)*

**82. (E)** The abducens nucleus is located in the dorsocaudal portion of the pons, separated from the fourth ventricle by the genu of the facial nerve. The abducens nuclear complex coordinates the action of both eyes to produce horizontal gaze by sending axons to the medial longitudinal fasciculus; these end in the contralateral nucleus of the third nerve. Axons of the abducens motor neurons ascend along the base of the pons in the prepontine cistern and enter Dorello's canal beneath the petroclinoid ligament. In the lateral wall of the cavernous sinus, the abducens nerve lies between the ophthalmic artery medially and the ophthalmic branch of the trigeminal nerve laterally. After passing through the orbital fissure, the abducens nerve innervates the lateral rectus muscle.

A pituitary tumor may compress the cavernous sinus, which can cause total ophthalmoplegia, Horner syndrome, and pain in the area innervated by the ophthalmic division of the trigeminal nerve. *(Brazis, Masdeu, and Biller, 191–196; Kline and Bajandas,119–124)*

**83. (E)** Gradenigo syndrome may be caused by a localized inflammation of the petrous apex following complicated otitis media. Contact with the tip of the petrous pyramid makes the portion of the abducens nerve within Dorello's canal susceptible to injury when the petrous bone is inflamed. Clinical findings include abducens nerve palsy, ipsilateral decreased hearing, facial pain, and ipsilateral facial palsy. *(Brazis, Masdeu, and Biller, 191–196; Kline and Bajandas, 85–93)*

**84. (A)** Millard–Gubler syndrome is caused by a lesion in the ventral pons that destroys the fascicles of the abducens and facial nerves and the corticospinal tract. It is characterized by ipsilateral abducens nerve palsy, ipsilateral peripheral-type facial paralysis, and contralateral hemiplegia. A facial palsy can occur independently of an abducens nerve palsy when the lesion is more lateral (based in the low pons). The ipsilateral facial palsy is of the lower motor neuron type, involving the forehead, eyelids, and eyebrows. *(Brazis, Masdeu, and Biller, 191–196; Kline and Bajandas, 85–93)*

**85. (D)** Elevation of intracranial pressure may result in downward displacement of the brainstem with stretching of the abducens nerve, which is tethered as it exits from the pons and in Dorello's canal. Pseudotumor cerebri may cause papilledema; in 30% of cases it also causes bilateral abducens nerve palsy. *(Brazis, Masdeu, and Biller, 191–196; Kline and Bajandas, 85–93)*

**86. (B)** Foville syndrome is caused by a lesion located in the pontine tegmentum that destroys the fascicles of the facial nerve, the paramedian pontine reticular formation, and the corticospinal tract. It is characterized by horizontal gaze palsy, dysfunction of the facial and vestibulocochlear nerves, ipsilateral Horner syndrome, and contralateral hemiplegia. *(Brazis, Masdeu, and Biller, 191–196; Kline and Bajandas, 85–93)*

**87. (D)** Petrous bone fracture may follow head trauma. The trigeminal, abducens, facial, and cochleovestibular nerves may be affected. Associated signs may include otorrhea, hemotympanum, and mastoid ecchymosis. *(Brazis, Masdeu, and Biller, 191–196; Kline and Bajandas, 85–93)*

**88. (C)** In Raymond–Cestan syndrome, the lesion is located in the basal pons but is less extensive than the lesion in Millard–Gubler syndrome: there is only ipsilateral abducens nerve palsy with contralateral hemiplegia. *(Brazis, Masdeu, and Biller, 191–196; Kline and Bajandas, 85–93)*

**89. (B)** Oculomotor nerve palsy secondary to a nuclear lesion is extremely rare. Each superior rectus is innervated by the contralateral oculomotor nerve nucleus; therefore a nuclear oculomotor nerve lesion results in contralateral superior rectus palsy. Both levator muscles are innervated by one subnuclear structure, the central caudal nucleus. Hence, a nuclear oculomotor nerve lesion results in bilateral ptosis. *(Kline and Bajandas, 95–96)*

**90. (B)** The pupillomotor fibers of the oculomotor nerve travel in the outer layers of the nerve and are therefore closer to the nutrient blood supply. This may explain their susceptibility to compressive lesions of the oculomotor nerve rather than to ischemic causes. The patient described in the vignette developed a pupil-sparing isolated oculomotor nerve palsy. This may suggest an ischemic oculomotor mononeuropathy. A follow-up examination revealed an Argyll–Robertson pupil in the affected eye, which is most likely a false Argyll–Robertson sign caused by aberrant regeneration of the oculomotor nerve. Some of the medial rectus fibers may end up innervating the pupillary sphincter muscle, so that there is more pupillary constriction during convergence than in response to light. Secondary aberrant regeneration does not occur after ischemic oculomotor nerve palsy. The diagnosis of ischemic oculomotor nerve palsy is unlikely in this case. Other diagnoses—such as neoplasm, aneurysm, and trauma—should be considered. Primary aberrant regeneration of the oculomotor nerve is not preceded by an acute oculomotor palsy. It has an insidious development accompanying signs of misdirection. *(Kline and Bajandas, 102–103)*

**91. (A)** If a patient has vertical misalignment due to recently acquired weakness of a single vertically acting muscle, then determination of the weak muscle follows the three steps of the Parks–Bielschowsky test. The median and lateral rectus muscles do not have vertical action. Therefore, vertical misalignment of paretic etiology is caused by weakness of one or more of the following eight vertically acting muscles: right inferior oblique, left inferior oblique, right superior oblique, left superior oblique, right inferior rectus, left inferior rectus, right superior rectus, and left superior rectus.

The first step is to find which is the higher eye. In the vignette, the right eye is higher than the left eye. The weak muscle is then a depressor of the right eye (right inferior rectus or right superior oblique) or an elevator of the left eye (left superior rectus or left inferior oblique).

The second step is to find if the misalignment is worse on right or left gaze. The vertical rectus muscles have their greatest vertical action and least torsional action when the eye is abducted. The oblique muscles have their greatest vertical and least torsional action when the eye is adducted. In the vignette, the patient's hypertropia is getting worse on left abduction of the left eye and adduction of the right eye (left gaze deviation). Therefore, the possible causes of right hypertropia are narrowed from four muscles to two: worsening of the right hypertropia on right eye adduction and left eye abduction is caused by right superior oblique weakness or left superior rectus weakness, respectively.

The third step is to find out if the hypertropia is worse on left or right head tilt (by moving the ear near the ipsilateral shoulder). The superior muscles intort the eyes (superior rectus and superior oblique) and the inferior muscles extort the eyes (inferior rectus and inferior oblique). When the head is tilted downward to the right shoulder, the eyes undergo corrective torsion: the right eye is intorted and the left eye is extorted. Therefore, when the head is tilted to the right, the right eye is intorted by contraction of the right superior rectus or right superior oblique. These two muscles work together in affecting the intorsion and neutralize each other's vertical action. If one of these muscles is weak and thus responsible for the misalignment, then the vertical action is not neutralized and the hypertropia will become worse, as in this case. From

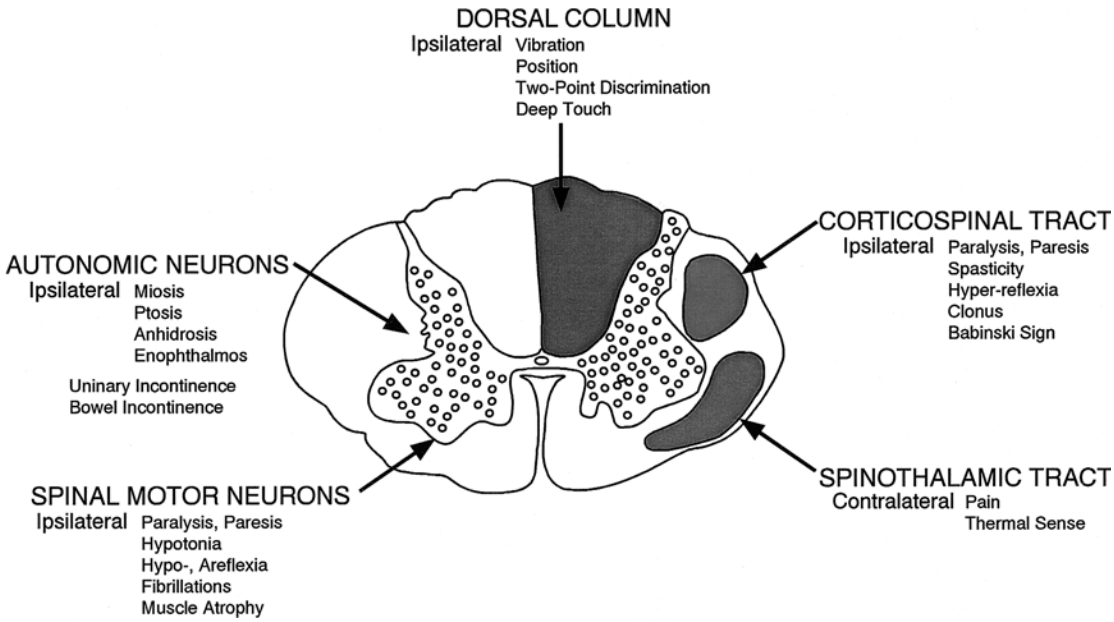


FIG. 2-11

steps one and two, weakness of only two muscles is left: the right superior oblique or left superior rectus. So, the muscle responsible for the misalignment in this case is the right superior oblique. *(Kline and Bajandas, 10–113)*

**92.** **(D)** In a C6 radiculopathy, the biceps and brachioradialis reflexes are absent or diminished, whereas the triceps reflex, mediated by the C7 nerve root and spinal cord segments and the finger flexor reflex, mediated by the C8 nerve root and spinal cord segments, are exaggerated as a result of injury of the corticospinal tract below the C6 spinal cord level. Thus, C5-C6 segmental lesions result in an inversion of the brachioradialis reflex. Tapping of the radius elicits exaggerated finger and hand flexion without flexion and supination of the forearm. *(Brazis, Masdeu, and Biller, 112–113)*

**93.** **(C)** The patient in this vignette developed signs of dorsal column dysfunction: loss of proprioception and vibration sense in both legs as well as sensory ataxia. He also has bilateral corticospinal tract dysfunction resulting in spasticity, hyperreflexia, and bilateral Babinski signs. The spinothalamic tract seems intact because temperature and pain are conserved. This selective damage of the posterior and lateral columns may occur in subacute combined degeneration of the spinal cord due to vitamin $B_{12}$ deficiency (Figures 2-11 and 2-12). Early in the course of $B_{12}$ deficiency, the patient first notices mild general weakness and paresthesias

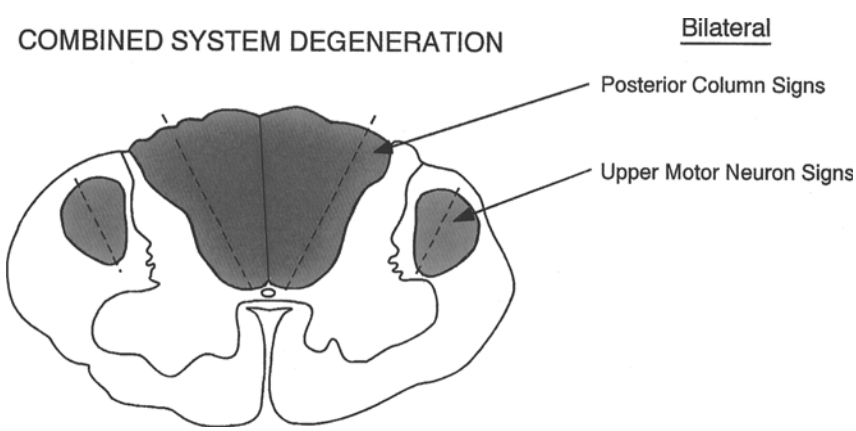


FIG. 2-12

consisting of tingling, "pins and needles" feelings, or other vaguely described sensations. The paresthesias involve the hands and feet, more often the former, and tend to be constant and steadily progressive; they are the source of much distress. As the illness progresses, the gait becomes unsteady and stiffness and weakness of the limbs, especially of the legs, develop. If the disease remains untreated, an ataxic paraplegia evolves, with variable degrees of spasticity. Sensory examination discloses a disorder of the posterior and lateral columns of the spinal cord, predominantly of the former. Loss of vibration sense is by far the most consistent sign; it is more pronounced in the feet and legs than in the hands and arms and frequently extends over the trunk. Nervous system involvement in subacute combined degeneration is roughly symmetric, and sensory disturbances precede the motor ones. Mental and visual impairment may occur. *(Afifi, 70–77; Brazis, Masdeu, and Biller, 103–108; Ropper, chapter 41)*

**94.** **(E)** The patient described in this vignette shows pure posterior column dysfunction with loss of proprioception and vibratory sensation and presence of the Romberg sign. Tabes dorsalis affects the posterior columns selectively (see again Figure 2-11). Tabes dorsalis is a form of neurosyphilis. All forms of neurosyphilis begin as a meningitis, and a more or less active meningeal inflammation is the invariable accompaniment of all forms of neurosyphilis. The early clinical syndromes are meningitis and meningovascular syphilis; the late ones are vascular syphilis (1 to 12 years), followed still later by general paresis, tabes dorsalis, optic atrophy, and meningomyelitis. The classic syndromes of tabes dorsalis as well as meningovascular syphilis of the spinal cord are now less frequent than in the past but must be considered in the differential diagnosis of spinal cord disorders. The characteristic symptoms of tabes are fleeting and repetitive lancinating pains, primarily in the legs or less often in the back, thorax, abdomen, arms, and face. Ataxia of the legs and gait due to loss of position sense occurs in half of these patients. Paresthesias, bladder disturbances, and acute abdominal pain with vomiting (visceral crisis) occur in 15% to 30% of patients. The cardinal signs of tabes are loss of reflexes in the legs; impaired position and vibratory sense; Romberg's sign; and, in almost all cases, bilateral Argyll–Robertson pupils, which fail to constrict to light but accommodate. *(Afifi, 70–77; Brazis, Masdeu, and Biller, 103–108; Hauser, chapter 372; Ropper, chapter 32)*

**95.** **(D)** The patient described in this vignette has pure chronic motor syndrome, including signs of upper motor neuron dysfunction (paresis, spasticity, increased deep tendon reflexes, and the Babinski sign) and lower motor neuron dysfunction (progressive muscular atrophy and fasciculations). The most likely diagnosis is amyotrophic lateral sclerosis. The disease is characterized by degenerative changes in the anterior horn cells of the spinal cord, the motor nuclei of the brainstem, and the corticospinal tract. Clinically, the onset of the disease is usually focal or appears in one limb. Sensation is usually preserved. Bulbar or pseudobulbar impairment is often superimposed, resulting in explosive dysarthria, dysphagia, emotional incontinence, tongue spasticity, and atrophy. Virtually, any striated muscle can be affected. However, the urinary and rectal sphincters are unaffected early in the illness because of the sparing of Onuf's nucleus, located in the ventral margin of the anterior sacral horns (Figure 2-13). These, as well as the extraocular muscles, are affected late in the illness. *(Afifi, 70–77; Brazis, Masdeu, and Biller, 103–108)*

**96.** **(A)** The patient in this vigentte shows a central spinal cord syndrome with dissociation of sensory loss that is best exemplified by syringomyelia. Cord damage starts centrally and spreads centrifugally to involve other spinal cord structures. Characteristically, the decussating fibers of the spinothalamic tract, conveying pain and temperature sensation, are affected first. This results in thermoanesthesia and analgesia with suspended bilateral distribution and preservation of sensation to light touch as well as proprioception (Figure 2-14). *(Afifi, 70–77; Brazis, Masdeu, and Biller, 103–108)*

**97.** **(C)** The patient described in this vignette developed a neurological deficit involving the

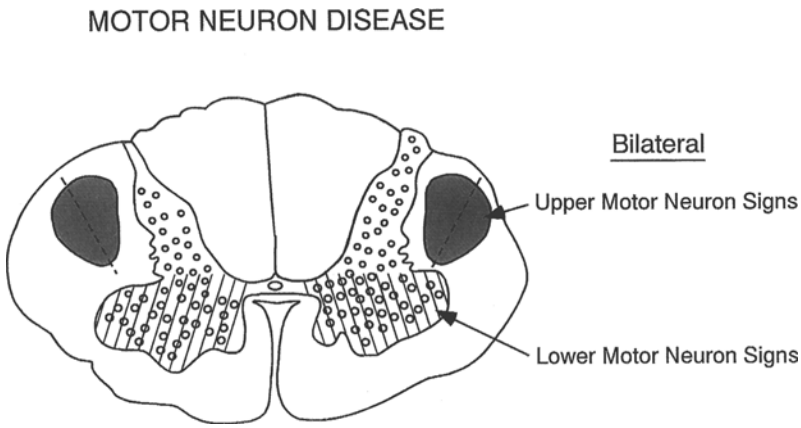


FIG. 2-13

territory of the anterior spinal artery. Spinal cord infarction is rare. The syndrome is characterized by the abrupt onset of leg weakness and urinary incontinence associated with loss of thermoanesthesia and analgesia below the level of the lesion. Position sense, vibration, and light touch remain intact owing to preservation of the dorsal columns (Figure 2-15). *(Afifi, 70–77; Brazis, Masdeu, and Biller, 103–108)*

**98.** **(A)** The patient described in this vignette developed weakness of the right lower extremity and loss of proprioceptive function below the T6 spinal cord level, with contralateral loss of pain and temperature. This is highly suggestive of right hemisection of the spinal cord at the T6 level. The weakness is caused by a lesion in the ipsilateral corticospinal tract; the loss of proprioception is related to interruption of the ipsilateral ascending fibers of the posterior columns. The loss of pain and temperature sensation in the contralateral side is related to a lesion of the decussating spinothalamic tract (Figure 2-16) *(Afifi, 70–77; Brazis, Masdeu, and Biller, 103–108)*

**99.** **(B)** This patient has funnel vision only when the central vision is intact. Funnel vision should

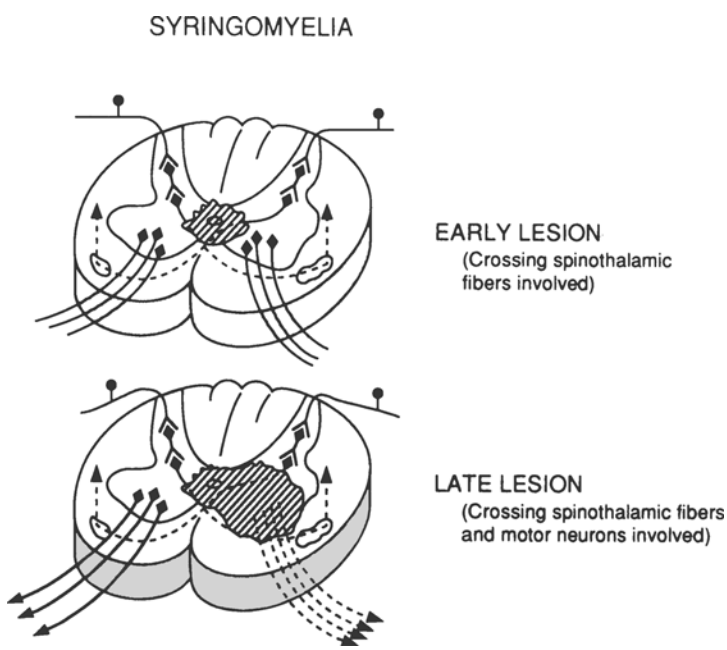


FIG. 2-14

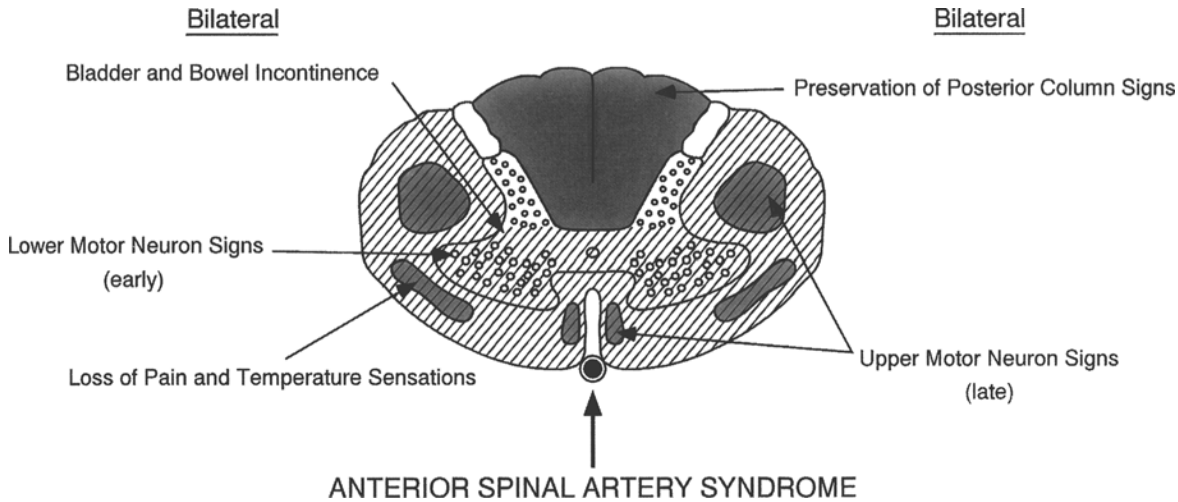


FIG. 2-15

not be confused with tunnel vision, a field defect characteristic of hysteria or malingering. The latter field can easily be mapped onto a tangent screen by plotting the fields with the patient seated 1 and 2 meters from the screen. In the case of organic defect, the field projected at 2 meters is larger than the field plotted at 1 meter. A constricted visual field with retained acuity may be seen in the case of glaucoma, retinitis pigmentosa, cancer-associated retinopathy, postpapilledema optic atrophy, and bilateral occipital infarct with macular sparing. *(Brazis, Masdeu, and Biller, 144)*

**100.** **(A)** Disease of the choroid, retinal pigment epithelium, retina, optic disk, or optic nerve almost always causes monocular visual defects. The early stage of a chiasmatic lesion may cause monocular loss of vision in the temporal field of the ipsilateral eye when the defect is

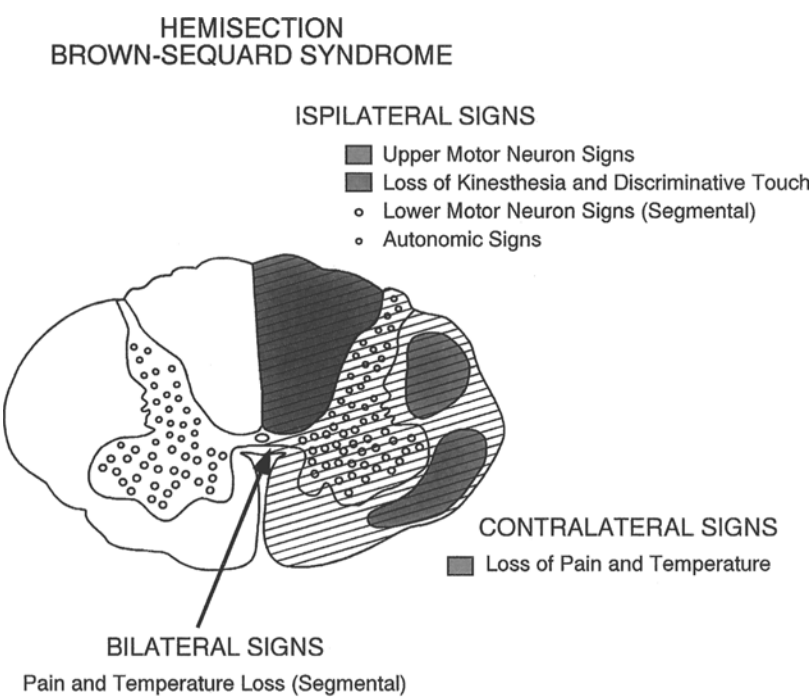


FIG. 2-16

located most anterior in the chiasm, affecting the nasal retinal fibers crossing from the contralateral eye. A lesion located in the most anterior aspect of the calcarine cortex causes a crescent-shaped defect restricted to the temporal field of the contralateral eye. This is the only retrochiasmatic lesion that may cause a unilateral visual defect. *(Brazis, Masdeu, and Biller, 144–146)*

**101. (E)** The facial nerve innervates the muscles of facial expression and all other muscles derived from the second branchial arch and carries the sensation of taste from the front of the tongue. It is both a sensory and a motor nerve. In addition, it has a parasympathetic role as described below. Its fibers originate at the pontomedullary junction, leave the posterior cranial fossa through the internal acoustic meatus, and enter the facial canal in the petrous part of the temporal bone. It has a motor root, and another root, the nervus intermedius, that is responsible for carrying the sensation of taste and for parasympathetic innervation (Figure 2-17).

The sensory component of the facial nerve carries two types of sensory afferents: exterioceptive fibers from the external ear and taste fibers from the anterior two thirds of the tongue. The exterioceptive fibers from the external ear are peripheral processes of neurons in the geniculate ganglion. Central processes project on neurons in the spinal trigemnal nucleus. The neurons of the taste fibers originate in the geniculate ganglion. Peripheral processes of these neurons reach the taste buds in the anterior two thirds of the tongue; central processes enter the brainstem with the nevus intermedius and project on neurons in the gustatory part of the nucleus solitarius, along with fibers carried by the glossopharyngeal (from the posterior third of the tongue) and vagus (from the epiglottic region) nerves. The sensory and the gustatory fibers, along with the visceral motor component, form a separate lateral root of the facial nerve, the nervus intermedius. The motor part of the facial nerve carries two types of motor fibers: somatic and secretomotor. The somatic motor fibers supply the muscles of facial expression and the stapedius, the stylohyoid and the posterior belly of the digastric. These fibers arise from the facial motor nucleus in the pontine tegmentum. They course dorsomedially and then rostrally in the tegmentum before bending laterally over the abducens nucleus and turning ventrolaterally to emerge at the lateral border of the pons. After emerging from the ventrolateral pons, the motor division enters

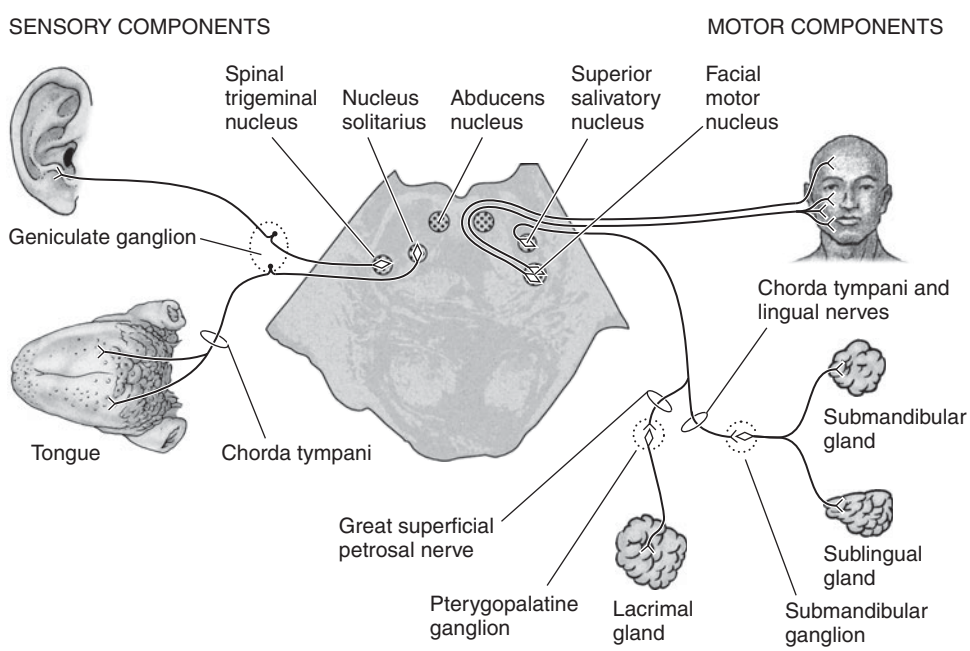


**FIG. 2-17**

the internal auditory meatus of the temporal bone. Four portions of the facial nerve can be distinguished within the temporal bone: the meatal segment, the labyrinthine segment (from which the greater superficial petrosal nerve arises), the horizontal segment, and the mastoid segment (from which the nerve to the stapedius muscle and the chorda tympani arises). After giving off the chorda tympani, the facial nerve exits the facial canal through the stylomastoid foramen. Near its exit, it gives rise to the posterior auricular nerve (to the occipitalis, posterior auricular, and transverse and oblique auricular muscles), the digastric branch (to the posterior belly of the digastric muscle), and the stylohyoid branch (to the stylohyoid muscles). The facial nerve then pierces the parotid gland, where it divides into the temporofacial and cervicofacial branches, which further divide into several branches to supply all the facial mimetic muscles and the platysma muscle. The secretomotor fibers arise from the superior salivary nucleus in the tegmentum of the pons. They are preganglionic fibers that leave the brainstem with the nevus intermedius and travel in the greater superficial nerve and the nerve of the pterygoid canal before synapsing in the pterygopalatine ganglion, from which postganglionic parasympathetic fibers travel in the maxillary, zygomatic, zygomaticotemporal, and lacrimal nerves to reach the lacrimal gland. Fibers destined for the submandibular and sublingual glands join the chorda tympani and the lingual nerves and synapse in the submandibular ganglion, from which postganglionic parasympathetic fibers arise. A lesion of the facial nerve at the stylomastoid foramen produces isolated ipsilateral motor palsy without loss of hearing or taste (Figure 2-17). *(Afifi, 112–114; Brazis, Masdeu, and Biller, 287–296)*

**102. (A)** A lesion located in the pontine tegmentum that destroys the fascicle of the facial nerve, the paramedian pontine reticular formation, and the corticospinal tract causes Foville syndrome. This is characterized by an ipsilateral peripheral-type facial palsy, paralysis of the conjugate gaze to the side of the lesion, and contralateral hemiplegia (Figure 2-17). *(Afifi, 112–114; Brazis, Masdeu, and Biller, 287–296)*

**103. (C)** Ramsay Hunt syndrome results from a herpes zoster infection of the geniculate ganglion. Clinical features may include hyperacusis, loss of taste in the anterior two thirds of the tongue, geniculate neuralgia, and herpetic vesicles of the external auditory meatus (Figure 2-17). *(Afifi, 112–114; Brazis, Masdeu, and Biller, 287–296)*

**104. (D)** A lesion affecting the facial nerve, between the departure of the nerve to the stapedius and the departure of the chorda tympani, results in ipsilateral facial palsy and loss of taste sensation in the anterior two thirds of the tongue. Hearing is spared (Figure 2-17). *(Afifi, 112–114; Brazis, Masdeu, and Biller, 287–296)*

**105. (B)** A lesion of the facial nerve within the facial canal, distal to the meatal segment but proximal to the departure of the nerve to the stapedius muscle, results in ipsilateral facial motor paralysis, loss of taste over the anterior two thirds of the tongue, and hyperacusis. Lacrimation is preserved if the lesion is distal to the greater superficial petrosal nerve (Figure 2-17). *(Afifi, 112–114; Brazis, Masdeu, and Biller, 287–296)*

**106. (C)** A lesion of the facial nerve in the meatal canal affects the facial and cochleovestibular nerves: there is ipsilateral facial nerve palsy, impaired taste sensation in the anterior two thirds of the tongue, impaired lacrimation, and deafness (Figure 2-17). *(Afifi, 112–114; Brazis, Masdeu, and Biller, 287–296)*

**107. (A)** A fascicular lesion of the facial nerve results in a peripheral type of facial nerve palsy (Figure 2-17). A lesion located in the ventral pons and the corticospinal tract, destroying the fascicles of the facial and abducens nerves, causes the Millard–Gubler syndrome. This syndrome is characterized by an ipsilateral peripheral facial nerve palsy, ipsilateral lateral rectus palsy, and contralateral hemiplegia. *(Afifi, 112–114; Brazis, Masdeu, and Biller, 287–296)*

**108. (B)** The patient described in this vignette has decreased pain and temperature sensation in the right face and left side of the trunk and

extremities. This results from a lesion affecting the right trigeminal spinal nucleus/tractus and the right spinothalamic tract, respectively. A right nucleus ambiguus lesion causes weakness of the right palate and vocal cord paralysis, resulting in hoarseness. Ataxia of the right limb may be explained by a right cerebellar lesion. All these clinical findings are highly suggestive of a lateral medullary lesion, also known as Wallenberg syndrome. It is most often related to obstruction of the intracranial vertebral artery or the posteroinferior cerebellar artery. The syndrome has been reported with cocaine abuse, medullary metastasis, trauma, abscess, and demyelination. The clinical features of this syndrome may include Horner syndrome (due to injury to the descending sympathetic fibers), vertigo, and vomiting from involvement of the vestibular nuclei. A lateral lesion of the rostral medulla is associated with more severe dysphagia and dysphonia, whereas a caudal lesion is associated with more marked vertigo, nystagmus, and gait ataxia. *(Brazis, Masdeu, and Biller, 352–356)*

**109.** **(A)** The patient described in this vignette has symptoms consistent with a lesion located in the right pyramidal system, right medial lemniscus, and right hypoglossal nerve, which explains the protrusion of the tongue away from the hemiplegia toward the side of the lesion. These symptoms are consistent with the diagnosis of right medial medullary syndrome. This may be caused by occlusion of the right anterior spinal artery or its parent, the vertebral artery. *(Brazis, Masdeu, and Biller, 351–352)*

**110.** **(D)** The neurological examination of the patient in this vignette demonstrates right facial palsy and contralateral hemiplegia. These findings point to a lesion affecting the right pons. The presence of gaze deviation to the left may suggest a lesion of the paramedian pontine reticular formation or a right abducens lesion. The association of these findings puts the lesion in the right dorsal pontine tegmentum in the caudal third of the pons. This is consistent with a diagnosis of Foville syndrome. *(Brazis, Masdeu, and Biller, 359)*

**111.** **(C)** In this vignette,, the patient's neurological assessment shows the association of quadriparesis, aphonia, and impairment of horizontal eye movement with preservation of vertical gaze and maintenance of consciousness. These signs are highly suggestive of the locked-in syndrome. It results from a ventral pontine lesion, which may be caused by a vertebral artery thrombosis, ventral pontine tumor, hemorrhage, trauma, or central pontine myelinolysis from rapid correction of hyponatremia. The quadriplegia is caused by bilateral corticospinal tract lesions, the aphonia is caused by a lesion in the corticobulbar fibers that innervate the lower cranial nerves, and the ophthalmoplegia with impairment of horizontal eye movement results from a lesion of the abducens nerve fascicles. The patient is fully awake because the reticular formation is spared. The supranuclear oculomotor pathways as well as the blinking pathways are also spared because they lie more dorsally. Thus, the patient is only able to blink and to look up and down. *(Brazis, Masdeu, and Biller, 358–359)*

**112.** **(A)** The patient described in this vignette has a right cerebellar syndrome and impairment of the right spinothalamic and corticospinal tracts. A lesion of the lateral pons would explain these signs, which correspond to Marie–Foix syndrome. *(Brazis, Masdeu, and Biller, 359–360)*

**113.** **(C)** The 40-year-old diabetic woman described in this question has signs highly suggestive of a lesion affecting the mesencephalic tegmentum (Benedict syndrome). Ophthalmoplegia is caused by fascicular damage to the third cranial nerve on the ipsilateral side of the lesion, which is on the right side in this case. The left sided tremor is caused by destruction of the right red nucleus, causing a rubral tremor. *(Brazis, Masdeu, and Biller, 362)*

**114.** **(B)** In this question, the patient developed right oculomotor paresis and left hemiplegia. This is compatible with a lesion in the right cerebral peduncle, which affects the right oculomotor nerve fascicles and right corticospinal tract, causing left hemiplegia. These signs are consistent with the diagnosis of Weber syndrome. *(Brazis, Masdeu, and Biller, 361–362)*

**115.** **(D)** The patient described in this question has signs highly suggestive of Sylvian aqueduct syndrome. This results from a dorsal rostral mesencephalic lesion. It is most often seen with pineal gland tumors that cause hydrocephalus. The syndrome may include a paralysis of conjugate upward gaze and convergence retraction nystagmus on upward gaze. *(Brazis, Masdeu, and Biller, 362)*

**116.** **(B)** The clinical case described in this vignette shows a 5-year-old boy complaining of axial ataxia without limb ataxia and spontaneous nystagmus. These symptoms are consistent with damage to the floculonodular lobe in the caudal part of the vermis, caused in this case by a medulloblastoma. *(Brazis, Masdeu, and Biller, 367–378)*

**117.** **(D)** The neurological abnormalities reported in the case described in this vignette suggest occlusion of the right anteroinferior cerebellar artery. The vertigo is caused by ischemia of the vestibular nuclei. The right facial palsy and the loss of sensation are caused by ipsilateral ischemia of the lateral–pontomedullary tegmentum and the trigeminal nuclei and tract, respectively. The right Horner syndrome is caused by a compromise of the descending oculosympathetic fibers. *(Brazis, Masdeu, and Biller, 367–378)*

**118.** **(A)** The patient described in this vignette has a predominant axial ataxia. With the history of ethanol abuse, the most likely diagnosis is cerebellar degeneration from chronic ethanol abuse. Ethanol results in atrophy of the anterior and superior vermis. *(Brazis, Masdeu, and Biller, 367-378)*

**119.** **(E)** The patient described in this vigentte has symptoms consistent with occlusion of the superior cerebellar artery. The vertigo and nystagmus are caused by ischemia of the vestibular nuclei. The Horner syndrome is caused by a compromise of the descending oculosympathetic fibers; the left deafness results from a lesion in the crossed right lateral lemniscus; and the right tremor is caused by a lesion of the dentate nucleus and the superior cerebellar peduncle. The left sided pain and temperature loss is caused by involvement of the spinothalamic tract. *(Brazis, Masdeu, and Biller, 367–378)*

**120.** **(C)** The case described in this vignette results most likely from an embolic obstruction of the posteroinferior cerebellar artery with infarction of the inferior cerebellum and lateral medulla. The loss of pain and temperature sensation is caused by damage to the trigeminal spinal nucleus and tract, the left limb ataxia is caused by damage of the inferior cerebellar peduncle, the dysarthria and left vocal cord palsy are caused by damage to the left nucleus ambiguus, and the loss of pain and temperature sensation on the right is caused by damage to the spinothalamic tract on the left. *(Brazis, Masdeu, and Biller, 367–378)*

**121.** **(B)** An acute hypothalamic lesion can cause gastrointestinal erosions (called neurogenic ulcers) that are most often located in the lower esophagus. *(Brazis, Masdeu, and Biller, 389)*

**122.** **(C)** The medial dorsal nucleus of the thalamus is found to be most consistently associated with memory loss in Wernicke–Korsakoff syndrome. *(Brazis, Masdeu, and Biller, 393)*

**123.** **(B)** Hemiballismus usually occurs with injury to the contralateral subthalamic nucleus or any lesion that disrupts its afferent or efferent fibers. Hemiballismus may also be caused by lesions affecting the caudate, putamen, globus pallidus, precentral gyrus, and thalamic nuclei. *(Brazis, Masdeu, and Biller, 428–429)*

**124.** **(A)** Sensory inattention occurs most commonly with a lesion of the contralateral inferior parietal lobe. Less commonly, it may occur with lesions of the temporoparietooccipital junction, dorsolateral frontal lobe, cingulate gyrus, thalamus, and mesencephalic reticular formation. *(Brazis, Masdeu, and Biller, 466–469)*

**125.** **(D)** The septal area has two divisions: the septum pellucidum and septum verum. The septum pellucidum is a thin leaf that separates the lateral vetricles. The septum verum is ventral to the septum pellucidum; it is located

between the subcallosal gyrus rostrally and the anterior commissure and the anterior hypothalamus caudally. The septal area has reciprocal connection with the following areas: hippocampus, amygdala, hypothalamus, midbrain, habenular nucleus, cingulated gyrus, and thalamus. Lesion of the septal area in animal species such as rats and mice produce rage reactions and hyperemotionality. These behavioral alterations are usually transitory and disappear 2 to 4 weeks after the lesion appears. Animals with septal damage tend to consume increased amounts of water, to demonstrate a high intitial state of activity in response to novel stimulation, to learn tasks quickly, and—once they have been learned—to perform them effectively. *(Afifi, 293–294)*

**126.** **(E)** The orbitofrontal cortex is the part of the frontal cortex resting above the orbits of the eyes. It is defined as the part of the prefrontal cortex that receives projections from the magnocellular, medial, or mediodorsal thalamus. Because the orbitofrontal cortex is interlinked with limbic and reticular areas, lesions of this area lead to disinhibition and changes of affect. Behavior is thus impulsive (pseudopsychopathic). Other characteristics include an inappropriate jocular affect, euphoria, emotional liability, poor judgment and insight, and distractibility. *(Brazis, Masdeu, and Biller, 503; Trimble, 89–104)*

**127.** **(C)** The lateral frontal cortex is closely linked to motor structures; therefore lesions of this area lead to disturbances of movement and action with preservation of inertia. Patients are apathetic, with occasional bursts of angry or aggressive behavior. Other characterestics include indifference, psychomotor retardation, motor preservation and impersistence, discrepant motor and verbal behavior, and poor word listing and visuospatial analysis. *(Brazis, Masdeu, and Biller, 503; Trimble, 89–104)*

**128.** **(B)** Medial frontal lobe syndrome is associated with mutism, gait disturbance, and incontinence. Patients demonstrate a paucity of spontaneous movement and gesture, sparse verbal output, lower extremity weakness, loss of sensation, and incontinence. *(Brazis, Masdeu, and Biller, 503; Trimble, 89–104)*

**129.** **(B)** Emotions and their expression depend on the individual's state of arousal (mediated by the reticular activating system), vegetative function (mediated in part by the hypothalamus), retrieval system for previous experience (mediated by the hippocampus and other portions of the limbic system), ability to perceive, ability to evaluate stimuli that carry an affective component, and ability to express emotion. A defect in the ability to perceive stimuli that carry affective components may be seen in right parietotemporal damage. The patient understands the semantic meaning of a verbal threat, but his or her perception of the emotional overtones that accompany the utterance is impaired. This condition is known as sensory aprosodia. *(Brazis, Masdeu, and Biller, 472–474; Trimble, 89–104)*

**130.** **(C)** Patients with bilateral anterior temporal lesions have a bland affect. Other manifestations of bilateral temporal damage were obtained from survivors of herpes simplex encephalitis. They include memory disturbance, hypermetamorphosis, irritability, eating and drinking problems, agnosia, inappropriate sexual display, and easy distractibility. *(Brazis, Masdeu, and Biller, 472–474; Trimble, 89–104)*

**131.** **(D)** The ability to evaluate the importance of stimuli may be impaired in the case of bilateral lesions of the anterior cingulate; the patient may be unconcerned in the presence of painful stimuli. *(Brazis, Masdeu, and Biller, 472–474; Trimble, 89–104)*

**132.** **(E)** A lesion of the left dorsofrontal lobe may cause anger and hostility, whereas a lesion of the right orbitofrontal area may cause depression. *(Brazis, Masdeu, and Biller, 472–474; Trimble, 89–104)*

**133.** **(E)** An epileptogenic right temporal lesion may cause paranoid behavior, whereas an epileptogenic lesion of the left temporal lobe may cause denial, sadness, and/or elation.

**134.** **(E)** Focal seizures arising from the neocortex of the temporal lobe may give rise to experiential

illusions such as déjà vécu (previously experienced) or jamais vécu (never previously experienced). They may also give rise to visual illusions such as déjà vu (previously seen) or jamais vu (never previously seen). *(Brazis, Masdeu, and Biller, 477–481)*

**135. (C)** In occipital epileptic seizures, hallucinations are predominantly multicolored with a circular or spherical pattern. They are also more stereotyped than hallucinations from impaired visual acuity and are associated with other seizure manifestations. *(Brazis, Masdeu, and Biller, 477–481)*

**136. (D)** A lesion of the upper midbrain bilaterally may cause a complex visual hallucination that has a dream-like quality. Hallucinations are often hypnagogic, known to be unreal, and may be pleasant to the patient. *(Brazis, Masdeu, and Biller, 477–481)*

**137. (A)** Charles Bonnet syndrome may occur in elderly patients with poor vision. Probably a release phenomenon, it is characterized by hallucinations in the evening of small, brightly colored people or objects with a cartoon-like appearance. The patient is usually aware of the unreality of these hallucinations. *(Brazis, Masdeu, and Biller, 477–481)*

**138. (B)** Simple visual hallucinations consisting of flashes of light or lines of different colors, but predominantly adopting zigzag or fortification patterns, are suggestive of migraine headache. *(Brazis, Masdeu, and Biller, 477–481)*

**139. (A)** Balint syndrome may result from bilateral parietooccipital lesions in the convexities of the hemispheres. It is characterized by the following symptoms: (1) simultagnosia, or the inability to appreciate the meaning of the whole, though the elemental parts are well recognized; (2) gaze apraxia, or failure to shift gaze on command and difficulty in the voluntary redirection of attention; (3) optic ataxia, or disturbance reaching a target under visual control, manifested by clumsiness of object-bound movements of the hand performed under visual guidance; and (4) decreased visual attention affecting mainly the peripheral visual field. Altitudinal neglect may also be seen. *(Brazis, Masdeu, and Biller, 481)*

**140. (A)** The presence of left homonymous hemianopia without neglect and preservation of response to threat as well as preservation of drawing and copying ability is highly suggestive of damage to the right occipitoparietal region in area 17 of the occipital cortex. It is usually caused by obstruction of the calcarine branch of the posterior cerebral artery. Right parietal and temporoparietal lesions involving areas 18 and 19 cause lack of awareness of visual loss, contralateral neglect and abnormal optokinetic nystagmus, lack of response to visual threat, and abnormal drawing and copying. Bilateral occipital lesions involving the visual cortex in areas 17, 18, and 19 cause blindness, agitation, and amnesia. A lesion of the inferior calcarine fissure bilaterally causes prosopagnosia, bilateral upper quadranopsia, and achromatopsia. A bilateral lesion of the superior calcarine fissure causes inferior quadranopsia and Balint syndrome. *(Brazis, Masdeu, and Biller, 477–482)*

**141. (C)** Alien limb signs includes failure to recognize ownership of one's limb when visual cues are removed, feeling that one's body part is foreign, personification of the affected body part, and autonomous activity of the limb that is perceived as being outside of the patient's voluntary control. Although the hand is most frequently affected, any limb or combination of limbs may fulfill the alien limb criteria. The diagnosis of alien hand sign should be reserved for cases where the hand feels foreign together with observable involuntary motor activity. Etiologies of this syndrome include multiple infarcts and corticobasal degeneration. Two distinct alien hand syndromes have been described: (1) The frontal hand alien limb syndrome occurs in the dominant hand and is associated with reflexive grasping, groping, and compulsive manipulation of tools. It results from damage to the supplementary motor area, anterior cingulate gyrus, medial prefrontal cortex of the dominant hemisphere, and anterior corpus callosum. (2) The callosal

form is characterized primarily by intermanual conflict and requires only an anterior callosal lesion. The occurrence of frontal alien hand syndrome in the dominant limb can be explained by an increased tendency for dominant limb exploratory reflexes coupled with release from an asymmetrically distributed, predominant nondominant-hemisphere inhibition. Callosal alien hand syndrome is best explained by hemispheric disconnection manifested during behaviors requiring dominant-hemisphere control. *(Doody and Jankovic, 806–810; Feinberg, Schindler, Flanagan, and Haber, 19–24)*

**142.** **(A)** Lesions in the perirolandic cortex cause impairment of the fine distal movements of the contralateral hand. Picking up small objects by opposing the index finger and the thumb or handling a small coin may become impossible. This type of apraxia has been termed limb-kinetic apraxia. Because separate fine movements of each finger are difficult, these patients pick up a pen or a coin by pressing it against the palm with the proximal portion of the thumb, much as infants do before they develop a pincer grip. *(Brazis, Masdeu, and Biller, 497)*

**143.** **(E)** A parietal postcentral gyrus lesion causes somatosensory disturbance with contralateral proprioception, pain, and temperature loss accompanied by tactile extinction, paresthesias, and pain. *(Brazis, Masdeu, and Biller, 506–507)*

**144.** **(E)** A lesion of the lateral frontal premotor area may cause impaired contralateral saccades, pure agraphia (dominant hemisphere), contralateral weakness of the shoulder (mainly in abduction and elevation of arm), and weakness of the hip muscles associated to limb-kinetic apraxia. *(Brazis, Masdeu, and Biller, 506–507)*

**145.** **(D)** A callosal lesion may cause lack of kinetic transfer with left-hand apraxia and agraphia, right-hand constructional apraxia, and inability to mimic the position of the contralateral hand. Other neurological findings include intermanual conflict (alien left hand) as well as perplexity and confabulation in trying to explain left-hand activity and double hemianopia. *(Brazis, Masdeu, and Biller, 506–507)*

**146.** **(A)** A mesial occipital lesion may cause a visual field defect with visual hallucinations, visual agnosia, alexia without agraphia, and cortical blindness. *(Brazis, Masdeu, and Biller, 506–507)*

**147.** **(D)** A lesion of the lateroinferior aspect of the nondominant temporal lobe causes impaired recognition of facial emotional expression and storage of nonverbal patterned materials such as geometric or tonal patterns. *(Brazis, Masdeu, and Biller, 506–507)*

**148.** **(D)** A lesion of the orbitofrontal area may cause blunted affect and impaired appreciation of social nuances, impaired goal-directed behavior, impotence, apraxia of speech, environmental dependency syndrome, and facetiousness. *(Brazis, Masdeu, and Biller, 506–507)*

**149.** **(B)** A lateral occipital lesion may cause alexia with agraphia, impaired optokinetic nystagmus, palinopsia, visual allesthesia, and impaired ipsilateral scanning. *(Brazis, Masdeu, and Biller, 506–507)*

**150.** **(C)** A bilateral lesion of the anterior tip of the temporal lobe causes Kluver–Bucy syndrome with visual agnosia, oral exploratory behavior, hypersexuality, hypomobility, and a marked tendency to take notice of and attend to every visual stimulus. *(Brazis, Masdeu, and Biller, 506–507)*

**151.** **(B)** A lesion of the parietal medial lobe may cause transcortical sensory aphasia when it affects the dominant lobe. *(Brazis, Masdeu, and Biller, 506–507)*

**152.** **(E)** A lesion of the medial frontal lobe, the cingulate gyrus, causes akinesia, perseveration, bilateral ideomotor apraxia, difficulties with intiating contralateral arm movement, and the alien hand sign. *(Brazis, Masdeu, and Biller, 506–507)*

**153.** **(C)** A lesion of the lateral parietal lobe results in alexia with agraphia (when the lesion affects the angular gyrus), finger agnosia, acalculia, and right–left disorientation. When the lesion

affects the dominant side, the patient may develop parietal apraxia, finger agnosia, acalculia, right–left disorientation, literal alexia, and conduction aphasia. When the lesion affects the nondominant side, the patient may develop anosognosia, autotopagnosia, spatial disorientation, hemispatial neglect, constructional apraxia, dressing apraxia, loss of topographic memory, allesthesia, hemisomatognosia, and asymbolia to pain. *(Brazis, Masdeu, and Biller, 506–507)*

**154. (C)** The cervical plexus is a plexus of the ventral rami of the first four cervical spinal nerves, which are located in the C1 to C4 cervical segment of the neck. They are located laterally to the transverse processes between prevertebral muscles from the medial side and the vertebral muscles (scalenus, levator scapulae, and splenius cervicis) from the lateral side. Nerves formed from the cervical plexus innervate the back of the head as well as some neck muscles. The cervical plexus has two types of branches: cutaneous and muscular. The cutaneous branches are the lesser occipital nerve (which innervates the lateral part of occipital region), the greater auricular nerve (which innervates skin near the concha acustica and external acoustic meatus), the transverse cervical nerve (which innervates the anterior region of neck), the supraclavicular nerves (which innervate the region of the suprascapularis, shoulder, and upper thoracic region). The deep branches of the cervical plexus innervate various muscles. The fibers from C1 innervate the deep muscles of the neck. Some fibers from C1 run to join the hypoglossal nerve, from which they innervate the thyrohyoid and geniohyoid muscles. Fibers from C1 and C2 join to form the superior root of the ansa cervicalis. Fibers of C2 and C3 join to form the inferior root of the ansa cervicalis. The inferior loop of the ansa cervicalis lies anterior to the internal jugular vein and passes upward to join the superior root. The ansa cervicalis supplies the strap muscles. Fibers from C2, C3, and C4 supply the sternocleidomastoid, trapezius, and levator scapulae. The spinal accessory nerve also supplies the sternocleidomastoid and trapezius. The phrenic nerve is formed by fibers from C3, C4, and C5. The nerve passes downward from its origin to lie on the scalenus anterior muscle. It enters the thorax by passing between the subclavian artery and vein. It lies anterior to the hilum of the lung, between the pleura and the pericardium. The right and left phrenic nerves pierce the diaphragm to supply it. The phrenic nerve supplies the mediastinal pleura with sensory fibers. Endarterectomy may cause injury to the cervical plexus. A lesion of the greater auricular nerve causes loss of sensation of the mandible and lower external ear. A lesion of the muscular branches of the cervical nerves causes weakness of the infrahyoid and scalene muscles, resulting in inability to flex the head and rotate it laterally. *(Brazis, Masdeu, and Biller, 73–74)*

**155. (E)** The sacral plexus is formed by the lumbosacral trunk, the anterior division of the first, and portions of the anterior divisions of the second and third sacral nerves. The lumbosacral trunk comprises the whole of the anterior division of the fifth and a part of the fourth lumbar nerve; it appears at the medial margin of the psoas major and runs downward over the pelvic brim to join the first sacral nerve. The anterior division of the third sacral nerve divides into an upper and a lower branch, the former entering the sacral and the latter the pudendal plexus. The nerves forming the sacral plexus converge toward the lower part of the greater sciatic foramen and unite to form a flattened band, from the anterior and posterior surfaces of which several branches arise. The band itself is continued as the sciatic nerve. which splits on the back of the thigh into the tibial and common peroneal nerves. The sacral plexus lies on the back of the pelvis between the piriformis and the pelvic fascia; in front of it are the hypogastric vessels, the ureter, and the sigmoid colon. The superior gluteal vessels run between the lumbosacral trunk and the first sacral nerve, and the inferior gluteal vessels between the second and third sacral nerves. All the nerves entering the plexus with the exception of the third sacral split into ventral and dorsal divisions. The nerves arising from these are the pudendal nerve (S2, S3, and S4), nerves to the piriformis and obturator internus muscles, pelvic splanchnic nerves (S2, S3, and S4), the sciatic nerve (L4, L5, S1, S2, and

S3), the superior gluteal nerve (gluteus medius and minimus), the inferior gluteal nerve (gluteus maximus), the nerve to the quadratus femoris, the posterior cutaneous nerve of the thigh (skin of buttock and back of thigh) and the perforating cutaneous nerve (medial part of the buttock). A lesion of the sacral plexus results in motor disturbances in the field of distribution of the superior gluteal, inferior gluteal, and sciatic nerves. Weakness of dorsiflexion and plantarflexion results in a flail foot. There is weakness of knee flexion, abduction, and internal rotation of the thigh as well as weakness of hip extension. The Achilles reflex is decreased or absent. *(Brazis, Masdeu, and Biller, 81–84)*

**156.** **(D)** The anterior rami of the spinal nerves of C5, C6, C7, C8, and T1 form the roots of the brachial plexus. These emerge from the transverse processes of the cervical vertebrae immediately posterior to the vertebral artery. The spinal nerves that form the brachial plexus run in an inferior and anterior direction within the sulci formed by these structures. The trunks of the brachial plexus pass between the anterior and middle scalene muscles. The superior trunk lies closest to the surface and is formed by the C5 and C6 roots. The C7 root continues as the middle trunk and the C8 and T1 roots join to form the inferior trunk. The trunks divide into anterior and posterior divisions, which separate the innervation of the ventral and dorsal halves of the upper limb. The C8 and T1 root and the lower trunk of the brachial plexus can be compressed, resulting in the rare entity called thoracic outlet syndrome, which may have vascular or neurological signs. Vascular signs are recurrent cyanosis, coldness, and pallor of the hand. Adson's test (turn head to the side of symptoms, extend head, take a deep breath, and pull down on the limb) usually reduces or eliminates the radial pulse. Neuropathic signs usually involve the lower trunk of the brachial plexus with pain in the ulnar border of the hand and the medial forearm and arm and prominent paresis and wasting of thenar muscles. *(Brazis, Masdeu, and Biller, 75–80)*

**157.** **(A)** The brachial plexus is formed from the anterior primary rami of the segments C4, C5, C6, C7, C8, and T1. The trunks of the brachial plexus pass between the anterior and middle scalene muscles. The superior trunk lies closest to the surface and is formed by the C5 and C6 roots. The suprascapular nerve and the nerve to the subclavius arise from the superior trunk. The suprascapular nerve contributes sensory fibers to the shoulder joint and provides motor innervation to the supraspinatus and infraspinatus muscles. The C7 root continues as the middle trunk and the C8 and T1 roots join to form the inferior trunk. The trunks divide into anterior and posterior divisions, which separate the innervation of the ventral and dorsal halves of the upper limb. The cords are called the lateral, posterior, and medial cord, according to their relationship to the axillary artery. The cords pass over the first rib close to the dome of the lung and continue under the clavicle immediately posterior to the subclavian artery. The lateral cord receives fibers from the anterior divisions of the superior and middle trunk and is the origin of the lateral pectoral nerve (C5, C6, and C7). The posterior divisions of the superior, middle, and inferior trunk combine to form the posterior cord. The upper and lower subscapular nerves (C7, C8, C5, and C6) leave the posterior cord and descend behind the axillary artery to supply the subscapularis and teres major muscles, respectively. The thorcodorsal nerve to the latissimus dorsi, also known as the middle subscapular nerve (C6, C7, and C8), also arises from the posterior cord. The inferior trunk continues as the medial cord and gives off the median pectoral nerve (C8, T1), the medial brachial cutaneous nerve (T1), and the medial antebrachial cutaneous nerve (C8, T1). The lateral cord divides into the lateral root of the median nerve and the musculocutaneous nerve. The musculocutaneous nerve leaves the brachial plexus sheath high in the axilla at the level of the lower border of the teres major muscle and passes into the substance of the coracobrachialis muscle. The posterior cord gives off the axillary nerve at the lower border of the subscapularis muscle and continues along the inferior and posterior surface of the axillary artery as the radial nerve. The axillary nerve supplies the shoulder joint, the surgical neck of the humerus, the deltoid, and the teres minor muscles before ending as the superior

lateral brachial cutaneous nerve. The radial nerve continues along the posterior and inferior surface of the axillary artery. The medial cord contributes the medial root of the median nerve and continues as the ulnar nerve along the medial and anterior surface of the axillary artery. The medial and lateral roots join to form the median nerve which continues along the posterior and lateral surface of the axillary artery. Erb–Duchenne palsy results from damage to the fifth and sixth cervical roots, which may be caused by sudden forceful depression of the shoulder during contact sports. Muscles supplied by these roots are weak and atrophic. These include the deltoid, biceps, brachioradialis, brachialis, supraspinatus, infraspinatus, and subscapularis. The limb has a characteristic position: it is internally rotated and adducted because of deltoid, supraspinatus, and infraspinatus (shoulder abduction and arm external rotation) weakness. Therefore, the weakness is of forearm flexion and of abduction and external rotation of the arm. The biceps and brachioradialis reflexes may be depressed or absent. *(Brazis, Masdeu, and Biller, 75–80)*

**158.** **(E)** A lesion of the lumbar plexus can be caused by a tumor of the pelvis. Its clinical signs include weakness of hip flexion (iliopsoas), leg extension (quadriceps), thigh eversion (sartorius), and thigh adduction. Sensory loss may involve the inguinal region; the lateral, anterior, and medial thigh; and the medial aspect of the lower leg. The patellar and cremasteric reflexes from the femoral nerve and the genitofemoral nerve, respectively, may be decreased or absent. *(Brazis, Masdeu, and Biller, 81–84)*

**159.** **(B)** Dejerine–Klumpke palsy results from injury to the eighth cervical and first thoracic roots or the lower trunk of the plexus. Mass compression from a lung tumor may damage the lower brachial plexus (Pancoast syndrome). The patient may present with weakness of finger and wrist flexion as well as weakness of the intrinsic hand muscles, causing a claw hand deformity. *(Brazis, Masdeu, and Biller, 81–84)*

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CHAPTER 3

# Pediatrics
## Questions

**1.** A 6-year-old fully immunized girl developed a fever of 39°C followed by weakness in her lower extremities and right upper extremity with numbness up to the midthoracic level. Cerebrospinal fluid (CSF) examination showed mild protein and cell elevation with no bacteria on Gram's stain. The most likely diagnosis is

(A) transverse myelitis
(B) tick-borne paralysis
(C) poliomyelitis
(D) botulism
(E) vascular malformation

**2.** Which of the following distinguish newborn benign nocturnal myoclonus from seizure?

(A) It occurs solely during sleep.
(B) It is activated by a stimulus.
(C) It may be accompanied by an abnormal electroencephalogram (EEG).
(D) Anticonvulsant drugs are the first-line treatment.
(E) It is usually seen in premature newborns.

**3.** Which of the following is true about neonatal seizures?

(A) They may arise from the hemisphere or brainstem.
(B) The lack of myelinated pathways facilitates the propagation of seizures from one hemisphere to the contiguous cortex.
(C) Prolonged epileptiform discharges are often associated with clinical symptoms of seizure.
(D) Jitteriness is never seen in the newborn.
(E) Isolated apneic discharge is always a seizure manifestation.

**4.** Which of the following is the *least* common among children with cerebral palsy?

(A) Spasticity
(B) Seizure
(C) Mental retardation
(D) Hearing impairment
(E) Ataxia

**5.** Which of the following is the *least* affected in kernicterus, a syndrome associated with cerebral palsy?

(A) Hippocampus
(B) Substantia nigra
(C) Basal ganglia
(D) Cortex
(E) Brainstem nuclei

**6.** A 5-year-old girl was brought to the emergency room because of recurrence of nocturnal right facial twitching and slurred speech over the previous 3 weeks. Her parents did not report any change in her mental status during these episodes. Her older brother has absence seizures. Which of the following is true about the patient's condition?

(A) The patient has absence seizures.
(B) The patient has complex partial seizures.
(C) The patient has an autosomal recessive disorder.
(D) The patient's electroencephalogram (EEG) may show central temporal spikes without overt seizure activity.
(E) The patient will need lifetime antiepileptic treatment.

**7.** In a full-term infant, the most frequent cause of neonatal seizure within the first 12 hours is

(A) hypoxic encephalopathy
(B) sepsis
(C) subarachnoid hemorrhage
(D) trauma
(E) intraventricular bleed

**8.** Which of the following is the best predictor of developing cerebral palsy?

(A) Low birth weight
(B) Prematurity
(C) The presence of echodense cystic lesions in the periventricular white matter with a diameter greater than 3 mm
(D) An Apgar score less than 3 after 10 minutes
(E) Hyperbilirubinemia

**9.** In neonatal adrenoleukodystrophy, seizures usually appear during

(A) the first 12 hours after birth
(B) the first 24 hours after birth
(C) the first 24 to 72 hours after birth
(D) the first 72 hours to 1 week after birth
(E) the first to fourth week after birth

**10.** The first seizure usually occurs within the first 24 hours after birth in case of

(A) kernicterus
(B) urea cycle disturbances
(C) drug withdrawal
(D) subarachnoid bleed
(E) tuberous sclerosis

**11.** In pyridoxine dependency, the first seizures usually occur within

(A) the fourth to eighth weeks after birth
(B) the first 24 hours after birth
(C) the first 24 to 72 hours after birth
(D) the first 72 hours to 1 week after birth
(E) the first to fourth weeks after birth

**12.** Which of the following disorders may follow a streptococcal infection?

(A) Restless legs syndrome
(B) Infantile masturbation
(C) Sydenham chorea
(D) Hepatolenticular degeneration
(E) Essential tremor

**13.** An elevated blood lactate level is seen in

(A) fructose 1,6 diphosphatase deficiency
(B) maple syrup urine disease
(C) citrullinemia
(D) propionic acidemia
(E) hypoparathyroidism

**14.** Which of the following is true about glycine encephalopathy?

(A) It is inherited as an autosomal dominant disorder.
(B) Hiccuping is an early and continuous feature of affected newborns.
(C) The EEG is usually normal during the acute phase.
(D) Hyperglycinemia is usually associated with hyperammonemia.
(E) Organic acidemia may be life-threatening.

**15.** A plasma ammonia concentration of 200 μml/l with a normal anion gap as well as a normal serum glucose concentration in a 6-day-old lethargic newborn is suggestive of

(A) maple syrup urine disease
(B) glycogen storage disease type 1
(C) urea cycle disorder
(D) fructose 1,6 diphosphatase deficiency
(E) methylmalonic acidemia

**16.** Seizure correlates with newborn serum ammonia concentrations greater than

(A) 120 μmol/L
(B) 180 μmol/L
(C) 300 μmol/L
(D) 400 μmol/L
(E) 500 μmol/L

**17.** Neonatal hypoglycemia in premature newborns is defined as a whole-blood glucose concentration less than

(A) 80 mg/dL
(B) 60 mg/dL
(C) 40 mg/dL
(D) 20 mg/dL
(E) 10 mg/dL

**18.** Impaired development of the vermis associated with increased CSF spaces causes

(A) microcephaly
(B) Dandy–Walker malformation
(C) type I lissencephaly
(D) periventricular heterotopia
(E) Joubert syndrome

**19.** Mutations in the genes coding for an actin-binding phosphoprotein that can promote actin branching causes

(A) subcortical band heterotopia
(B) Dandy–Walker malformation
(C) type I lissencephaly
(D) periventricular heterotopia
(E) Joubert syndrome

**20.** Subcortical band heterotopias can be attributed to loss of function of the

(A) doublecortin gene
(B) ASPM gene (abnormal spindle protein-like, microcephaly-associated gene)
(C) filamin A gene
(D) Fukutin gene
(E) ADP-ribosylation factor guanine exchange factor gene

**21.** The association of hydrocephaly, agyria, and retinal dysplasia is suggestive of

(A) subcortical band heterotopia
(B) Dandy–Walker malformation
(C) type I lissencephaly
(D) cobblestone lissencephaly
(E) Joubert syndrome

**22.** By the age of 15 years, the prevalence of recurrent headaches reaches

(A) 2.5%
(B) 5.1%
(C) 15%
(D) 23%
(E) 75%

**23.** The most common form of migraine in elementary school boys is

(A) migraine without aura
(B) migraine with aura
(C) basilar-type migraine
(D) familial hemiplegic migraine
(E) abdominal migraine

**24.** A 7-year-old boy was brought to the emergency room because of recurrence of migraine headaches. Which of the following clinical history findings is suggestive of an alternative diagnosis?

(A) Irritability
(B) Pounding headache
(C) Photophonia
(D) Photophobia
(E) Morning headache

**25.** Missense mutation in the calcium channel gene (CACNA1A) causes

(A) retinal migraine
(B) benign paroxysmal vertigo of childhood
(C) basilar-type migraine
(D) familial hemiplegic migraine
(E) abdominal migraine

**26.** The most frequent of migraine variants is

(A) retinal migraine
(B) benign paroxysmal vertigo of childhood
(C) basilar-type migraine
(D) familial hemiplegic migraine
(E) abdominal migraine

**27.** The most frequent manifestation of vertebrobasilar migraine is

(A) vertigo
(B) weakness
(C) nausea and vomiting
(D) ataxia
(E) diplopia

**28.** The first-line pharmacological treatment for a 12-year-old boy who developed an acute migraine headache is

(A) ibuprofen
(B) triptans
(C) dihydroergotamine
(D) opiates
(E) intravenous fluids

**29.** In response to a common insult such as hypoxia, the preterm brain exhibits more susceptibility than the term brain of the

(A) gray matter
(B) white matter
(C) brain stem
(D) cerebellum
(E) basal ganglia

**30.** Sleepwalking

(A) is a non–rapid-eye-movement (NREM) sleep parasomnia
(B) typically starts at the age of 2 years
(C) is caused by a mutation in a gene regulating the expression of nicotinic acetylcholine receptors
(D) is a nocturnal frontal lobe seizure
(E) responds to treatment with phenytoin, which is used as a first-line treatment

**31.** Which of the following brain structures is smaller in children with attention deficit–hyperactivity disorder than in age-matched controls?

(A) Caudate nucleus
(B) Thalamus
(C) Gray matter
(D) Midbrain
(E) Pons

**32.** In children with attention deficit–hyperactivity disorder, functional magnetic resonance imaging (fMRI) may demonstrate hypoactivity of the

(A) temporal cortex
(B) occipital cortex
(C) cerebellum
(D) thalamus
(E) midbrain

**33.** Apneic spells in an otherwise normal-appearing newborn are suggestive of

(A) brainstem immaturity
(B) seizure
(C) subarachnoid hemorrhage
(D) bacterial meningitis
(E) hypoxic ischemic encephalopathy

**34.** The usual EEG pattern during the early stage of infantile spasm

(A) is normal
(B) indicates hypsarrhythmia
(C) shows a burst-suppression pattern
(D) has polyspikes and waves
(E) shows triphasic waves

**35.** The most frequent central nervous system tumor observed in neurofibromatosis type 1 is

(A) ependymoma
(B) oligodendroglioma
(C) teratoma
(D) astrocytoma
(E) pineoblastoma

**36.** Narcolepsy is associated with loss of

(A) hypocretin
(B) dopamine
(C) serotonin
(D) glutamate
(E) acetylcholine

**37.** Which of the following drugs is the first-line pharmacological treatment for narcolepsy with excessive daytime sleepiness in a 12-year-old boy?

(A) Ritanserin
(B) Clomipramine
(C) Sodium oxybate
(D) Modafinil
(E) Zaleplon

**38.** Which of the following drugs is the most effective in treating a 17-year-old boy who has narcolepsy with excessive daytime sleepiness and cataplexy?

(A) Modafinil
(B) Amphetamine
(C) Sodium oxybate
(D) Armodafinil
(E) Methylphenidate

**39.** Defects in voltage-gated calcium channels have been associated with

(A) nocturnal frontal lobe epilepsy
(B) benign epilepsy with centrotemporal spikes
(C) juvenile absence epilepsy
(D) benign neonatal familial convulsions
(E) childhood absence epilepsy

**40.** Juvenile myoclonic epilepsy is associated with a defect in the

(A) $GABA_A$-gated chloride channel
(B) acetylcholine receptor
(C) voltage-gated potassium channel
(D) voltage-gated sodium channel
(E) voltage-gated calcium channel

**41.** Which of the following gene defects is a single-gene disorder maternally derived and associated with autism and gross motor delay?

(A) Fragile-X syndrome
(B) The 15q duplication
(C) Tuberous sclerosis complex
(D) Rett syndrome
(E) Joubert syndrome

**42.** Malignant migrating partial seizures in infancy are characterized by

(A) onset after the age of 3 years
(B) occurrence of progressive microcephaly
(C) frequent myoclonus
(D) mutation in sodium ion channels
(E) hypsarrhythmia

**43.** A 3-year-old boy was referred because daily spells consisting of atypical absences and clonic seizures, lateralized either on the left or on the right. The patient demonstrated normal psychomotor development until the age of 10 months, when he developed a first unilateral febrile seizure on the left side for about 10 minutes. EEG was normal, and the patient was treated with phenobarbital. Other convulsive seizures, febrile and afebrile, occurred in the following months, either generalized or lateralized on the left. At 13 months, myoclonic attacks and brief atypical absences with progressive and jerky head fall or complete fall appeared several times a day. Psychomotor development and hyperkinetic behavior then began to slow. Computed tomography (CT) and MRI scans were then performed; biological investigations were normal. The EEGs showed numerous generalized spike and polyspike waves. Different antiepileptic drugs were prescribed, but without success. At his neurological examination at the age of 3 years, the patient presented with a slight ataxia. These findings are suggestive of

(A) myoclonic astatic epilepsy
(B) West syndrome
(C) cryptogenic late-onset epileptic spasm
(D) Dravet syndrome
(E) Lennox–Gastaut syndrome

**44.** Epileptic encephalopathy with suppression bursts is characterized by

(A) paroxysmal choreoathetosis
(B) paroxysmal polyspikes lasting several seconds alternating with episodes of low-amplitude tracing
(C) a spike followed by a bell-shaped slow wave
(D) a favorable prognosis
(E) mutation in voltage-gated sodium channels

**45.** Tear of the tentorium near its junction with the falx may be complicated by neonatal seizures and

(A) subdural hemorrhage
(B) subarachnoid hemorrhage
(C) cerebral venous thrombosis
(D) intracerebral hemorrhage
(E) extradural hemorrhage

**46.** Tear of the superficial veins by shearing forces during prolonged delivery may be complicated by neonatal seizures and

(A) subdural hemorrhage
(B) subarachnoid hemorrhage
(C) cerebral venous thrombosis
(D) intracerebral hemorrhage
(E) extradural hemorrhage

**47.** Sepsis may be complicated by neonatal seizures and

(A) subdural hemorrhage
(B) subarachnoid hemorrhage
(C) cerebral venous thrombosis
(D) intracerebral hemorrhage
(E) extradural hemorrhage

**48.** A newborn developed generalized seizures in the second week of life. He was doing well at birth and then progressively became mildly lethargic, with feeding difficulties and progressive hypotonia. Serologic studies showed an increased concentration of branched-chain amino acids. The addition of 2,4 dinitrophenylhydrazine reagent colored his urine yellow. The most likely diagnosis is

(A) carbamyl phosphate synthetase deficiency
(B) glycine encephalopathy
(C) bilirubin encephalopathy
(D) maple syrup urine disease
(E) isovaleric acidemia

**49.** Which of the following is true about DiGeorge syndrome?

(A) It results from a duplication of chromosome 22q11.
(B) There is hypoplasia of the second pharyngeal pouch.
(C) Hypercalcemia and stroke are among the main features of the syndrome.

(D) Cardiac defect may be a cause of death.
(E) Apnea, jitteriness, and high-pitched cry may complicate the course of the disease.

**50.** A 12-month-old boy was brought to the emergency room because of multiple episodes of stiffening, upward eye deviation, pupillary dilatation, and alteration of respiratory pattern. Most of these episodes occurred during sleep and were complicated by enuresis. The mother, 1 month earlier, noted a brief episode of trembling of the eyelids and mouth with loss of facial tone. An EEG showed a generalized burst of 2.5 spike-wave complexes per second. Which of the following is true about the patient's condition?

(A) Mental retardation is an unusual complication.
(B) Twenty percent of patients with this condition may have a history of febrile seizure.
(C) Seizures in this condition are difficult to control.
(D) An underlying cause is rarely found.
(E) Phenytoin may improve seizure control.

**51.** Which of the following statements is true about infantile spasms?

(A) Onset always occurs after the age of 1 year.
(B) Pertussis immunization is a cause of infantile spasms.
(C) It may be associated with agenesis of the corpus callosum.
(D) Hypsarrhythmia is the usual EEG pattern recorded during the late stages of infantile spasm.
(E) High-dose pyridoxine is the first line treatment of seizure in infantile spasms.

**52.** A 17-year-old male developed daily multiple sleep attacks over the previous 2 months. He recently lost his job as a waiter because of multiple falls caused by a sudden loss of tone. Which of the following is true about his condition?

(A) His symptoms are caused by increased latency from sleep onset to REM sleep of greater than 90 minutes.
(B) Sleep paralysis rarely complicates this condition.
(C) Vivid and usually pleasant visual and auditory perceptions occur at the transition between sleep and wakefulness.
(D) During the loss of tone, partial paralysis affecting just the face and hands is more common than total paralysis.
(E) Clonidine is the treatment of choice.

**53.** Lafora disease is characterized by

(A) mental retardation complicating myoclonic seizures
(B) ataxia and spasticity occurring early in the course of the disease
(C) age of onset between 3 and 7 years
(D) easily controlled seizures
(E) inclusion bodies present in all stages of the disease

**54.** A 4-year-old boy with normal language and cognitive abilities developed progressive loss of his cognitive skills. He had difficulty following commands and in language comprehension. This was followed by a reduction in the volume and content of speech. Three months later the patient presented with multiple episodes of staring, followed by confusion. Physical examination and brain MRI were normal. The most likely diagnosis is

(A) progressive myoclonic epilepsy
(B) temporal lobe tumor
(C) benign rolandic epilepsy
(D) Landau–Kleffner syndrome
(E) Rasmussen syndrome

**55.** A 7-year-old boy living in Philadelphia developed the following symptoms over a period of 4 days in January: progressive weakness, clumsiness, and loss of facial expression. Neurological evaluation showed that the patient was ataxic when walking or reaching, with decreased deep tendon reflexes and bilateral facial weakness. Which of the following is true?

(A) The condition is caused by a block of the neuromuscular junction due to a neurotoxin produced by a tick.
(B) Respiratory failure and autonomic dysfunction may complicate the course of the disease.
(C) Positive response to edrophonium will be a definitive diagnostic test in this patient.
(D) Impairment in swallowing, in pupillary reflex response, and in extraocular muscle motility are classic findings in this patient's disease.
(E) An electromyogram (EMG) may show a decremental response after repetitive stimulation in this patient.

**56.** The most common cause of chorea in a school-aged child is

(A) Sydenham chorea
(B) Tourette syndrome
(C) Huntington disease
(D) Wilson disease
(E) lupus erythematosus

**57.** In which of the following cases would discontinuation of prophylactic antiseizure medications be strongly considered?

(A) Seizure caused by a surgically treated arteriovenous malformation (AVM) in remission for 6 months
(B) Absence seizures in remission for 8 months with normal EEG and MRI studies
(C) Generalized tonic–clonic seizure in remission for 2 years with normal EEG and MRI studies
(D) Cerebral palsy with seizures in remission for 3 years
(E) Adolescent-onset myoclonic epilepsy in remission for 3 years

**58.** A newborn developed an asymmetric Moro reflex after a complicated delivery. The poorly responsive arm hung in adduction, rotated internally at the shoulder, extended and pronated at the elbow, and flexed at the wrist. The most likely affected roots are

(A) C7-C8
(B) T1-T2
(C) C3-C4
(D) T3-T4
(E) C5-C6

**59.** A 10-year-old boy was brought for a neurology consultation by his mother because he had been disturbing his classmates with sniffing and grunting sounds for the previous 2 months. Neurological examination was normal. The most likely diagnosis is

(A) attention deficit–hyperactivity disorder (ADHD)
(B) anxiety
(C) tics
(D) autism
(E) Sydenham chorea

**60.** Which of the following is the least reliable sign for a ventriculoperitoneal shunt obstruction in a 4-month-old boy?

(A) Grade I bruit
(B) Strabismus
(C) Splitting of the sutures
(D) A setting-sun sign
(E) A bulging fontanelle

**61.** Which of the following is true about Tourette syndrome?

(A) Onset after the age of 15 years
(B) Preservation of school performance
(C) Motor tics as the most common initial symptoms
(D) Inability to temporarily suppress symptoms
(E) Greater incidence in girls than in boys

**62.** You are consulted about a 14-year-old boy with shoulder weakness and changes in facial expression. Physical examination showed a smooth, unlined face, protuberant lips, horizontal smile, and muscle wasting in both shoulders with sparing of the forearms. Lab workup showed a creatine kinase level of 600 UI/L. An EMG showed a myopathic pattern. Which of the following is true about the patient's condition?

(A) This is an autosomal recessive myopathy.
(B) The abnormal gene is located in Xp 21.2.
(C) The abnormal gene is responsible for the reduced amount of dystrophin in the muscles.
(D) Retinal vascular abnormalities may complicate the course of the disease.
(E) Cardiac arrhythmia is a frequent symptom.

**63.** A 16-month-old boy with a history of Down's syndrome developed his first generalized tonic–clonic seizure, which lasted for 20 minutes. On physical examination, his temperature was 39.5°C and there was no evidence of neurological abnormality. His older sister had a history of febrile seizure. His risk of developing epilepsy in later life is closest to

(A) 4%
(B) 10%
(C) 30%
(D) 50%
(E) 90%

**64.** A 10-year-old girl developed restless behavior, deterioration in school performance, uncoordinated movements, and angry outbursts. Physical examination showed slow writhing of limbs interrupted by high-amplitude, violent flinging of her upper extremities with an inward compulsion to move. The most likely cause of her condition is

(A) Wilson disease
(B) Sydenham chorea
(C) Tourette syndrome
(D) ADHD
(E) vascular accident

**65.** A 10-year-old girl was reported by her parents to have been "spacing out" at home and in school over the past month. Sometimes these spells were associated with lip smacking. Which of the following is the most suggestive of absence seizure rather than complex partial seizure?

(A) Urinary incontinence during spells
(B) Centrotemporal spikes on EEG
(C) Spells lasting 1 to 2 minutes
(D) Presence of automatism
(E) Prompt recovery after spells

**66.** The most frequent cause of athetoid cerebral palsy is

(A) prematurity
(B) perinatal asphyxia
(C) intraventricular bleed
(D) bilirubin encephalopathy
(E) low birth weight

**67.** A preterm newborn male was evaluated in the nursery. He was delivered 8 weeks before the expected date, with an Apgar score of 3 at 5 minutes. Neurological examination demonstrated generalized hypotonia and increased deep tendon reflexes. Which of the following is the correct answer to the mother's concern about her baby developing cerebral palsy?

(A) His low Apgar score indicates a high risk of cerebral palsy.
(B) It is very difficult to make the diagnosis of cerebral palsy before the age of 6 months.
(C) The presence of hypotonia on the initial neurological examination of the newborn is highly suggestive of cerebral palsy.
(D) The presence of progressive neurological deficit is suggestive of cerebral palsy.
(E) Seizure is the most frequent complication of cerebral palsy.

**68.** A newborn with the diagnosis of myelomeningocele should be evaluated for

(A) genitourinary dysfunction
(B) gastrointestinal dysfunction
(C) pulmonary complications
(D) Arnold–Chiari malformation type I
(E) seizure

**69.** You are asked to see a 10-year-old boy because of facial weakness and increased hand clumsiness progressing over a period of 6 months. On physical examination, the patient has an inverted V-shaped upper lip, thin cheeks, and a concave temporalis muscle. He is unable to close his eyelids tightly. Hand examination shows mild intrinsic muscle wasting and use of the wrist flexor to release grasp. The most likely diagnosis is

(A) Duchenne muscular dystrophy
(B) Werdnig–Hoffman disease
(C) myotonic dystrophy
(D) myasthenia gravis
(E) chronic demyelinating polyradiculopathy

**70.** Which of the following drugs may cause pseudotumor cerebri in a 5-year-old boy?

(A) Ampicillin
(B) Phenobarbital
(C) Vitamin A
(D) Acetazolamide
(E) Furosemide

**71.** Which of the following is the latest sign or symptom of an acute rise in intracranial pressure in a 12-year-old boy?

(A) Decreased consciousness
(B) Headache
(C) Vomiting
(D) Irritability
(E) Symptomatic papilledema

**72.** A 15-month-old boy was diagnosed with bacterial meningitis and started on antibiotics. On the third day of his hospitalization, he developed an episode of left-sided twitching of his arm, face, and leg followed by left-sided weakness that did not improve over the next 3 days despite the improvement of his general status and appetite and the disappearance of fever. The most likely diagnosis is

(A) right hemispheric ischemic stroke
(B) subdural empyema
(C) focal seizure with Todd paralysis
(D) brain abscess
(E) increased intracranial pressure

**73.** A premature neonate was diagnosed with gram-negative bacterial meningitis and started on antibiotics. The follow-up examination showed an improvement of his clinical status and CSF examination. On the fourth day, the patient presented with episodes of bradycardia and apnea. Head CT showed fluid of different contrast densities in the ventricles with an enhancing ependymal rim. A repeat lumbar CSF examination was unchanged. The most likely diagnosis is

(A) brain abscess
(B) subdural empyema
(C) ventriculitis
(D) idiopathic seizure
(E) encephalitis

**74.** A 17-year-old girl experienced 15 pressure-type headaches per month for the previous 8 months. Each headache lasted from 2 hours to 2 days. There has been no disturbance of her school performance or attendance. Her neurological examination is normal. The best treatment for her headache is

(A) low-dose amitriptyline at bedtime
(B) acetaminophen and codeine
(C) valproic acid
(D) propranolol
(E) clorazepate

**75.** Familial hemiplegic migraine

(A) is characterized by a sudden onset of hemiparesis or hemisensory loss that is usually followed by a contralateral headache
(B) occurs more frequently in adults than in children
(C) improves rapidly, since the neurological impairment lasts no more than a few hours
(D) always affects the same side
(E) is transmitted by an autosomal recessive inheritance

**76.** Which of the following is a migraine variant?

(A) Recurrent abdominal pain
(B) Recurrent chest pain
(C) Recurrent urinary incontinence.
(D) Sleepwalking
(E) Choreoathetotic movements

**77.** A 2-year-old boy developed a 5-minute febrile seizure. Which of the following conditions does *not* increase his risk of developing subsequent epilepsy?

(A) Preexisting cerebral palsy
(B) Family history of epilepsy
(C) History of complex febrile seizure
(D) Two febrile seizures in 1 year
(E) Preexisting development delay

**78.** Which of the following is a major form of encephalitis in Asia?

(A) California La Crosse encephalitis
(B) Eastern equine encephalitis
(C) Japanese B encephalitis
(D) St. Louis encephalitis
(E) Western equine encephalitis

**79.** A 10-year-old boy developed an episode of fever, headache, nausea and vomiting, and irritability. Three days later, he was brought to the emergency room because of a brief episode of twitching of his right face and arm with decreased consciousness. Neurological examination showed mild right arm and leg weakness. An EEG demonstrated periodic lateralizing epileptiform discharge. The most likely diagnosis is

(A) measles encephalitis
(B) Reye syndrome
(C) herpes simplex encephalitis
(D) postinfectious encephalitis
(E) St. Louis encephalitis

**80.** Which of the following may exacerbate brain ischemia during the management of increased intracranial pressure?

(A) Head elevation
(B) Hypothermia
(C) Osmotic diuretics
(D) Hyperventilation to lower the arterial carbon dioxide pressure from 40 to 20 mmHg
(E) Pentobarbital coma

**81.** A 15-year-old boy is brought for a neurological consultation because of exacerbation of headache and difficulties of accommodation. Neurological examination demonstrates loss of pupillary light reflex, palsy of upward gaze with preservation of downward gaze, retraction convergence nystagmus when upward gaze is attempted, and loss of accommodation. Head MRI shows an enlarged, dense, noncalcified pineal gland area with irregular margins. Which of the following is true about this condition?

(A) Pineal germinoma is the most likely diagnosis.
(B) It is more common in females than males.
(C) It is highly radioresistant.
(D) The 5-year survival rate is less than 20%.
(E) Bitemporal hemianopia is one of the earliest signs of this condition.

**82.** A 5-year-old boy with autistic behavior, long face, enlarged ears, and macroorchidism may have which of the following gene defects?

(A) 5 p monosomy
(B) Trisomy 21
(C) Fragile-X syndrome
(D) Trisomy 18
(E) Trisomy 13

**83.** A 3-year-old boy with hypotonia and a round flat face as well as flat nape of neck may have which of the following gene defects?

(A) 5 p monosomy
(B) Trisomy 21
(C) Fragile-X syndrome
(D) Trisomy 18
(E) Trisomy 13

**84.** A 4-week-old newborn girl with pointed ears micrognathia, occipital protuberance, narrow pelvis, and rocker bottom feet may have which of the following gene defects?

(A) 5 p monosomy
(B) Trisomy 21
(C) Fragile-X syndrome
(D) Trisomy 18
(E) Trisomy 13

**85.** A 3-year-old boy with cri du chat syndrome may have which of the following gene defects?

(A) 5 p monosomy
(B) Trisomy 21
(C) Fragile-X syndrome
(D) Trisomy 18
(E) Trisomy 13

**86.** A 3-year-old boy was evaluated for mental retardation. He was found to have bilateral hearing loss, interstitial keratitis, and peg-shaped upper incisors. The most likely cause of his mental retardation is

(A) trisomy 21
(B) cytomegalovirus infection
(C) amino acid–abnormal metabolism
(D) congenital syphilis
(E) toxoplasmosis

**87.** Hexosaminidase deficiency causes

(A) $G_{M1}$ gangliosidosis
(B) Tay–Sachs disease
(C) Krabbe disease
(D) metachromatic leukodystrophy
(E) Niemann–Pick disease

**88.** Beta-galactosidase deficit causes

(A) $G_{M1}$ gangliosidosis
(B) Tay–Sachs disease
(C) Krabbe disease
(D) metachromatic leukodystrophy
(E) Niemann–Pick disease

**89.** Sphingomyelinase deficit causes

(A) $G_{M1}$ gangliosidosis
(B) Tay–Sachs disease
(C) Krabbe disease
(D) metachromatic leukodystrophy
(E) Niemann–Pick disease

**90.** Arylsulfatase deficit causes

(A) $G_{M1}$ gangliosidosis
(B) Tay–Sachs disease
(C) Krabbe disease
(D) metachromatic leukodystrophy
(E) Niemann–Pick disease

**91.** Galactosylceramidase deficit causes

(A) $G_{M1}$ gangliosidosis
(B) Tay–Sachs disease
(C) Krabbe disease
(D) metachromatic leukodystrophy
(E) Niemann–Pick disease

**92.** Which of the following is true of Leigh disease?

(A) It is a disorder caused by multiple sulfatase deficiency.
(B) The Hurler phenotype is prominent in affected patients.

(C) Hypotonia, ocular motility, and respiratory abnormalities are typical features.
(D) Glucose load may improve symptoms.
(E) The brainstem and basal ganglia are typically spared.

**93.** Subacute necrotizing encephalomyelopathy results from

(A) defect in intestinal transport of copper
(B) sphingomyelinase deficit
(C) glucocerebrosidase deficit
(D) mitochondrial abnormalities
(E) lack of regulation of fusion of primary lymphocytes

**94.** Gaucher disease results from

(A) defect in intestinal transport of copper
(B) sphingomyelinase deficit
(C) glucocerebrosidase deficit
(D) mitochondrial abnormalities
(E) lack of regulation of fusion of primary lymphocytes

**95.** Menkes syndrome is caused by

(A) defect in intestinal transport of copper
(B) sphingomyelinase deficit
(C) glucocerebrosidase deficit
(D) mitochondrial abnormalities
(E) lack of regulation of fusion of primary lymphocytes

**96.** Chediak–Higashi syndrome is caused by

(A) defect in intestinal transport of copper
(B) sphingomyelinase deficit
(C) glucocerebrosidase deficit
(D) mitochondrial abnormalities
(E) lack of regulation of fusion of primary lymphocytes

**97.** Niemann–Pick syndrome is caused by

(A) defect in intestinal transport of copper
(B) sphingomyelinase deficit
(C) glucocerebrosidase deficit
(D) mitochondrial abnormalities
(E) lack of regulation of fusion of primary lymphocytes

**98.** A 4-year-old mentally retarded girl was brought by her mother to the neurology clinic because she developed a new onset of seizure. Skin examination demonstrated leaf-shaped hypochromic nevi on her left buttock and an angiokeratoma on her face. The most likely diagnosis is

(A) cerebral palsy
(B) tuberous sclerosis
(C) neurofibromatosis type I
(D) Down's syndrome
(E) Gaucher disease

**99.** Which of the following is a criterion for the diagnosis of neurofibromatosis type II?

(A) Six café au lait spots greater than 15 mm in the postpubertal individual
(B) Optic glioma
(C) Iris hamartoma
(D) Acoustic neurinomas
(E) Sphenoid dyplasia

**100.** Which of the following is a necessary criterion for the diagnosis of Rett syndrome?

(A) Retinopathy
(B) Severe progressive dementia
(C) Microcephaly at birth
(D) Optic atrophy
(E) Evidence of acquired neurological disease

**101.** The most likely diagnosis of a newborn with vomiting, hepatomegaly, and the presence of reducing substances in the urine is

(A) Mucopolysaccharide enzyme deficit
(B) Krabbe disease
(C) Gaucher disease
(D) Tay–Sachs disease
(E) Galactosemia

**102.** Zellweger syndrome is caused by

(A) a mitochondrial defect
(B) hypoxic ischemic encephalopathy
(C) acid maltase deficiency
(D) a neuromuscular transmission defect
(E) a peroxisomal disorder

**103.** Which of the following is true about spinal muscular atrophy type I?

(A) The age of onset is between 12 and 24 months after birth.
(B) Arthrogryposis is usually present.
(C) Facial expression and extraocular movements are affected early and severely.
(D) There is a hypertrophy of type II fibers.
(E) DNA analysis of chorionic villi may be used for prenatal diagnosis.

**104.** A male newborn with normal development started to have poor feeding, constipation, and failure to thrive after the age of 4 weeks. Neurological examination demonstrated generalized hypotonia with areflexia, weak cry, ptosis, and dilated pupils that reacted poorly to light. An EMG showed an incremental response to repetitive stimulation between 20 and 50 Hz. The most likely diagnosis is

(A) Guillain–Barré syndrome
(B) myasthenia gravis
(C) infantile spinal muscle atrophy
(D) botulism
(E) Lowe syndrome

**105.** Congenital myotonic dystrophy in newborns is characterized by

(A) an autosomal recessive disorder
(B) less than 50 DNA triplet repeats on chromosome 19
(C) myotonia usually elicited by muscle percussion
(D) a high incidence of polyhydramnios during pregnancy
(E) a change in repeat DNA triplet size that is greater from father to child than from mother to child

**106.** Which of the following is true about Duchenne muscle dystrophy?

(A) The gene defect is located at chromosome X p21.
(B) The dystrophin content in Duchenne muscular dystrophy is less reduced than in Becker dystrophy.
(C) The disease has an autosomal dominant transmission.
(D) Motor function declines sharply before the age of 3 years.
(E) Arthrogryposis is usually present.

**107.** The gene defect of myotonic dystrophy is located in

(A) 19q 13.3
(B) 1q 31-32
(C) Xp21.2
(D) 17q23-25
(E) 17p11

**108.** The gene defect of Duchenne muscular dystrophy is located in

(A) 17q25.3-q25.3
(B) 1q 31-32
(C) Xp21.2
(D) 17q23-25
(E) 17p11

**109.** The gene defect of acid maltase deficiency is located in

(A) 17q25.2-q25.3
(B) 1q 31-32
(C) Xp21.2
(D) 17q23-25
(E) 17p11

**110.** The gene defect of familial hyperkalemic periodic paralysis is located in

(A) 17q25.3-q25.2
(B) 1q31-32
(C) Xp21.2
(D) 17q23-25
(E) 17p11

**111.** The gene defect of familial hypokalemic periodic paralysis is located in

(A) 17q23-35
(B) 1q 31-32
(C) Xp21.2
(D) 17q23-25
(E) 17p11

**112.** The gene defect of Dejerine–Sottas syndrome is located in

(A) 17q23
(B) 17p11
(C) 19q 13.3
(D) Xq28
(E) 1p35

**113.** The gene defect of Emery–Dreifuss muscular dystrophy type 1 is located in

(A) 17q23
(B) 17p11
(C) 19q 13.3
(D) Xq28
(E) 1p35

**114.** A 12-year-old boy is brought for a neurological consultation because of recurrent numbness and tingling in his lower extremities with unsteady gait over several months. His parents report that, as of 3 months earlier, the patient had decreased nocturnal visual acuity. Neurological examination showed cerebellar ataxia, nystagmus, and decreased deep tendon reflexes. CSF examination shows a protein level of 300 mg/dL. Nerve conduction studies show a marked decrease in conduction velocity throughout. EMG results are consistent with chronic denervation. The most likely diagnosis is

(A) Refsum disease
(B) Dejerine–Sottas disease
(C) Charcot–Marie–Tooth neuropathy
(D) metachromatic leukodystrophy
(E) Emery–Dreifuss muscular dystrophy

**115.** A 12-year-old boy is brought for a neurological consultation because of muscle stiffness and difficulty in moving. Neurological examination demonstrates a painless myotonia at rest that improves with activity as well as generalized muscle hypertrophy. EMG shows myotonic discharges. The creatine kinase level is normal. The most likely diagnosis is

(A) myotonia congenita
(B) stiff-man syndrome
(C) hypothyroidism
(D) Schwartz–Jampel syndrome
(E) neuromyotonia

**116.** A 7-year-old boy is evaluated for pain, muscle weakness with exercise, and recurrent rhabdomyolisis. Neurological examination and EMG are normal. The creatine kinase level is 600 UI/L. An ischemic exercise test shows abnormal ammonia and lactate levels. The most likely diagnosis is

(A) Kearns–Sayre syndrome
(B) Menkes syndrome
(C) myoadenylate deaminase deficiency
(D) carnitine palmitoyl transferase deficiency
(E) Brody disease

**117.** Child ataxia with a pellagra-like skin rash after exposure to sunlight may be seen in

(A) Hartnup disease
(B) basilar migraine
(C) maple syrup urine disease
(D) Miller Fisher syndrome
(E) myoclonic encephalopathy

**118.** Which of the following causes of progressive ataxia in a child is associated with an increased blood level of very long chain fatty acids?

(A) Ataxia telangiectasia
(B) Sulfatide lipidosis
(C) Hypobetalipoproteinemia
(D) Ramsay Hunt syndrome
(E) Adrenoleukodystrophy

**119.** A 15-year-old boy developed night blindness, mental retardation, and dystonic dysarthria. Head MRI shows an eye-of-tiger appearance of the pallidum. Acanthocytes are seen in washed erythrocytes. The most likely diagnosis is

(A) Fahr disease
(B) Hallervorden–Spatz disease
(C) neuroacanthocytosis
(D) Sydenham chorea
(E) Harp syndrome

**120.** A 10-year-old girl developed progressive dystonic rigidity and choreoathetotic movements. On T2-weighted MRI of the head, low-intensity images from the globus pallidus show a central area of increased intensity. The most likely diagnosis is

(A) Fahr disease
(B) Hallervorden–Spatz disease
(C) neuroacanthocytosis
(D) Sydenham chorea
(E) Harp syndrome

**121.** The most common cause of acquired chorea in children is

(A) tardive dyskinesia
(B) Fahr disease
(C) Hallervorden–Spatz disease
(D) neuroacanthocytosis
(E) Sydenham chorea

**122.** The association between encephalopathy and progressive calcification of the basal ganglia is suggestive of

(A) tardive dyskinesia
(B) Fahr disease
(C) Hallervorden–Spatz disease
(D) neuroacanthocytosis
(E) Sydenham chorea

**123.** A 13-year-old boy with a history of asthma treated by theophylline developed abnormal movements of the tongue and face, including tongue protrusion and lip smacking. The most likely diagnosis is

(A) tardive dyskinesia
(B) Fahr disease
(C) Hallervorden–Spatz disease
(D) neuroacanthocytosis
(E) Sydenham chorea

**124.** A 7-year-old boy developed dystonia of the face and limbs associated with self-mutilation of the lips. Lab workup shows abnormal erythrocytes with thorny projection from the cell surface but no lipoprotein abnormalities. The most likely diagnosis is

(A) tardive dyskinesia
(B) Fahr disease
(C) Hallervorden–Spatz disease
(D) neuroacanthocytosis
(E) Sydenham chorea

# Answers and Explanations

1. **(A)** The acute onset of symptoms in this child is most likely related to acute transverse myelitis. This diagnosis is supported by the occurrence of a rapid asymmetric neurological deficit and a sensory level suggesting cross-sectional involvement of the spinal cord. Magnetic resonance imaging (MRI) of the spinal cord would be the procedure of choice to confirm the diagnosis. It may show evidence of cord swelling at the level of demyelination and rule out any acute cord compression in the epidural space. Transverse myelitis is an acute demyelination of the spinal cord that may progress over hours or days. It may be associated with optic neuritis in Devic disease and uncommonly with multiple sclerosis in childhood. The mean age of onset is 9 years. The level of demyelination is usually thoracic. The motor deficit is commonly asymmetric, and maximum weakness is reached within 48 hours. Recovery begins after 6 days. Fifty percent of patients make a full recovery, 10% have no recovery, and 40% recover incompletely. Relapsing myelitis may occur. Corticosteroids remain the most common treatment despite the absence of controlled studies. Poliomyelitis may cause asymmetric weakness, but the presence of a sensory level excludes this diagnosis. Tick-bite paralysis is unlikely to be the diagnosis because of the presence of fever and the abnormal CSF. The absence of ophthalmoplegia, the presence of fever, and abnormal CSF results are against the diagnosis of botulism. Finally, a spinal cord vascular malformation is unlikely to be the diagnosis because of the presence of fever and the absence of red blood cells in the CSF. In this case, respiratory failure is the major concern because of the involvement of the thoracic spinal cord. Vital capacity should be measured multiple times per day. Pulmonary emboli are a rare complication during acute paralysis. Hypotension and sphincter incontinence, like other autonomic instabilities, are usually not life-threatening. However, cardiac rhythm and blood pressure should be monitored closely. *(Fenichel, 264–265)*

2. **(A)** Nocturnal myoclonus can be distinguished from seizures and jitteriness because it occurs solely during sleep, it is not activated by a stimulus, and the EEG is normal. *(Fenichel, 3)*

3. **(A)** Newborns with hydranencephaly or atelencephaly are able to generate seizures, supporting the fact that the brainstem may generate seizure activity. These seizures are confined to the brainstem because of the absence of myelinated fibers. Propagation of seizure activity to a contiguous cortical area is enhanced by the maturity of myelinated pathways. Fifty percent of prolonged epileptiform discharges are not associated with visible clinical seizures. Jitteriness is an excessive response to stimulation by low-frequency, high-amplitude shaking of limbs and jaw. It may occur in a newborn with perinatal asphyxia and may be confused with myoclonic seizures when it occurs without apparent stimulation. The absence of eye movement or alteration in respiration pattern and the normal EEG can distinguish the two entities. However, the most practical way to distinguish between seizures and jitteriness is in the following maneuver: grasping the jittering limb will stop normal jitteriness but not seizure activity. Apneic spells of 10 to 15 seconds may be seen in the premature newborn. They should

be considered as a sign of brainstem immaturity rather than a pathologic condition. Apnea is seldom a seizure manifestation unless it is associated with tonic deviation of the eyes or body stiffness. *(Fenichel, 1–4)*

4. **(E)** Cerebral palsy comprises a spectrum of static lesions of the central nervous system that produce chronic problems with motor strength and/or control; it is not the result of a recognized malformation. While the lesion is static by definition, it appears in a central nervous system that is undergoing developmental change during a period of rapid growth. As a result, its manifestations are not stable. Motor disability is the most frequent symptom, and it is the first disability to be identified in affected children. Other central nervous system impairments may be associated with the motor deficit. Mental retardation is the most common associated disability, estimated to occur in 50% to 66% of patients with cerebral palsy. Hearing deficits may be seen in up to 30% of affected children, with higher prevalence in those who have the athetoid form of cerebral palsy. Seizures are seen in 30% to 50% of children with cerebral palsy, especially in hemiplegic patients. Ataxic cerebral palsy is the rarest form of cerebral palsy, most likely denoting dysfunction of the cerebellum or its pathways. Truncal and gait ataxias are more striking than limb ataxia. *(Fenichel, 269–270; Nelson, 7380; Rosenbloom, 350–354)*

5. **(D)** Kernicterus is a syndrome associated with cerebral palsy. Unbound bilirubin can cross the blood–brain barrier in the neonatal period, enter the nervous system, and produce neuronal damage. Neuronal necrosis and bilirubin staining in specific neuronal regions are the specific pathological features of kernicterus. The most commonly affected regions of the brain are the basal ganglia, hippocampus, substantia nigra, cranial nerve, brainstem nuclei, cerebellar nuclei, and anterior horn cells of the spinal cord. Cortical neurons are the least affected in kernicterus. This reflects the predominance of extrapyramidal, gaze, and auditory abnormalities as clinical symptoms of kernicterus. *(Ahdab-Barmada and Moossy, 45–56)*

6. **(D)** The patient in this case developed a motor seizure with preservation of consciousness, most likely involving the left cortical areas controlling speech and right face movements. Benign rolandic epilepsy is the most likely diagnosis. It is an autosomal dominant condition with incomplete penetrance occurring typically between the age of 3 and 12 years. The area of the brain around the sensorimotor fissure is involved in the genesis of seizure. In around 40% of cases, a family history of febrile seizure or epilepsy is found. Seventy percent of children have seizures only while asleep, and 15% only when awake. Interictal EEG may show unilateral or bilateral spike discharges in the central or centrotemporal region. Seizures resolve spontaneously by the age of 14 in most cases. Treatment of benign rolandic seizure is indicated only in the case of frequent seizures or the occurrence of major motor seizures. Carbamazepine is a popular choice because of its effectiveness in treating partial complex seizures and its lack of cognitive side effects. Absence seizure is unlikely to be the diagnosis. It generally occurs during the daytime with brief stares with or without eyes blinking. The preservation of consciousness rules out a complex partial seizure in this patient. Other patients with benign rolandic epilepsy may have complex partial seizures. *(Fenichel, 31–32)*

7. **(A)** Seizures may complicate any brain disorder in full-term infants. The time of onset of the first seizure is helpful in establishing the cause. Hypoxic-ischemic encephalopathy is the most frequent cause of seizure in the first 12 hours, followed by sepsis, meningitis, and subarachnoid hemorrhage. Trauma and intrauterine infection may cause a seizure in the first 24 hours. Pyridoxine dependency, intraventricular bleed in a term infant, and direct drug effects are rare causes of seizure in the first 24 hours. *(Fenichel, 4)*

8. **(C)** Despite taking a comprehensive genetic history, doing a complete physical examination, and performing extensive metabolic, chromosomal, and neuroimaging studies, 50% of patients with cerebral palsy have no evident cause of their brain damage. Although prematurity is the most common antecedent of cerebral

palsy, the majority of infants who develop cerebral palsy are full term. Lower birth weight increases the risk of developing cerebral palsy; however, even for very low birth weights (less than 1500 g), the risk of developing cerebral palsy is only 15% to 20%. Preterm infants who develop intraventricular hemorrhage with extension to the white matter are at the greatest risk for developing cerebral palsy. It seems that in premature infants the best predictor of cerebral palsy is the presence of echodense cystic lesions in the periventricular white matter with a diameter greater than 3 mm, which increases the risk of developing diplegic spastic cerebral palsy to 90%. The Apgar score has been a poor indicator of babies at risk of cerebral palsy. Only 10% to 15% of newborns have an Apgar score of 3 or less at 10 to 15 minutes, and the majority of full-term newborns who develop cerebral palsy have normal Apgar scores. Bilirubin encephalopathy may cause athetoid cerebral palsy. Bilirubin is especially toxic to the basal ganglia and auditory nuclei in the brainstem. It makes the infant with athetoid cerebral palsy at high risk of developing neurosensory hearing loss. It is not the best predictor of cerebral palsy. *(Pidcock et al., 417–422; Taft, 411–418)*

**9.** **(E)** The time of onset of seizures is helpful in determining their causes during the neonatal period. Neonatal adrenoleukodystrophy is an autosomal recessive inheritance characterized by poor adrenal function with accumulation of very long chain fatty acids in the plasma. Initial symptoms are hypotonia and failure to thrive. Other clinical manifestations include, facial abnormalities, seizures, retinal degeneration, poor muscle tone, enlarged liver, and adrenal dysfunction. Seizures generally appear between the first and fourth week. *(Fenichel, 4–5)*

**10.** **(A)** An excessive level of unconjugated free bilirubin in the blood causes kernicterus during the neonatal period. Unconjugated free bilirubin is neurotoxic, especially to the basal ganglia and hippocampus. Seizures may occur from the third day of birth during the second phase of bilirubin encephalopathy. The newborn shows increasing tone with opisthotonos. Urea cycle disturbances are related to a defect in the enzyme systems responsible for urea synthesis. Symptoms are caused by ammonia intoxication. Seizures may complicate the initial hypotonia and lethargy after the first week of birth. The most common drug withdrawal in the newborn is narcotic withdrawal. Tremor, irritability, hyperactivity, and autonomic instability are the earlier symptoms, which may be complicated by seizures in up to 5% of cases. First seizures typically occur from 24 to 72 hours after birth. Subarachnoid hemorrhage may cause unexpected seizures during the first day. Seizures may occur after the first 24 hours in tuberous sclerosis. *(Fenichel, 4–5)*

**11.** **(B)** Pyridoxine dependency is a rare autosomal recessive disorder that may result from an impairment of glutamic acid decarboxylase activity. Seizures may begin immediately after birth or at any time thereafter. *(Fenichel, 4–5)*

**12.** **(C)** Sydenham chorea is the neurological sequela of rheumatic fever and the prototypical immune disorder. Based on immunohistochemical studies using concentrated IgG from patients with Sydenham chorea, specific cross-reactivity of IgG to neuronal cytoplasmic antigens in subthalamic and caudate nuclei were identified in 47% of acutely ill patients. Further, the streptococcal-induced aspect in Syndenham chorea was proven by the absence of neuronal staining following preabsorption of antibodies with streptococcal membranes. Recent studies focusing on the specific target site of the autoantibodies in rheumatic fever have suggested lysogangliosides and [beta]-tubulin; these compounds are a molecular mimic of the group A streptococal carbohydrate epitope N-acetyl-[beta]-D-glucosamine. Mechanistically, it is proposed that antibodies in Sydenham chorea can induce signal transduction involving calcium calmodulin dependent protein kinase II activation resulting in increased tyrosine hydroxylase and dopamine. *(Wolf 491–496)*

**13.** **(A)** Fructose-1.6-diphosphatase (FDPase) deficiency is a rare in autosomal recessive inherited disease characterized by hyperventilation, seizure, hypoglycemic attacks or even coma, lactic acidosis, nausea, and tremor. The absence

of FDPase impairs the gluconeogenesis; this explains the occurrence of lactic acidosis and the accumulation of some amino acids. In the absence of FDPase, the organism depends on alimentary glucose and glycogenolysis to maintain a normal blood glucose level This results in life-threatening attacks of hypoglycemia associated with metabolic acidosis. *(Fenichel, 4–5)*

**14.** **(B)** Glycine encephalopathy results from a defect of glycine cleaving system. It is an autosomal recessive disorder. Affected newborns are normal at birth but become irritable and refuse feeding 6 to 8 hours after delivery. The onset is usually within 48 hours, but delays by few weeks occur in milder allelic forms. Hiccupping is an early and continuous feature. Progressive lethargy, hypotonia, respiratory disturbances, and myoclonic seizures follow. Some newborns survive the acute illness, but mental retardation, epilepsy, and spasticity characterize the subsequent course. *(Fenichel, 5)*

**15.** **(A)** The patient described in this question developed lethargy and hyperammonemia without organic academia; the serum glucose was normal. These findings are suggestive of urea cycle disturbance. Six inborn errors in the urea cycle have been described. Five of these represent a lesion at each of the five steps in the conversion of ammonia to urea. They include argininosuccinic aciduria, citrullinuria, hyperargininemia, and two conditions termed hyperammonemia, the more common one attributable to a defect of ornithine transcarbamylase (OTC) and the other the result of a defect in mitochondrial carbamyl phosphate synthetase (CPS). The genes for all components of the urea cycle have been cloned. Additionally, a deficiency of N-acetylglutamate synthetase has been reported. This enzyme is responsible for the formation of N-acetylglutamate, a required activator for mitochondrial CPS. More recently, two genetic defects affecting the citrulline and ornithine transporters have also been documented.

The diagnosis of urea cycle disturbances is strongly suspected by the presence of clinical manifestations of ammonia intoxication—a blood ammonia concentration of 150 μmol/L or higher—associated with a normal serum glucose concentration and normal anion gap. Plasma quantitative amino acid analysis differentiates the specific urea disorder. *(Fenichel, 6–7)*

**16.** **(C)** The clinical features of urea cycle disturbance are due to ammonia intoxication. Prorgressive lethargy, vomiting, and hypotonia develop the first day after delivery, even before the initiation of protein feeding. Progressive loss of consciousness and seizures follow on subsequent days. Vomiting and lethargy correlate well with a plasma ammonia concentration greater than 120 μmol/L, coma correlates with concentrations greater than 180 μmol/L, and seizures correlate with concentration greater than 300 μmol/L. Death follows quickly in untreated newborns. *(Fenichel, 6–7)*

**17.** **(D)** Neonatal hypoglycemia is defined as a whole blood glucose concentration of less than 20 mg/dL in premature and low-birth-weight newborns, less than 30 mg/dL in term newborns during the first 72 hours, and less than 40 mg/dL in full-term newborns after 72 hours. *(Fenichel, 10)*

**18.** **(B)** Within the broad spectrum of dysgenetic abnormalities in the posterior fossa, the most common lesions involve impaired development of the vermis associated with increased CSF spaces. The most striking of these anomalies is Dandy–Walker malformation (DWM), in which the enlarged CSF space results from cystic distention of the fourth ventricle, with complete or partial agenesis of the cerebellar vermis, hypoplasia of the cerebellar hemispheres, and enlargement of the posterior fossa with elevation of the torcula and anterior displacement of the brainstem; hydrocephalus develops in most cases. The pathogenetic mechanism(s) leading to the DWM remain poorly understood. In one view, the cyst develops after failed incorporation of the anterior membranous area into the choroid plexus and failed or delayed development of the foramen of Magendie in the posterior membranous area. Isolated inferior vermian hypoplasia may occur with normal cerebellar hemispheres and brainstem. This lesion appears to represent an arrested incomplete dow growth of the vermis, leaving an enlarged midline CSF

space that may be mistaken for a cystic lesion. Joubert syndrome is an autosomal recessive condition that presents with hypotonia, disturbances in respiratory (hyperventilation and central apnea) and oculomotor control, and later psychomotor disturbances. The essential brain morphology of Joubert syndrome includes vermian hypoplasia, impaired axonal decussation (with a deep interpeduncular notch), and thick, abnormally oriented superior cerebellar peduncles. Together, these features produce the neuroradiologic picture known as the molar tooth sign. *Microcephaly vera* refers to a reduction in brain size in the absence of other gross structural abnormalities both within and outside of the brain. Clinically, affected patients have mental retardation and, infrequently, epilepsy. *Periventricular heterotopia* refers to clusters of neuronal nodules ectopically located along the walls of the lateral ventricles and beneath an otherwise normal-appearing cortex. Clinically, affected patients present with seizures in late adolescence, are generally of normal intelligence, but may have learning problems (dyslexia). Disruption of the actin cytoskeleton and impairment in cell motility have long been thought to be the major cause of X-linked periventricular heterotopias. Classical lissencephaly (type I lissencephaly) is characterized by the loss of the folds of the brain (sulci and gyri), an abnormally thick cortex, and the loss of cortical lamination. Most (70% to 80%) of lissencephaly can be attributed to deletions in the microtubule binding lissencephaly 1 (LIS1) and doublecortin (DCX) genes. Clinically, affected individuals tend to develop severe epilepsy (early onset at 6 months of age, infantile spasms), as well as profound mental retardation, diffuse hypotonia, and, later, spastic quadriplegia. *(Lian, 614–620; Limperopoulos, 621–627)*

**19.** **(D)** Disruption of the actin cytoskeleton and impairment of cell motility have long been thought to be the major cause of X-linked periventricular heterotopia (PH) due to mutations in filamin A (FLNA). FLNA is an actin-binding phosphoprotein that can promote actin branching, tether large actin filaments, and hold them in a perpendicular arrangement. The resulting three-dimensional orthogonal network of actin filaments represents a characteristic cortical actin structure at the leading edge of migrating cells. In this respect, FLNA is believed to be essential for mammalian cell locomotion by stabilizing loose microfilament nets. Recent studies have suggested that filamin helps tether neural progenitors to the ventricular zone and that it is rapidly degraded in the neural progenitor cells and highly expressed in migratory neurons, consistent with a role for initial migration. FLNA also appears to control migrating cell shape. However, the identification of a second causative gene for PH due to autosomal recessive mutations in the ARFGEF2 gene has raised the possibility that this cortical malformation may not entirely reflect a disorder in cell motility. ARFGEF2 encodes an ADP-ribosylation factor guanine exchange factor that converts GDP to GTP and thereby activates the ADP-ribosylation factor. The ADP-ribosylation factors have been implicated in vesicle transport; thus mutations in ARFGEF2 are thought to disrupt certain transmembrane proteins or adhesion molecules and also, potentially, neuroblast migration. *(Lian, 614–620)*.

**20.** **(A)** Subcortical band heterotopia is characterized by heterotopic neurons positioned midway between the gyrencephalic cortex and underlying the subventricular zone. Females harboring mutations in the X-linked doublecortin (DCX) gene develop subcortical band heterotopia, whereas males develop classical lissencephaly. Females have two X chromosomes; because of X-inactivation, only some neurons lose doublecortin function. Presumably, those neurons with the mutant DCX protein fail to migrate into the cortex and form the underlying heterotopic band. The severity of epilepsy and developmental delay in affected individuals correlates inversely with the thickness of the subcortical band heterotopia. The DCX protein is thought to play a key role in neural progenitor motility. It may exert its effect on neuronal migration through its polymerization with microtubules. RNA interference–mediated knockdown of DCX shows abnormal positioning of cortical neurons within the intermediate zone and white matter as well as inappropriate neocortical lamina in rats. While genetic DCX mouse

mutants do not demonstrate a clear cortical phenotype, loss of DCX function disrupts the rostral migratory stream and delays neuronal migration along this pathway. DCX appears to be required for nuclear translocation and maintenance of bipolar morphology during migration of these cells. *(Lian, 614–620)*.

**21.** **(D)** Cobblestone lissencephaly (or type II lissencephaly) is characterized as a HARD(E) syndrome [hydrocephaly (H), agyria (A) and retinal dysplasia (RD), with or without encephalocele (E)]. Based on the gradient of syndrome severity, the autosomal recessive cobblestone lissencephalies can be divided into three subclasses ranging from the more mild Fukuyama congenital muscular dystrophy affecting primarily the Japanese population to the moderate Finnish muscle-eye-brain disorder and the most severe Walker–Warburg syndrome generally leading to early postnatal death. Four genes have been associated with type II lissencephaly (POMT1 and POMT2 for Walker–Warburg syndrome, POMGnT1 for Finnish muscle-eye-brain disorder, and fukutin for Fukuyama congenital muscular dystrophy); each of these is implicated in the glycosylation of [alpha]-dystroglycan. *(Lian, 614–620)*

**22.** **(C)** By age 15, over 75% of children have experienced at least one headache. The prevalence of recurrent headaches is 2.5% at 7 years and 15% at 15 years. Of headaches that are acute and recurrent, migraines and tension-type headaches (TTHs) are the first and second most prevalent. One study found a prevalence of 5.1% for TTH in children aged 14 to 18. *(Walker, 248–254)*

**23.** **(A)** Migraine without aura is the most frequent form of migraine seen in pediatrics, accounting for 60% to 85% of all migraine. Families or patients may recognize prodromal features: mood changes (euphoria to depression), irritability, lethargy, yawning, food cravings, or increased thirst. Perhaps the most frequent heralding feature is a change in behavioral patterns or withdrawal from activities. The headache phase begins gradually and the pain is usually frontal or temporal in location; it may or may not be unilateral. The quality is generally described as pounding, pulsing, and throbbing, but the key feature is its intensity. Activities will be interrupted. Photophobia and/or phonophobia are common and often prompt the adolescent to seek a quiet, dark place to rest or even to sleep, as sleep often produces significant relief. Nausea, vomiting, and abdominal pain may be the most disabling features, as a student with headache may be able to stay in the classroom with pain, but the onset of nausea or vomiting necessitates a visit to the school nurse. A migraine headache typically last hours, even days (1 to 72 hours), but does not generally occur more frequently than 6 to 8 times per month. More than 8 to 10 attacks per month must warrant consideration of alternative diagnoses. *(Lewis, 207–246)*

**24.** **(E)** Evaluation of the child with a complaint of headache must include a thorough medical history and complete physical, including a neurological examination. The clinician's first priority is to eliminate secondary (and potentially life-threatening) causes of headache, such as tumors, infection, intoxication, or hydrocephalus. The headache history itself will, in most instances, yield the necessary information to suggest a secondary cause of headache. Age below 3 years, morning or nocturnal headache, morning or nocturnal vomiting, headache increased by Valsava or straining, explosive onset, progressive worsening over time (chronic progressive pattern), declining school performance or personality changes, and altered mental status warrant the performance of ancillary diagnostic testing to exclude an organic cause. *(Lewis, 207–246)*

**25.** **(D)** Familial hemiplegic migraine (FHM) is an uncommon autosomal-dominant form of migraine with aura caused by a missense mutation in the calcium channel gene (CACNA1A) mapping to chromosome 19p13 in about 50% of the families. Mapping to chromosome 1q31 has been reported in other families with FHM. Clinically, FHM is a migraine headache heralded by an aura, which has "stroke-like" qualities producing some degree of hemiparesis. *(Lewis, 207–246)*

**26.** **(C)** The migraine variants represent a heterogeneous group of disorders characterized by headache accompanied by disturbing neurological signs, such as hemiparesis, altered consciousness, nystagmus, or ophthalmoparesis. Basilar-type migraine (BM), also known as basilar artery or vertebrobasilar migraine, is the most common of the migraine variants. It is estimated to represent 3% to 19% of all migraines. The wide range of frequency relates to the rigor of the definition. Some authors included any headache with dizziness within the spectrum of BM, whereas others require the presence of objective signs or symptoms of posterior fossa involvement before establishing this diagnosis. The onset of BM tends to occur in young children with a mean age of 7 years, although the clinical entity probably appears as early as 12 to 18 months as episodic pallor, clumsiness, and vomiting in the condition know as benign paroxysmal vertigo. Affected patients will have attacks of intense dizziness, vertigo, visual disturbances, ataxia, and diplopia. The key features of BM include vertigo, nausea and vomiting, ataxia, visual field defect, tinnitus, dysarthria, and weakness. These transient features may last for minutes or up to an hour and are then followed by the headache phase. *(Lewis, 207–246)*

**27.** **(A)** Vertigo is the most frequent manifestation of vertebrobasilar migraine (73%). Nausea and vomiting is seen in 30% to 50% of cases, ataxia in 43% to 50%, visual field defects in 43%, diplopia in 30%, tinnitus in 13%, and weakness (hemiplegia, quadriplegia, diplopia) in 20%. *(Lewis, 207–246)*

**28.** **(A)** The American Academy of Neurology (AAN) recommends a trial of ibuprofen as first-line pharmacological treatment for migraine in children. Acetaminophen should be utilized in those with allergy, intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs), or with contraindications to NSAID use. For those over 12 years of age who fail ibuprofen and/or acetaminophen, it is reasonable to move to sumatriptan nasal spray. For those under age 12, one source proposes repeating the initial nonspecific analgesic in 2 hours if symptoms do not resolve. Additionally, antiemetics can be utilized for those in whom nausea and/or vomiting represent a significant disability and/or prevents oral intake. *(Walker, 248–254)*

**29.** **(B)** Despite a similar insult mechanism, preterm and term brains respond very differently to hypoxia/ischemia. Major regional differences in the distribution of injury, network excitability, and long-term outcome have been observed in these two populations. Although these differences are not absolute, the white matter of the preterm brain exhibits a higher degree of susceptibility while the gray matter of the term brain is more reflective of injury. These relative susceptibilities underlie the prevalence of periventricular leukomalacia (PVL) in the preterm infant and that of hypoxic encephalopathy, seizures, and stroke in the term infant. *(Jensen, 628–633)*

**30.** **(A)** Confusional arousals, sleep terrors, and sleepwalking are the key NREM sleep parasomnias. They are also termed *arousal parasomnias* as they appear during partial arousals from NREM sleep. Typically, they occur at the time of transition from deep NREM (stage N3) sleep into the lighter stages of NREM sleep and appear time-locked to the first third of night sleep because N3 sleep is most abundant at this time of the night. Sleep deprivation and fever can trigger all three forms of arousal parasomnia. A genetic predisposition and acquired disturbances that trigger an increase in shifts from slow-wave sleep to lighter stages of sleep (such as sleep-disordered breathing, periodic limb movement, gastroesophageal reflux), combined with a vulnerable age (generally 2 to 12 years), seem to precipitate arousal parasomnias. Separation anxiety may be a predisposing factor for both sleep terrors and sleepwalking. Cyclic alternating patterns, which are periodic EEG events of NREM sleep characterized by repeated and spontaneous high-voltage EEG periods that recur at regular intervals of up to 2 minutes in duration, are a reliable marker of unstable sleep and as such are increased during the slow-wave sleep of children with sleep terrors.

The age of onset of sleepwalking is typically between 5 and 10 years. Mild episodes in

which a toddler sits up and crawls around the bed or the child walks quietly in sleep to come and stand by the bed of the parents may go unnoticed. Other children may become agitated and run around the house. Some patients have injured themselves by unconsciously carrying out dangerous behaviors like jumping out of a second-story window. Others may unknowingly risk injury with behaviors such as walking outdoors on a cold winter night and consequent exposure to hypothermia. Autonomic dysfunction may occur in the form of sweating and flushing of the face. Some patients exhibit a combination of sleep terrors and sleepwalking, although one manifestation or another will predominate. The main differential diagnosis of arousal parasomnias is nocturnal seizures. Nocturnal frontal lobe seizures are due to mutations in the genes CHRNA2, CHRNA4, or CHRNB2, which regulate the expression of nicotinic acetylcholine receptors. A full EEG montage should be incorporated into the polysomnogram for the investigation of any nocturnal events suspected to be seizures. *(Kotagal, 659–665)*

**31.** **(A)** Structural MRI studies of abnormalities in children with ADHD have reliably shown smaller than normal regional brain volumes. In addition to an overall reduction in total brain volume, four major findings regarding regional differences were notable. Relative to controls, individuals with ADHD showed smaller MRI-based volumes of the basal ganglia, specifically in the caudate nucleus and globus pallidus; larger posterior regions and smaller anterior brain regions; a smaller cerebellar vermis; and smaller white matter tracts. A recent meta-analysis of structural imaging findings showed reliable regional reductions in the caudate, cerebellar vermis, and corpus callosum. Longitudinal MRI-based anatomic studies of individuals with ADHD suggest that these abnormalities are present early in childhood. *(Casey, 119–124)*

**32.** **(C)** Functional MRI imaging studies of ADHD show that multiple neural systems are involved in this disorder, including the prefrontal cortex, caudate nucleus, cerebellum, and parietal cortex. Most of these studies show hypoactivation of these regions, which appears to normalize with stimulant medication. *(Casey, 119–124)*

**33.** **(A)** Apneic spells in an otherwise normal-appearing newborn are sign of brainstem immaturity and do not point to a pathological condition. The sudden onset of apnea and states of decreased consciousness, especially in premature newborns, suggests an intracranial hemorrhage with brainstem compression. Apneic spells are almost never a seizure manifestation unless they are associated with tonic deviation of the eyes, tonic stiffening of the body, or characteristic limb movement. *(Fenichel, 3)*

**34.** **(B)** West syndrome is a triad of infantile spasms, developmental retardation or regression, and hypsarrhythmia on EEG. The syndrome presents in infants aged between 6 and 18 months. Presence of a hypsarrhythmic EEG confirms the diagnosis of infantile spasms. EEG patterns may evolve over time; they initially appear in the sleep EEG record and subsequently present during the awake state. Hypsarrhythmia is seen in 75% of patients with West syndrome. It consists of diffuse giant waves (high voltage, above 400 $\mu$V) with a chaotic background of irregular, multifocal spikes and sharp waves and very little synchrony between the cerebral hemispheres. During sleep, the EEG may display bursts of synchronous polyspikes and waves. A pseudoperiodic pattern may be evident. Persistent slowing or epileptiform discharges in the hypsarrhythmic background may be present and may represent an area of focal dysfunction. Hypsarrhythmia rarely persists beyond the age of 24 months. It may evolve into slow spike-and-wave discharges. *(Fenichel, 20)*

**35.** **(D)** Neurofibromatosis type 1 (NF1) is the most common form of autosomal dominant phakomatoses. Although many cases are heritable, approximately 30% to 50% arise de novo from spontaneous mutations. The diagnosis of NF1 is made on the basis of clinical features, requiring the presence of at least two of the following major criteria: six or more café au lait spots, axillary or inguinal freckling, two or more cutaneous

neurofibromas, one plexiform neurofibroma, characteristic bony defects, optic glioma, two or more Lisch nodules of the iris, or a first-degree relative with NF1. Brain tumors occur with increased frequency and are exclusively astrocytic in NF1 patients. Nearly 15% of patients have optic gliomas; however, a rapid deterioration of visual acuity is not common. Nevertheless, these tumors require careful monitoring because they can progress to the point where they compromise vision. The brainstem and cerebellum are common sites of tumors although they can also be supratentorial. Most tumors identified on MRI are grade I astrocytomas and do not progress. Unidentified bright signals are areas of increased signal in the basal ganglia, thalamus, brainstem, and cerebellum visible on T2-weighted images. They are thought to be either hamartomas or proliferations of blood vessels with surrounding increased tissue edema. They occur more commonly in children but decrease in size and frequency with age. *(Lee, 135–141)*

**36.** **(A)** Narcolepsy is a rare disorder characterized by symptoms of excessive daytime sleepiness (EDS), which varies through the day and is associated with almost daily naps. A history of cataplexy (sudden loss of muscle tone triggered by emotion) is a specific and common symptom. Other symptoms include hypnagogic hallucinations, sleep paralysis, and disturbed nocturnal sleep. The etiology of narcolepsy is unknown; however, human and animal data suggest that it is associated with abnormalities in the hypocretin system, with loss of hypocretin neurons in the hypothalamus of humans with narcolepsy and cataplexy. Hypocretin appears to stabilize and prevent inappropriate changes in conscious state, such as the rapid switches between wakefulness and REM sleep and disordered sleep patterns characteristic of narcolepsy. *(Kothare, 666–675; Dauvilliers 499–451; Keam, 699–703)*

**37.** **(D)** In pediatric patients, stimulant medications for the treatment of narcolepsy are used with the goal of providing optimal alertness during school hours and other social situations. Most clinicians prescribe methylphenidate or amphetamines, with dosage titration based on side effects and clinical response. However modafinil, a wakefulness-promoting agent, was recently found to be effective in the treatment of children with narcolepsy. Although its mechanism of action is unclear, the drug is recommended as first-line therapy for narcolepsy in adults. It also showed efficacy in 10 of 12 children with narcolepsia. Several studies have outlined its possible effect on dopamine, adrenaline, noradrenaline, serotonin, and gamma-aminobutyric acid (GABA) systems. The elimination half-life is 13.8 hours and the maximum concentration is achieved in 2 to 4 hours. The most common adverse events are mild, including headache (13%), nervousness (8%), and nausea (5%), with no evidence of tolerance. Methylphenidate is a widely used, potent stimulant. It primarily blocks the reuptake of monoamines (mainly dopamine) and, unlike amphetamines, does not inhibit the vesicular monoamine transporter. Clinical experience shows that methylphenidate improves daytime sleepiness in narcolepsy patients at daily doses of 10 to 100 mg. The duration of action is 4 hours and the elimination half-life is 6 hours. The short-acting effect of methylphenidate is useful in cases where modafinil must be supplemented at a specific time of the day or in situations where maximum alertness is required. Amphetamines have been used to treat narcolepsy since 1935. They promote monoamine (catecholamine but also serotonin) release through multiple mechanisms. At low doses, amphetamines produce a reverse efflux of dopamine (and other monamines) through monoaminergic reuptake sites. At higher doses, they also inhibit vesicular monoamine transporters and monoamine oxidase. Cytotoxicity for dopaminergic neurons can occur at high doses in animals. Amphetamines are very effective against sleepiness in narcolepsy but also induce frequent adverse effects, including irritability, aggressiveness, insomnia, hypertension, and abnormal movements. *(Kothare, 666–675; Dauvilliers 499–451; Keam, 699–703)*

**38.** **(C)** Sodium oxybate is a GABA B receptor agonist currently approved by the U.S. Food and Drug Administration (FDA) for the treatment

of narcolepsy with cataplexy in patients above 16 years of age. According to the American Academy of Sleep Medicine (AASM) practice parameters, sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy and may be effective for treatment of hypnagogic hallucinations and sleep paralysis. Although the administration of sodium oxybate is associated with a modulation of serotoninergic, dopaminergic, and opioid activity, along with an increase in slow-wave sleep, its pharmacologic action on cataplexy remains unknown. When used for the treatment of narcolepsy, one-half of a therapeutic dose of sodium oxybate is administered at bedtime and repeated 2.5–4.0 h later, providing effective plasma concentrations throughout the night while ensuring that the majority of the drug has been eliminated when the patient awakens in the morning. *(Kothare, 666–675; Dauvilliers, 499–451; Keam, 699–703)*

**39.** **(E)** Absence epilepsy represents about 10% to 15% (range 1.4% to 13.0%) of childhood epilepsy cases. Large epidemiological studies in Europe and the United States have shown an incidence of about 6 to 8 per 100,000 in children aged 0 to 15 years, with a prevalence of 5 to 50 per 100,000 in the general population. Peak age of onset is 6 to 7 years with a typical range of 2 to 13 years. Less than 3% are younger than 2 years of age at onset. Girls are more often affected by a 3:2 to 2:1 ratio. Family history of epilepsy is present in about 15% to 45% of cases. The etiology for childhood absence epilepsy (CAE) is genetic, with complex, multifactorial inheritance. To date, linkage in some families has been correlated with defects in both the $GABA_A$ receptor [gamma]2 subunit and the voltage-gated $Ca^{2+}$ channel [alpha]1A subunit (CACNA1A). Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is characterized by clusters of nocturnal motor seizures, which are often stereotyped and brief (5 seconds to 5 minutes in duration). They vary from simple arousals from sleep to dramatic, often bizarre hyperkinetic events with tonic or dystonic features. Affected individuals may experience aura. Retained awareness during seizures is common. A minority of individuals experience daytime seizures. Onset ranges from infancy to adulthood. About 80% of individuals develop ADNFLE in the first two decades of life, with a mean age of 10 years. Neurological examination is normal and intellect is usually preserved. Within a family, the manifestations of the disorder may vary considerably. ADNFLE is lifelong but not progressive. As an individual reaches middle age, attacks may become milder and less frequent. Molecular genetic testing reveals mutations in CHRNA4 or CHRNB2 encoding, respectively, the α4 and β2 subunits of the neuronal nicotinic acetylcholine receptor in some 20% to 30% of individuals with a positive family history and less than 5% of individuals with a negative family history. Juvenile absence epilepsy (JAE) is believed to represent a smaller fraction of absence epilepsies and makes up about 0.2% to 3.0% of childhood epilepsy, with a prevalence of 0.1 per 100,000 persons in the general population. The etiology for JAE is genetic; allelic association with a glutamate receptor gene (GRK1) polymorphism has been demonstrated in some families. Benign neonatal familial convulsions (BNFCs) have Mendelian transmission and are considered an autosomal dominant–transmitted epilepsy within complete penetrance. Significant clinical and genetic heterogeneity exists. BNFC belongs to the group of genetic disorders caused by a channelopathy. The defect is in the voltage-dependent potassium channel (KCNQ1, KCNQ2, and KCNQ3). The loci corresponding to these areas have been identified on both chromosomes 20q13 and 8q24. The KCNQ gene regulates neuronal excitability by controlling the duration of the action potential and reducing the M-current by 20% to 25%, thereby creating hyperexcitability. Benign childhood epilepsy with centrotemporal spikes (BECTS) is the most common partial epilepsy of childhood and accounts for 16% of epilepsies beginning before age 15 and 24% of epilepsies between ages 5 and 14. At least two thirds of all idiopathic partial epilepsies are classified as BECTS. The prevalence is 1 to 2 per 1,000. Onset of seizures typically occurs between ages 3 and 16 years, with a peak frequency around 5 to 8 years. Rare cases of BECTS may present as early as 1 year of age. There is a slight male predominance, and 60% of

children with this syndrome are boys. The genetic basis for BECTS is complicated. Centrotemporal spikes are present in EEG in 11.0% of the siblings of the probands but in only 1.6% of the general population. The centrotemporal spikes in the EEG pattern have an autosomal dominant inheritance with incomplete penetrance and age dependency but does not necessarily lead to BECTS. A recent multicenter linkage study using monozygotic twins failed to show any concordant data. The low absolute prevalence of BECTS in siblings (2.3%) and family members makes it difficult to determine whether the etiology is purely genetic. The most current opinion on the genetic cause of BECTS therefore is that major nonfamilial environmental factors determine the development of the disease. *(Bergqvist, 106–120)*

**40.** **(A)** The etiology of juvenile myoclonic epilepsy (JME) is genetic, but inheritance is complex, with significant heterogeneity. Multiple genes have been linked to JME. A defect in the $GABA_A$-gated chloride channel was associated with one family with JME (GABARA1). The $GABA_A$-gated chloride channel mediates fast inhibition; a defect could reduce GABA current and thereby increase neuronal hyperexcitability. A defect in the calcium channel CACNB4 is linked to the T-type calcium current and the synchronized activity of the thalamus. Finally, defects in non–ion channel ligands such as EFHC1 and BRD2 have been associated with some families with JME. The functions of these genes are not clear at this time. *(Bergqvist, 106–120)*

**41.** **(B)** Autism is also observed in many single-gene disorders. Duplication of 15q is probably the most important known cause of idiopathic autism in the maternally derived duplication of a region on proximal 15q, which overlaps with the region involved in Prader–Willi and Angelman syndromes. These duplications occur at a rate of 1% to 3%. The patients with 15q duplication syndrome almost always meet the diagnostic criteria for autistic disorder; as a group, however, they show more significant cognitive impairment coupled with gross motor delays, hypotonia, epilepsy, and mild facial dysmorphisms. Fragile-X syndrome (FRAX) is probably the best-known association with autism and is the leading cause of inherited mental retardation. Current estimates are that FRAX accounts for 1% to 2% of all cases of autism spectrum disorder (ASD), similar to the rate of duplication (15q). Recently, associations between autism and the premutation "carrier" status of FRAX and FRAX mosaics with partial methylation have been reported as well. Tuberous sclerosis complex (TSC) also is not a major cause of autism, occurring in only 1% to 4% of large unselected autism samples, although the frequency is higher (8% to 14%) in autism patients with epilepsy. The genes for TSC are located on chromosomes 9q34 (TSC1) and 16p13 (TSC2). Rett syndrome is a rare disorder (1 in 10,000 to 15,000) now known to be a single-gene disorder caused by mutations in the MECP2 gene on the X chromosome. The frequency of MECP2 mutations or duplications in ASD has been variable but may be as high as 1% to 2% in populations at academic centers. Joubert syndrome and related cerebellar disorders (JSRD) are autosomal recessive disorders characterized by congenital ataxia, diffuse hypotonia, developmental delay, abnormal respiratory patterns, and oculomotor apraxia. The pathognomonic neuroradiological finding in JSRD is the presence of the molar tooth sign (MTS) on brain imaging, which is the result of cerebellar vermis hypoplasia (CVH), thick and maloriented superior cerebellar peduncles, and an abnormally deep interpeduncular fossa. The genetic basis of JSRD has been partially elucidated with the identification of three causative genes and two other unique loci where the genes have not yet been found. The JBTS1 locus (OMIM %213300), located on 9q34.3, is associated with Joubert syndrome (JS, herein referring to the pure form of the disease with restricted involvement of retinal, renal, or other system). The JBTS2 locus (OMIM %608091), located on 11cent, is associated with extreme phenotypic variability, including frequent retinal dystrophy and renal involvement. The JBTS3 locus (OMIM #608629), on 6q23.3 and due to mutations in the AHI1 gene, is associated with JS and variably associated with cortical polymicrogyria. However, there are rare patients with renal cystic disease with AHI1

(JBTS3) mutations. Mutations were observed in about 8% to 11% of patients with JSRD. The JBTS4 locus (OMIM #609583), on 2q13 and due to mutations in NPHP1, was first implicated in juvenile nephronophthisis. Mutations were subsequently identified in 2% to 3% of patients with JSRD, exclusively in those with renal involvement. The JBTS5 locus (OMIM #610188), on 12q21.3 and due to mutations in the CEP290 gene, is associated with pleiotropic forms of the disease including severe retinal and renal involvement. *(Geschwind, 49–64; Zaki, 556–565)*

**42.** **(B)** Malignant migrating partial seizure in infancy (MMPSI) is an epileptic encephalopathy characterized by onset in the first 6 months of life, of rapidly progressive partial seizures that become subcontinuous. Their onset migrates from one area of the cortex to the other and major deterioration of the psychomotor abilities appears. Early seizures have motor and autonomic components, later seizures are more polymorphic, varying from one seizure to the next in a given patient. Seizures last several minutes longer than usual partial seizures in infancy. They tend to be more frequently generalized as time goes by. Myoclonus is rare and spasms are exceptional. By the end of the first year of life, seizures become almost continuous and occur in clusters: seizures lasting several weeks, during which the infant deteriorates considerably, and followed by disappearance of seizures during a few weeks with slow improvement of the condition. Microcephaly progressively occurs. To date, no cause has been identified by historical, biochemical, radiological, or histological investigations. No familial case or consanguinity has been reported. A genetic study failed to find mutations in sodium (SCN1A, SCN2A), potassium (KCNQ2, KCNQ3), and chloride (CLCN2) ion channels in three children with migrating partial seizures in infancy. *(Nabbout, 161–166)*

**43.** **(D)** The clinical picture of the patient described in this vignette is suggestive of Dravet syndrome. It is characterized by the occurrence, in an otherwise normal infant, of generalized or unilateral clonic or tonic–clonic seizures, mostly with fever, in the first year of life. Later, other seizure types occur, including myoclonus, atypical absences, and partial seizures. Developmental delay progressively appears from the second year. Seizures remain fever-sensitive and tend to evolve to status epilepticus. This sensitivity to fever seizures led to the identification of mutations in SCN1A, which account for 75% of Dravet syndrome cases. Seizures in Dravet syndrome are highly pharmacoresistant. The combination of clusters of spasms, psychomotor deterioration, and hypsarrhythmia defines West syndrome, which occurs mainly between 3 and 12 months of age. Cryptogenic cases account for 9% to 15% of the cases, the rest being symptomatic. The symptomatic cases are associated with several prenatal, perinatal, and postnatal factors. Various brain dysgeneses (lissencephaly, hemimegalencephaly, focal cortical dysplasia, septal dysplasia, or callosal agenesis), chromosomal (including Down's syndrome, del1p36) or single gene (mutations of ARX or STK9 gene) causes are reported. Cryptogenic late-onset epileptic spasms is a cryptogenic, late-onset epileptic spasms beginning between 12 and 48 months of age; they have a particular pattern that is intermediate between West and Lennox–Gastaut syndromes. EEG does not show classical hypsarrhythmia but a temporal or temporofrontal slow-wave or spike focus combined with slow spike waves. Ictal events combine spasms in clusters, tonic seizures, and atypical absences. Ictal EEG discloses a generalized high-voltage slow wave followed by diffuse voltage attenuation with superimposed fast activity, typical of the epileptic spasms, occurring in clusters.

Childhood epileptic encephalopathy (Lennox–Gastaut syndrome [LGS]) constitutes 1% to 4% of childhood epilepsies. The mean age of epilepsy onset is 26 to 28 months. The syndrome is characterized by multiple types of seizures, mental retardation or regression, and abnormal EEG with generalized slow spike-and-wave discharges (1.5 to 2 Hz). The most common seizure types are tonic–axial, atonic, and absence seizures, but myoclonic, generalized tonic–clonic, and partial seizures

can be observed. Seizures often are resistant to therapy. *(Nabbout, 161–166)*

**44. (B)** Epileptic encephalopathy with suppression bursts is a severe condition that begins within the first 3 months of life. EEG demonstrates bursts of paroxysmal activity (polyspikes) lasting several seconds and alternating with episodes of flat or low amplitude tracing, a combination called suppression bursts. This pattern is present in both awake and sleep states or mainly during sleep. It is associated with partial seizures variably combined with myoclonus or spasms. The classification of the International League Against Epilepsy recognizes two conditions with suppression bursts: early infantile epileptic encephalopathy (EIEE) or Ohtahara syndrome and neonatal myoclonic encephalopathy (EME). In EIEE, there are spasms and the suppression burst pattern is often asymmetric, mainly affecting the side of a cortical malformation, usually hemimegalencephaly or focal cortical dysplasia. Aicardi syndrome, olivary–dentate dysplasia, and schizencephaly are other conditions in which such tracings are encountered. In EME, there is no radiological evidence of a brain lesion, the patients exhibit erratic and massive myoclonus, and there is familial recurrence. Nonketotic hyperglycinemia, Menkes disease, pyridoxine and pyridoxal phosphate dependencies, and glutamate transporter defect may be involved and share excess of glutamate transmission. Seizures onset in benign infantile focal epilepsy with midline spikes and waves during sleep in infants between 4 and 30 months of age. Seizure manifestations are typical, characterized by cyanosis, staring, and rare lateralizing signs of short duration. There is a strong EEG marker, a spike followed by a bell-shaped slow wave, localized in the midline regions that is present in all subjects only during sleep. *(Nabbout, 161–166)*

**45. (A)** Subdural hemorrhage is the consequence of a tear in the tentorium near its junction with the falx. Excessive vertical molding of the head in vertex presentation or anteroposterior elongation of the head in face and brow presentation may be the cause of the tear. The accumulation of blood in the posterior fossa may produce a delayed compression of the brainstem. *(Fenichel, 4–14; Rivkin, Anderson, and Kaye, 51–56)*

**46. (B)** Subarachnoid hemorrhage results from tearing of the superficial veins by shearing forces during a prolonged delivery with the head engaged. Seizures occurring in a normal newborn in the first or second day of life may be the only clinical manifestation. *(Fenichel, 4–14; Rivkin, Anderson, and Kaye, 51–56)*

**47. (C)** Cerebral venous thrombosis may complicate sepsis, asphyxia, and coagulopathy. Superior sagittal thrombosis may occur without known predisposing factors. Head MRI is the best examination to assess the involved vessels. *(Fenichel, 4–14; Rivkin, Anderson, and Kaye, 51–56)*

**48. (D)** The decarboxylation of leucine, isoleucine, and valine is accomplished by a complex enzyme system, branched-chain alpha-ketoacid dehydrogenase. Deficiency of this enzyme causes maple syrup urine disease. Affected newborns are normal at birth but develop poor feeding and vomiting during the first week of life, in addition to hypotonia. Convulsion and hypoglycemia are frequent complications. The correction of hypoglycemia does not improve the clinical condition. The diagnosis is suspected by the odor of maple syrup found in the urine, sweat, and cerumen. It is confirmed by finding increased plasma concentration of the three branched-chain amino acids or enzyme deficiency in peripheral leukocytes. The urine contains a high level of branched-chain amino acids and their keto acids. These keto acids may be detected by adding 2,4 dinitrophenylhydrazine to the urine; if the result is the formation of yellow precipitate, maple syrup urine disease is the most likely diagnosis. Lowering of the branched-chain amino acids may be attempted by exchange transfusions, peritoneal dialysis, and special diet. Isovaleric acidemia is a rare autosomal recessive condition related to a deficiency of isovaleryl CoA dehydrogenase. Clinical manifestations include lethargy, vomiting, convulsions, and severe acidosis in the first few days of life. The characteristic odor of

sweaty feet may be present. The diagnosis is established by demonstrating marked elevation of isovaleric acid or its metabolites in urine.

Glycine encephalopathy is an autosomal recessive disorder caused by a defect of the glycine cleaving system. Affected newborns are normal at birth but become irritable with hiccuping usually within 48 hours to several weeks. Myoclonic seizures, hypotonia, and lethargy may follow. The diagnosis is made after seeing hyperglycinemia and a high glycine concentration in the CSF.

Carbamoyl phosphate synthetase deficiency may cause progressive lethargy, vomiting, and hypotonia in the first day of life. The diagnosis is made by demonstrating serum hyperammonemia without organic acidemia.

Bilirubin encephalopathy results from the neurotoxic effect of a high unconjugated free bilirubin level. It may cause hypotonia, lethargy, and seizures. The branched-chain amino acid level in the serum is normal but the bilirubin level is high. *(Behrman, 410–412; Fenichel, 4–6)*

**49. (D)** DiGeorge syndrome is a congenital hypoplasia of organs derived from the third and fourth pharyngeal pouches. It results in hypoplasia or agenesis of the thymus and parathyroid glands, the auricle, and the external auditory canal; congenital cardiac anomalies; cleft palate; and short stature. It is associated with microdeletion of chromosome 22q11. The main features are hypocalcemia, seizures, congenital heart disease, lymphocytopenia, and multiple minor anomalies. Affected newborns may die from cardiac causes during the first month. Frequent infections due to a defect of cell-mediated immunity and failure to thrive may complicate the course of the surviving newborn. *(Behrman, 694; Fenichel, 9)*

**50. (C)** The patient described in this case developed symptoms of tonic seizures and atypical absence seizures. The EEG pattern is compatible with absence or atonic seizures. The association of these symptoms to the EEG findings makes Lennox–Gastaut syndrome (which is characterized by the triad of seizure, slow spike-wave complexes on EEG, and mental retardation) the most likely diagnosis. Mental retardation will appear later, since more than 90% of patients will be mentally retarded by the age of 5 years. Sixty percent of patients with Lennox–Gastaut syndrome may have an identified underlying cause and 20% have a history of infantile spasms. EEG during a tonic seizure may show a one-spike wave per second followed by generalized rapid discharges without postictal depression. Seizures are difficult to control. Valproate and clonazepam are the drugs of choice. Felbamate, lamotrigene, and topiramate have shown promise as add-on drugs in refractory cases. *(Fenichel, 22–23)*

**51. (C)** Infantile spasms are age-dependent myoclonic seizures that are always seen before the age of 1 year, with a peak age of onset between 4 and 7 months. An underlying cause is found in 75% of cases. Perinatal asphyxia, congenital malformations, and tuberous sclerosis are common causes. The association of infantile spasms, agenesis of the corpus callosum or other midline cerebral malformations, and retinal malformation is called Aicardi syndrome. Pertussis immunization is not a cause of infantile spasms. Spasms can be extensor or flexor movements and generally occur in clusters after the infant awakens from sleep. During the early stages of infantile spasm, the EEG may show hypsarrhythmia and a chaotic and continuously abnormal background of very high voltage and slow waves and spikes. Within few weeks, greater interhemispheric synchrony replaces the original chaotic pattern of hypsarrhytmia. ACTH or corticosteroids may be effective in the control of infantile spasms. *(Fenichel, 19–20)*

**52. (D)** The symptoms of this patient are consistent with the diagnosis of narcolepsy and cataplexy: a sleep disorder characterized by abnormal latency from sleep onset to REM sleep. REM sleep is attained in less than 20 minutes. Hypotonia and dreaming occur normally during REM sleep. In narcolepsy and cataplexy, these phenomena occur during wakefulness. This may induce hypnagogic hallucinations: vivid, frightening visual and

auditory perceptions occurring at the transition between wakefulness and sleep. The sudden loss of tone in cataplexy may be induced by excitement; the paralysis most commonly affects the face or hands more than the total body. Sleep paralysis, a generalized hypotonia occurring in the transition between sleep and wakefulness, complicates two thirds of cases of narcolepsy and cataplexy and is generally experienced once or twice each week. The diagnosis of narcolepsy and cataplexy is made by a multiple sleep latency test showing a REM onset sleep latency of less than 4 to 5 minutes. Pharmacological treatment of narcolepsy has depended on the use of central nervous system stimulants to increase wakefulness, vigilance, and performance. The medications considered effective in the treatment of narcolepsy include dextroamphetamine, pemoline, methylphenidate, and methamphetamine. These stimulants are associated with sympathomimetic side effects, limitations in efficacy, and negative effects on nighttime sleep. Modafinil, a new wakefulness-promoting agent, has been shown to be effective and is well tolerated. *(U.S. Modafinil in Narcolepsy Multicenter Study Group, 43–48)*

**53.** **(A)** Lafora disease is a progressive myoclonic epilepsy probably transmitted by autosomal recessive inheritance. The age of onset is between 11 and 18 years. Mental retardation appears early in the course of the disease, whereas ataxia, spasticity, and involuntary movements occur late. In later stages of the disease, EEG may show nonspecific generalized polyspike discharges that are not activated by sleep. Seizures are generally refractory to most anticonvulsant drugs as the disease progresses. Inclusion bodies, an aggregate of filaments composed of polyglucosans, are seen on liver biopsy. In rare cases, they may be absent even in late stages of the disease. *(Fenichel, 28–29)*

**54.** **(D)** This case describes a previously normal child with progressive loss of language skills associated with a seizure disorder. The most likely diagnosis is Landau–Kleffner syndrome. This is a condition of unknown cause, more common in boys, with a mean onset at 5.5 years. At least 70% of these patients have an associated seizure disorder. The aphasia may be primarily receptive or expressive, and auditory agnosia may be so severe that the child is unaware of everyday sounds. Hearing is normal, but behavioral problems, including irritability and poor attention span, are particularly common. Formal testing often shows normal performance and visuospatial skills despite poor language. The seizures are of several types, including focal or generalized tonic–clonic, atypical absence, partial complex, and occasional myoclonic. High-amplitude spike-and-wave discharges predominate and tend to be bitemporal but can be multifocal or generalized. In the very early stages of the condition, the EEG findings may be normal. The spike discharges are always more apparent during non-REM sleep; thus a child suspected to have Landau–Kleffner syndrome should have an EEG during sleep, particularly if the awake record is normal. CT and MRI studies typically yield normal results. Microscopic examination of surgical specimens has shown minimal gliosis but no evidence of encephalitis. Progressive myoclonic epilepsy is unlikely to be the diagnosis because of the speech involvement in this patient and the absence of myoclonus, cerebellar ataxia, or involuntary movements. Temporal lobe tumor is a rare diagnostic possibility that may cause seizures with speech disturbance. The normal head MRI rules out that diagnosis. In the Rasmussen syndrome, the affected children have progressive motor seizures that are resistant to anticonvulsive treatment. Progressive hemiplegia may develop in the body side of seizures and may persist after seizures have stopped. *(Behrman, 1998–1999; Fenichel, 30)*

**55.** **(B)** The most likely diagnosis in this case is Guillain–Barré syndrome (GBS), which is the most common cause of acquired paralysis in an otherwise well child. A nonspecific viral or bacterial infection may occur prior to the onset of paralysis, but in 25% of cases there is no antecedent of infection or vaccination. Typically, the onset of weakness is insidious, following an ascending progression from lower extremities to upper extremities, and may involve the trunk or the cranial nerves. Pain in the extremities is reported in 80% of cases. The patient in

this case developed symmetric weakness in all extremities that caused an ataxic gait, decreased deep tendon reflexes, and no sensory level: these are key findings for the diagnosis of GBS. The facial paresis reported in this patient reflects the involvement of the facial nerve, which is the most frequent cranial nerve affected by this disease. Respiratory failure, unstable blood pressure, and arrhythmia are less common but grave complications of GBS. Activation of T cells, cytokine synthesis, demyelination of the peripheral nervous system by antibodies, and axonal damage by antiglycolipid antibodies are key features of the pathogenesis of Guillain–Barré syndrome.

Tick-bite paralysis results from a neuromuscular blockage by a tick-produced neurotoxin. It can cause paralysis that may mimic GBS, but it is unlikely to be considered a first diagnosis in a child living in Philadelphia in January.

Edrophonium, a cholinesterase inhibitor, is used for the diagnosis of myasthenia gravis. The type of weakness described in this patient is unlikely to be seen in myasthenia gravis, in which ptosis, extraocular muscle paresis, dysphagia, and fluctuant weakness are prominent features. In myasthenia, the EMG may show a decremental response on repetitive stimulation. Impairment of pupillary response, paresis of the extraocular muscles, dysphagia, hypotonia, descending paralysis, and constipation are classic findings in botulism. The diagnosis is made by an EMG showing an incremental response to repetitive stimulation and by isolation in the stool of *Clostridium botulinum* or its toxin. *(Bradshaw and Jones, 500–506; Ropper, 1130–1136)*

**56.** **(A)** Sydenham chorea (chorea minor, St. Vitus dance, rheumatic encephalitis), described by Thomas Sydenham in 1686, is considered the most common cause of chorea in a school-age child. Clinically, it is characterized by involuntary movements, hypotonia, dysarthria, emotional disorders, and less frequently by other neurological manifestations, such as weakness and headache. The motor disorders may be generalized or unilateral, in which circumstance they constitute a hemichorea. Chorea may present with other rheumatic fever manifestations during an acute episode, or it may present in isolated form in the so-called pure chorea. Its etiology and pathophysiological mechanisms are still unclear, although its relation with a previous group A beta-hemolytic streptococcus infection is well established. There is also evidence of the participation of immunological mechanisms in its pathogenesis, such as the finding of serum anticaudate and subthalamic nuclear antibodies and an increase in IgG levels in the CSF of patients with chorea. *(Goldenberg et al., 152–157; Nausieda et al., 331–334)*

**57.** **(C)** Prophylactic treatment of epilepsy is indicated if there is major motor seizure, if two or more seizures occur in close temporal proximity, or if the seizures are associated with falls. The age and situation of the patient may influence the decision to prescribe antiseizure medications. Most authors agree to discontinue anticonvulsant medication if the patient is free of major motor seizures or absence seizures for 1 or 2 years with normal EEG and brain MRI studies. In Janz syndrome, a variant of myoclonic epilepsy, antiseizure medications should not be stopped even after a remission as long as 3 years, because seizures often recur. Seizure medications should be a lifelong treatment if the seizures are caused by permanent damage of the brain, as in many cases of cerebral palsy or operated arteriovenous malformations. *(Callaghan, Garrett, and Goggin, 942–946; Shinnar et al., 534–565)*

**58.** **(E)** The patient described in this case has the classic signs of Erb palsy, a paralysis of the muscles innervated by the C5-C6 roots. It occurs in approximately 0.6% of all vaginal deliveries; shoulder dystocia is typically diagnosed when there is impaction of the anterior fetal shoulder behind the symphysis pubis. The spinal roots have approximately one-tenth the tensile strength of the peripheral nerves because of lesser amounts of collagen and the absence of epineurial and perineurial sheaths in the roots. Therefore, the nerve roots are the weak link in the nerve root–spinal, nerve–plexus complex, and nerve root. Avulsion from the spinal cord may result from the severe traction injury

caused by a shoulder dystocia. Brachial plexus injury complicates approximately 8% to 23% of shoulder dystocia cases. Nearly 80% of brachial plexus injuries involve the nerve roots of C5 to C6. Clinical findings in Erb palsy may include C5 root avulsion signs, which result in virtually complete paralysis of the rhomboids and spinatus muscles and a varying degree of weakness of the deltoid, biceps, brachioradialis, and serratus anterior, which receive additional innervation from C6. More than 90% of these injuries will resolve by 1 year of life, with only a 5% to 8% rate of persistent nerve injury. Dejerine–Klumpke palsy occurs less frequently than Erb palsy and involves the lower trunk of the brachial plexus, C8, and T1 roots. It accounts for only 2.5% of brachial plexus injuries. Clinical findings include weakness in the flexor of the wrist and fingers, absent grasp reflex, and possible unilateral Horner syndrome. C3 to C4 and T2 to T4 nerve root lesions will not affect the muscles of the upper extremity. *(Pollack et al., 236–246)*

**59. (C)** The patient described in this case developed repetitive sniffing and grunting over a period of time, most likely related to verbal tics. Tics are defined as sudden, rapid, recurrent, and nonrhythmic stereotyped movements or vocalizations. Motor tics are characterized as simple (such as eye blinking, facial grimacing, and head turning) or complex (such as jumping, thumping, echopraxia, and copropraxia). Simple vocalizations can consist of grunts, coughing, and throat clearing, while examples of complex vocalizations include echolalia, word repetitions, and coprolalia. Tics are unusual examples of movement disorders in that the abnormal movements are often preceded by a feeling of inner tension and a compulsion to move, or in some cases by unpleasant focal sensory symptoms, sometimes termed sensory tics. The subsequent performance of the tic temporarily relieves the sensory symptoms. Some individuals claim that their tics are voluntary, in response to dysphoric sensory symptoms. Tics can usually be suppressed but only at the expense of increasing internal tension, which often causes a rebound exacerbation of the tic. The type, severity, location, and frequency of tics often vary as the years pass. While tics are common in childhood, they are usually a transient phenomenon; if persistent, they tend to improve during adolescence. Tourette syndrome is the most severe form of the spectrum of tic disorders and is defined by the presence of both motor and vocal tics for a duration of a year or more, with onset before the age of 18 years. The vast majority of cases are idiopathic. There is a close relationship between tics and obsessive–compulsive disorder. The reported prevalence of obsessive–compulsive disorder in Tourette syndrome patients is approximately 50%, and there is also an increased prevalence of obsessive–compulsive disorder in relatives of tic patients. *(Weeks, Tujanski, and Brooks, 401–408)*

**60. (A)** Grade I cerebral bruit is usually a physiological murmur heard in hyperdynamic states such as anemia or fever. Cerebral bruit may indicate an arteriovenous malformation of the vein of Galen or increased intracranial pressure by a subdural effusion or other causes. Of the five choices mentioned in this question, cerebral bruit is the least reliable sign of increased intracerebral pressure. Setting-sun sign is a downward deviation of the eyes. It is thought to be caused by compression of the upward gaze center in the upper part of the brainstem by the dilated third ventricle. Setting-sun sign, strabismus, bulging of fontanelle, and splitting of the sutures are signs of increased intracranial pressure in a 4-month-old patient. *(Fenichel, 91–94)*

**61. (C)** Tourette syndrome arises during childhood or early adolescence, usually between the ages of 2 and 15 years, with a mean age of 7 years. It occurs in boys four times as often as in girls. The most common initial symptoms are motor tics involving the cranial region, especially around the eyes. Subsequently, patients develop a constellation of motor and vocal tics of either a simple or complex nature. Tics occur many times a day, usually daily for at least a year, and there is never a tic-free period of more than 3 consecutive months. Tics are increased during time of stress and disappear during sleep. Patients may suppress their tics for a period of time, which leads to increased dysphoric sensation. Two points about the course of Tourette syndrome

are notable. One is the changing display of tics, and the other is the tendency toward periodic remissions and exacerbations. A high frequency of various behavioral abnormalities attends Tourette syndrome, and these are often the most disabling aspects of the clinical picture. Given the usual age of onset, they may translate into poor school performance caused by disruptive activity and attentional difficulty; such patients may be relegated to special education. *(Behrman, 81; Fenichel, 294–296)*

**62. (D)** The patient described in this case has the features of fascioscapulohumeral syndrome. This is an autosomal dominant myopathy that affects mainly the muscles of the face, shoulder girdle, and upper arms. The gene, localized in chromosome 4q35, has a complete penetrance but variable expression. The patient may give a history of inability to whistle or difficulty using straws or inability to fully close his eyes during sleep. As the extraocular muscles are intact, Bell's phenomenon remains and consequently the cornea is protected. The diagnosis is made by the association of insidious muscle weakness involving the shoulder girdle and the face, normal or mildly increased creatine kinase level, and myopathic pattern on EMG. Histological examination may show inflammatory signs in addition to the degenerative changes. Retinal telangiectasia, exudation, and detachment are the most severe retinal vascular abnormalities that may be seen by angiography in most patients with fascioscapulohumeral syndrome. *(Fenichel, 336–337; Patterson and Gomez, 73–82)*

**63. (B)** The patient described in the vignette presented with a febrile seizure. Typically, it is a generalized type of seizure, occurring between the age of 6 months and 3 years, at a temperature greater than 38°C. The risk factors that may increase the recurrence of febrile seizures or the development later in life of epilepsy include long duration of seizure (more than 15 minutes), a known developmental disorder, a positive family history of febrile seizure or epilepsy, focal seizures, repeated febrile seizures within a single illness, and occurrence of febrile seizures outside the usual age range (6 months to 3 years). The patient in the vignette has three risk factors that increase his risk of developing epilepsy in later life from approximately 4% to 10% or 15%. *(Annegers et al., 493–498)*

**64. (B)** The patient described in the vignette developed choreoathetotic movements associated with episodes of ballismus and akathisia. The most common cause of new-onset chorea in that age is Sydenham chorea. It occurs most frequently in females between the age of 5 and 15 years. Cardiac disease may not be evident at the time of chorea. Careful cardiac examination with echocardiogram and ECG is recommended to assess the extent of cardiac involvement. The differential diagnosis of Sydenham chorea may include ADHD because restlessness may be confused with mild chorea. The careful history given by the parents, the cardiac findings, and the relatively short-term progression of the disease (a few days to weeks compared with the months-to-years chronic progression of ADHD) suggest Sydenham chorea. Tourette syndrome is a combination of motor and verbal tics. These latter findings are not seen in Sydenham chorea. Wilson disease may present with chorea. The association of Kayser–Fleischer rings, low ceruloplasmin level, and liver function abnormalities suggest the diagnosis of hepatolenticular degeneration. Vascular accident is rare in this age. It could be considered in the differential diagnosis in the case of unilateral chorea. An MRI of the brain is helpful to rule out a stroke. *(Fenichel, 285–286)*

**65. (E)** Prompt recovery after spells is most suggestive of absence seizures rather than partial complex seizure. Urinary incontinence is rare in absence seizure and is occasionally present in complex partial seizure. The spells last 5 to 10 seconds in absence seizure and up to a few minutes in complex partial seizure. Automatism may complicate absence seizure when prolonged and is more frequently present in complex partial seizures. An EEG reveals generalized three-per-second spike-wave discharges in absence seizures, whereas in complex partial seizure it shows (in 60% of cases) variably located focal spikes. *(Fenichel, 26–28; Panayiotopoulos, 351–355)*

**66. (B)** Athetosis, a distal slow writhing movement of the extremities, is usually a manifestation of damage to the basal ganglia. Bilirubin encephalopathy selectively involves the globus pallidus and subthalamic nuclei and characteristically produces athetotic cerebral palsy. Perinatal asphyxia has become the most frequent cause of athetotic cerebral palsy because kernicterus has become less common with better prevention and management of hyperbilirubinemia in the newborn period. *(Fenichel, 8–11)*

**67. (B)** The diagnosis of cerebral palsy is difficult to establish before the age of 6 months because abnormalities in tone, reflexes, or involuntary movements rarely manifest during the newborn period. The primary reason for this is that most of the movements observed in newborns are of reflex origin and not under voluntary control. The maturation of the cortex allows the clinical picture of cerebral palsy to emerge clearly. Also, tone and reflex abnormalities occurring after a perinatal insult to the brain may falsely suggest permanent damage to the central nervous system, since they may improve after 2 to 12 months. The presence of progressive neurological deficit excludes the diagnosis of cerebral palsy because the latter condition is defined as an abnormal control of movement and posture that begins early in life and is not the result of an underlying progressive condition. Clues to a progressive disorder may include mental or motor regression, neurocutaneous signs, and skeletal anomalies. A low Apgar score at 5 minutes does not correlate with high risk of developing cerebral palsy or any other neurological disease. *(Fenichel, 269–270; Taft, 411–418)*

**68. (B)** Myelomeningocele is a congenital defect of spinal cord closure. It is most commonly located in the lumbar region and may contain spinal cord or nerve roots involved in the innervation of the urinary bladder. To avoid urologic problems and ensure timely and appropriate intervention, the genitourinary system must be evaluated in all infants who have this malformation. Myelomeningocele may be accompanied by cerebellar tonsillar herniation as part of a Chiari II malformation or aqueductal stenosis, which occurs in approximately 80% of cases and leads to a noncommunicating hydrocephalus that may need a shunt within the first 2 weeks of life. Orthopedic or physical therapy referral may be appropriate with complications such as talipes equinovarus. *(Behrman, 1984–1985)*

**69. (C)** The patient described in this vignette has a long, thin face because of wasting of the temporal and masseter muscles; there is also hand intrinsic muscles wasting with muscle relaxation difficulties. These findings are compatible with the diagnosis of myotonic dystrophy. It is an autosomal dominant multisystem disorder with variable penetrance. The disease is caused by amplification of an unstable DNA region in chromosome 19. In addition to the striated muscle, which is primarily involved in this disease, smooth muscle of the digestive tract, cardiac muscle, the endocrine system, the immune system, vision (cataract), and intelligence may be affected. Myotonia can be demonstrated by percussion of the thenar eminence, which remains dimpled at the site of the percussion with thumb abduction for several seconds. In this vignette, the myotonia is demonstrated by the use of wrist flexors to force the flexors of the fingers to open. In Duchenne muscular dystrophy, muscle deficit in dystrophin causes an unsteady gait in males always before the age of 5 years. Myasthenia gravis, Werdnig–Hoffman disease, and chronic demyelinating polyradiculopathy are unlikely to cause myotonia. *(Fenichel, 190–191)*

**70. (C)** Pseudotumor cerebri is a chronic condition characterized by an increase in intracranial pressure, normal CSF content, and normal brain with normal or small ventricles on brain imaging studies. A specific cause can usually be found in children younger than 6 years, while most idiopathic cases occur after the age of 12 years. Administration of tetracycline or nalidixic acid has been postulated as a cause of pseudotumor cerebri. Hypervitaminosis A as well as hypovitaminosis A has been documented as a cause of pseudotumor cerebri, but not furosemide, acetazolamide, phenobarbital, or ampicillin administration. *(Fenichel, 113–114)*

**71.** **(E)** The most sensitive and one of the earliest signs of critically increased intracranial pressure is a decreased level of consciousness. Headache, vomiting, irritability, and abducen nerve palsy may develop sequentially. Headache is caused by traction on the intracranial arteries. Pain fibers from supratentorial intracranial vessels are innervated by the trigeminal nerve and pain is referred to the eyes, forehead, and temple. Infratentorial vessels are innervated by cervical nerves and pain is referred to the occiput and neck. Papilledema is a passive swelling of the optic disk, probably caused by the obstruction of venous return from the retina and nerve head. It does not develop in all patients with acute increased intracranial pressure. Early papilledema is asymptomatic; only when it is advanced or chronic does the patient experience a transitory decrease in vision. This preservation of visual acuity may differentiate papilledema from a primary optic nerve disturbance such as optic neuritis. *(Fenichel, 91–94)*

**72.** **(A)** The patient described in the vignette showed the emergence of a left sided focal seizure during the course of his meningitis, followed by the persistence of left sided weakness despite the improvement of his meningitis. A cerebral ischemic event is the most likely cause. It complicates the course of bacterial meningitis in 2% to 19% of cases and may be due to focal brain ischemia from venous thrombosis or arterial vasculitis. Brain abscess is an uncommon complication of bacterial meningitis in children and unlikely to be the right diagnosis in this case, where all signs of infection improved. Transient paresis may complicate a focal seizure. However, such a neurological deficit classically improves within a few hours. Persistent motor deficit suggests an underlying structural lesion rather than Todd paralysis. Subdural empyema and hydrocephalus with increased intracranial pressure may complicate meningitis. These entities are expected to cause generalized rather than focal seizures. *(Fenichel, 107–109)*

**73.** **(C)** The patient in the vignette has a clinical worsening of his symptoms, with ependymal rim enhancing and fluid of different contrast in the ventricles. The most likely diagnosis in this case is ventriculitis, a common complication in gram-negative meningitis in newborns. Necrotic bits of choroid plexus can block the cerebral aqueduct, making the lateral cerebral ventricles a closed space. The diagnosis is confirmed by a neurosurgical ventricular puncture that might yield the infecting organism. Subdural empyema usually occurs in an infant with a severe gram-negative meningitis. Head CT with contrast will reveal the subdural collection of fluid surrounded by an enhancing rim. Brain abscess is an uncommon complication of bacterial meningitis in the newborn. It may occur as a complication of severe *Haemophilus influenzae* infant meningitis. Surgical drainage is indicated if the abscess is large and accessible. *(Smith, 11–18)*

**74.** **(A)** The frequency and duration of headaches described in this vignette suggest the diagnosis of chronic tension-type headaches. A pressure or tightening quality that is dull and nonpulsatile is typical. Depression is a common comorbidity of this condition and should be assessed appropriately. The frequency of the headaches in this case warrants prophylactic treatment. Amitriptyline has been the most successful medication with patients who have tension-type headaches. Sedation that may interfere with daytime activity and anticholinergic side effects can be avoided by administrating the drug at bedtime and using low dosages. *(Fenichel, 85)*

**75.** **(A)** Familial hemiplegic migraine is characterized by a sudden onset of hemiplegia or hemisensory loss that is usually followed by a contralateral headache. The trait is transmitted by autosomal dominant inheritance. The gene is located on chromosome 19p. Attacks are stereotyped, occur primarily in childhood or adolescence, and may be precipitated by minor head trauma. The hemiplegia, although more severe in the face and arm, affects the leg and may be present on alternate sides during different episodes. Aphasia may occur when the dominant hemisphere is affected. Stupor, confusion, and psychosis may complicate attacks. The episode may last 2 or 3 days and

may suggest a stroke-like syndrome. The neurological deficit usually resolves completely, but permanent sequelae, such as gaze-evoked nystagmus, may persist between attacks. *(Fenichel, 251)*

**76. (A)** Abdominal migraine refers to the condition of children who have recurrent abdominal pain, nausea, and vomiting as well as recurrent headaches. This problem ceases by the teenage years and is often replaced by more conventional headaches. Benign paroxysmal vertigo is seen predominantly in children between 2 and 6 years of age. Such episodes, which last only minutes, are characterized by the sudden onset of vertigo, pallor, and nystagmus. There is a positive family history of migraine. Most patients will develop a typical migraine by adolescence. Recurrent episodes of head tilt associated with headache, nausea, and vomiting are characteristic of paroxysmal torticollis, an uncommon benign disorder. Ocular migraine consists of episodes of transient monocular blindness in a patient who has previously had migraine attacks or has a history of migraine in the family. Most attacks last for only minutes, but permanent ocular changes have been reported. No choreoathetotic movement disorder, sleepwalking, recurrent chest pain, or recurrent urinary retention is attributed to migraine variant. *(Singer, 94–101)*

**77. (D)** In a child with febrile seizure, the risk of developing subsequent epilepsy increases if there is a family history of epilepsy or a history of febrile seizures in parents or siblings. A history of complex febrile seizure, which is defined as a seizure that lasts longer than 15 minutes or that occurs in a prolonged series for more than 30 minutes, may increase the risk of having subsequent epilepsy. A preexisting neurological disease such as cerebral palsy or developmental delay may also increase the risk of epilepsy. Children who have one of the above risk factors have a 2% chance of developing epilepsy by the age of 7 years. Those who have two or more risk factors have a 10% chance. Having two febrile seizures in a single year does not increase the risk of developing epilepsy but increases the risk of having a third febrile seizure, as 50% of children who experience a second seizure will experience a third one within the next 6 to 12 months. *(Berg et al., 1122–1127; Fenichel, 17–18; Verity and Golding, 1373–1376)*

**78. (C)** LaCrosse virus is the most common cause of encephalitis due to California subgroup viruses in the United States. Most cases were reported in Wisconsin and Minnesota before 1984. Later epidemics occurred in Indiana. Small woodland mammals serve as a reservoir and mosquitoes as the vector. Eastern equine encephalitis is a perennial infection of horses from New York to Florida. Human cases follow epidemics in horses. Wild birds serve as a reservoir and mosquitoes as a vector. Japanese B encephalitis is a major form of encephalitis in Asia and is an important health hazard to nonimmunized travelers during summer months. St. Louis encephalitis is endemic in the western United States. The vector is a mosquito and birds are the major reservoir. Western equine encephalitis is a rare disorder. All recent cases have been reported in North Dakota, South Dakota, and Canada. *(Fenichel, 56–58)*

**79. (C)** The patient described in the vignette developed complex febrile seizure complicated by right-sided hemiparesis and periodic lateralizing epileptiform discharge. These findings are consistent with the diagnosis of herpes encephalitis. Herpes simplex is the single most common cause of nonepidemic encephalitis and accounts for 10% to 20% of cases. The annual incidence is estimated at 2.3 cases per million people. Thirty-one percent of cases occur in children. Primary infection is the most common cause of encephalitis in children, and only 22% of patients give a history of recurrent labial herpes infection. The diagnosis is made by the examination of CSF, which may show a pleocytosis in 97% of cases. Many red blood cells, up to 500/$mm^3$, may be present, with a median protein concentration of 80 mg/dL. The demonstration of lateralizing epileptiform discharges on EEG is considered presumptive evidence of herpes encephalitis. However, MRI has proved to be an early indicator of herpes encephalitis; the T2-weighted images show increased signal intensity in one or both temporal lobes. The identification of the

organism in the CSF has been made possible by a polymerase chain reaction, which obviates the need for brain biopsy to confirm the diagnosis. Measles encephalitis is a rare complication of measles, since compulsory immunization has almost eliminated natural measles infection in the United States. Symptoms of encephalitis are usually abrupt, following the rash by 1 day to 3 weeks, and are characterized by lethargy, which may rapidly progress to coma; generalized seizure occurs in 50% of patients. Hemiplegia, ataxia, involuntary movement disorders, and acute transverse myelitis may occur. Postinfectious encephalomyelitis is unlikely to be the diagnosis in this case. The clinical picture would be lethargy and weakness followed by declining consciousness, seizures, optic neuritis, and/or transverse myelitis. Postinfectious encephalomyelitis is a demyelinating disorder that occurs during or after a systemic viral illness and is presumed to be an immune-mediated disease. The diagnosis is based on a T2-weighted MRI scan that shows a marked increase in signal intensity throughout the white matter. Reye syndrome is a systemic disorder of mitochondrial function that occurs during or following a viral infection and/or after the use of salicylate. The clinical picture may progress from vomiting and lethargy to flaccid coma. Typical blood abnormalities include hypoglycemia, hyperammonemia, and increase in hepatic enzymes. CSF is normal except for increased pressure. EEG shows diffuse encephalopathy. The diagnosis is confirmed by liver biopsy, which may, on electron microscopy, show characteristic mitochondrial abnormalities. St. Louis encephalitis may present with headache, fever, and a spectrum of neurological illness that varies from aseptic meningitis to severe encephalitis. Decreased consciousness is common, but seizures or focal neurological disturbances are rare. *(Fenichel, 56–61)*

**80. (D)** Hyperventilation immediately reduces the intracranial pressure through vasoconstriction, induced by lowering the arterial pressure of carbon dioxide. However, excessive lowering of carbon dioxide below 25 mmHg is contraindicated because it may cause brain ischemia. Elevation of the head of the bed 30 to 45 degrees above horizontal decreases intracranial pressure by improving jugular venous drainage. Mannitol and glycerol are the most widely used osmotic diuretics in the United States. These agents remain in the plasma and create an osmotic gradient that draws water from the brain into the capillaries. Hypothermia between 27°C and 31°C reduces cerebral blood flow. It is frequently used with pentobarbital, which also decreases cerebral flow and edema formation at a dosage causing burst suppression on EEG. *(Fenichel, 96–97)*

**81. (A)** The patient described in this question has Parinaud syndrome, which results from dysfunction of the midbrain due to periaqueductal compression from a pineal region tumor. Tumors of the pineal region are most frequently derived from germ cells. They are more frequent in boys than girls and generally become symptomatic during the second decade. Symptoms of pineal tumors are caused either by tumor mass effect on local tissues or by hydrocephalus (from the tumor blocking the normal CSF drain pathway). Head MRI is a valuable tool in assessing the location and extension of pineal tumors; in some cases it may suggest the tumor's histological type. Germinomas are isodense and have irregular margins. Teratomas may appear lobulated and have both hyperdense and multicystic areas. Tumors that spread into the ventricles and show intense contrast enhancement are likely to be malignant. Tumors with abundant amounts of calcium are likely to be benign. Pineal germinomas are more radiosensitive than other pineal tumors, with a 5-year survival rate up to 80%. *(Fenichel, 101)*

**82. (C)** The patient described in this question has the features of fragile-X syndrome. It is the most common chromosomal cause of mental retardation in boys. The fragile-X gene (FMR-1) has been isolated, cloned, and characterized. It contains a trinucleotide sequence (CGG) that in the normal genome is repeated from 6 to 55 times. In persons with the fragile-X syndrome, this repeat is expanded (amplified) to several hundred copies (full mutation), whereas asymptomatic carriers for fragile X carry between 50 and 230 copies (premutation). The

premutation tends to remain stable during spermatogenesis but frequently expands to a full mutation during oogenesis. All male individuals with a full mutation but only 53% of female individuals with a full mutation are mentally impaired. The condition is relatively common, second only to Down's syndrome as a genetic cause of mental retardation. It is a clinically subtle dysmorphic syndrome. The male patient has a long face, prominent brow, somewhat square chin, large floppy ears, and macroorchidism without any obvious evidence of endocrine dysfunction. Although macroorchidism can be present at birth, it is difficult to recognize in the prepubertal boy, as are most of the other physical features. Approximately 10% of patients have a head circumference greater than the 97th percentile, and the fragile-X syndrome may mimic the features of cerebral gigantism. A number of clinical features reflect connective tissue dysplasia. These include hyperextensible finger joints, flat feet, aortic root dilatation, and mitral valve prolapse. A Prader–Willi phenotype has also been encountered. The neurological picture is highlighted by retarded language development and hyperactivity. Delayed motor development is seen in some 20% of male patients, and seizures have been experienced by 25% to 40%. These are major motor or partial complex seizures; as a rule they respond well to anticonvulsant therapy. Because folic acid antagonists must be added to the culture medium (to create a folate-free culture) to detect the abnormality, high doses of folate have been used to treat children with fragile-X syndrome, with some behavioral improvement. *(Fenichel, 120; Menkes, 244–247)*

**83.** **(B)** Hypotonia, mongoloid facies, flat nape of neck, and Brushfield spots are features of trisomy 21. Down's syndrome is the most common chromosomal abnormality affecting live-born children. It results from the presence of three copies of chromosome 21 rather than the normal two copies. Affected individuals most often exhibit mild to moderate mental retardation and have characteristic facial and physical abnormalities as well as possible congenital defects in the cardiac, visual, gastrointestinal, and endocrine systems. The frequency is 1 in 600 to 700 births, and this condition accounts for approximately 10% of all cases in every large series of cases of severe mental retardation. Familiarity with the condition permits its recognition at birth, but it becomes more obvious with advancing age. The round head, open mouth, stubby hands, slanting palpebral fissures, and short stature impart an unmistakable appearance. The ears are low-set and oval, with small lobules. The palpebral fissures slant slightly upward and outward owing to the presence of medial epicanthal folds that partly cover the inner canthi (hence the old term *mongolism*). The bridge of the nose is poorly developed and the face is flattened (hypoplasia of the maxillae). The tongue is usually enlarged, heavily fissured, and protruded. Gray–white specks of depigmentation are seen in the irides (Brushfield spots). The little fingers are often short (hypoplastic middle phalanx) and incurved (clinodactyly). The fontanels are patent and slow to close. The hands are broad, with a single transverse (simian) palmar crease and other characteristic dermal markings. Lenticular opacities and congenital heart lesions (septal and other defects) as well as gastrointestinal abnormalities (stenosis of duodenum) are frequent. Hypotonia of limbs is a prominent finding. At first, the Moro response is reduced or absent, and feeding is difficult. Most affected children do not walk until 3 to 4 years of age; their acquisition of speech is delayed, but over 90% talk by 5 years. The intelligence quotient (IQ) is variable; that of a large group follows a Gaussian curve with the median IQ being 40 to 50 and the range 20 to 70. *(Ropper and Brown, chapter 38)*

**84.** **(D)** The patient described in this question has the features of trisomy 18. The disorder is seen in 1 in 4,000 live births, more in females, with an average maternal age of 34 years. It is characterized by slow growth, occasional seizures, severe mental retardation, hypertonia, ptosis and lid abnormalities, low-set ears, small mouth, mottled skin, clenched fists with index fingers overlapping the third finger, syndactyly, rocker-bottom feet, shortened big toe, ventricular septal defect, umbilical and inguinal hernias, short sternum, small pelvis, and small mandible. *(Ropper and Brown, chapter 38)*

**85.** **(A)** Cri-du-chat syndrome is caused by a deletion in short arm of chromosome 5. It is characterized by an abnormal cry, like that of a kitten, severe mental retardation, hypertelorism, epicanthal folds, brachycephaly, moon face, antimongoloid slant of palpebral fissures, micrognathia, hypotonia, and strabismus. *(Ropper and Brown, chapter 38)*

**86.** **(D)** Hutchinson triad—defined as the combination of deafness, interstitial keratitis, and peg-shaped upper incisors—is characteristic of congenital syphilis. The more common features in symptomatic infants with congenital syphilis are condylomata lata, periostitis or osteochondritis, persistent rhinorrhea, and maculopapular rash. *(Fenichel, 122)*

**87.** **(B)** Tay–Sachs disease is an autosomal recessive disease, mostly of Jewish infants of eastern European (Ashkenazic) background. The disease becomes apparent in the first weeks and months of life, almost always by the fourth month. The first manifestations are a regression of motor activity and an abnormal startle to acoustic stimuli, accompanied by listlessness, irritability, and poor reactions to visual stimuli. These are followed by a progressive delay in psychomotor development or regression (by 4 to 6 months), with inability to roll over and sit. At first, axial hypotonia is prominent, but later spasticity and other corticospinal tract signs and visual failure become evident. Degeneration of the macular cells exposes the underlying red vascular choroid surrounded by a whitish gray ring of retinal cells distended with ganglioside. The resulting appearance is of the cherry-red spot with optic atrophy. In the second year, there are tonic–clonic or minor motor seizures and an increasing size of the head and diastasis of sutures with relatively normal-sized ventricles; in the third year, the clinical picture is one of dementia, decerebration, and blindness. Cachexia becomes increasingly severe and death occurs at 2 to 4 years. The EEG becomes abnormal in the early stages (paroxysmal slow waves with multiple spikes). The basic enzymatic abnormality is a deficiency of hexosaminidase A, which normally cleaves the N-acetylgalactosamine from gangliosides. As a result of this deficiency, $G_{M2}$ ganglioside accumulates in the cerebral cortical neurons, Purkinje cells, retinal ganglion cells, and, to a lesser extent, larger neurons of the brainstem and spinal cord. *(Ropper and Brown, chapter 37)*

**88.** **(A)** $G_{M1}$ gangliosidosis is an autosomal recessive lysosomal storage disorder characterized by the generalized accumulation of $G_{M1}$ ganglioside, oligosaccharides, and the mucopolysaccharide keratan sulfate (and their derivatives). The amount and type of residual activity determine whether the phenotype is generalized gangliosidosis, as in $G_{M1}$ gangliosidosis (deficiency of the lysosomal hydrolase acid b-galactosidase causes $G_{M1}$ gangliosidosis) or visceral storage of mucopolysaccharidosis with little brain disease, as in Morquio disease type B. Three clinical subtypes of $G_{M1}$ gangliosidosis exist, classified by age of onset as infantile form, juvenile form, and adult form. In the infantile form, the infants appear abnormal at birth. They have dysmorphic facial features, like those of individuals with the mucopolysaccharidoses: depressed and wide nasal bridge, frontal bossing, hypertelorism, puffy eyelids, long upper lip, gingival and alveolar hypertrophy, macroglossia, and low-set ears. These features, with the bone changes mentioned below, account for the term *pseudo-Hurler*. Other indications of the disease are the onset of impaired awareness and reduced responsivity in the first days or weeks of life; lack of psychomotor development after 3 to 6 months; hypotonia and later hypertonia with lively tendon reflexes and Babinski signs. Seizures are frequent. The head size is variable (microcephaly more often than macrocephaly). Loss of vision, coarse nystagmus and strabismus, macular cherry-red spots (in half the cases), flexion pseudocontractures of elbows and knees, kyphoscoliosis, and enlarged liver and sometimes enlarged spleen are the other important clinical findings. Radiographic abnormalities include subperiosteal bone formation, midshaft widening and demineralization of long bones, and hypoplasia and beaking of the thoracolumbar vertebrae. Vacuoles are seen in 10% to 80% of blood lymphocytes and foam cells in the urinary sediment. The juvenile

subtype is marked by a slightly later age of onset and clinical variability in the classic physical features. The adult subtype is marked by normal early neurological development with no physical stigmata and subsequent development of a slowly progressive dementia with parkinsonian features, extrapyramidal disease, and dystonia. *(Fenichel 129–130; Ropper and Brown, chapter 37)*

**89. (E)** Infantile Niemann–Pick disease is an autosomal recessive disease. Two thirds of the affected infants have been of Ashkenazi Jewish parentage. The onset of symptoms in the usual type A disease is between 3 and 9 months of age, frequently beginning with marked enlargement of liver, spleen, and lymph nodes and infiltration of the lungs; rarely there is jaundice and ascites. Cerebral abnormalities are definite by the end of the first year, often earlier. The usual manifestations are loss of spontaneous movements, lack of interest in the environment, axial hypotonia with bilateral corticospinal signs, blindness and amaurotic nystagmus, and a macular cherry-red spot (in about one quarter of the patients). Seizures may occur but are relatively late. There is no acoustic-induced startle or myoclonus, and head size is normal or slightly reduced. Loss of tendon reflexes and slowed conduction in peripheral nerves have been recorded but are rare. Protuberant eyes, mild hypertelorism, slight yellowish pigmentation of oral mucosa, and dysplasia of dental enamel have also been reported but are rare. Most patients succumb to an intercurrent infection by the end of the second year. *(Fenichel, 132; Ropper and Brown, chapter 37)*

**90. (D)** Metachromatic leukodystrophy is a lysosomal (sphingolipid) storage disease. The basic abnormality, localized in chromosome 22, is the absence of the gene for enzyme arylsulfatase A, a deficiency of which prevents the conversion of sulfatide to cerebroside (a major component of myelin) and results in an accumulation of the former. The disease is transmitted as an autosomal recessive trait and usually becomes manifest between the first and fourth years of life. The disease in the infantile form is characterized clinically by progressive impairment of motor function (gait disorder, spasticity) in combination with reduced output of speech and mental regression. At first, the tendon reflexes are usually brisk, but later, as the peripheral nerves become more involved, the tendon reflexes are decreased and eventually lost. Or, there may be variable hypotonia and areflexia from the beginning, or spasticity may be present throughout the illness, but with hyporeflexia and slowed conduction velocities. Signs of mental regression may be apparent from the onset or appear after the motor disorder has become established. Later, there is impairment of vision, sometimes with squint and nystagmus; intention tremor in the arms, and dysarthria; dysphagia and drooling; and optic atrophy (one third of patients), sometimes with grayish degeneration around the maculae. Seizures are rare, and there are no somatic abnormalities. The head size is usually normal, but rarely there is macrocephaly. Progression to a bedridden quadriplegic state without speech or comprehension occurs over a 1- to 3-year period, somewhat more slowly in late-onset types. The CSF protein is elevated. There is widespread degeneration of myelinated fibers in the cerebrum, cerebellum, spinal cord, and peripheral nerves. The presence of metachromatic granules in glial cells and engorged macrophages is characteristic and enables the diagnosis to be made from a biopsy of a peripheral nerve. *(Fenichel, 132; Ropper and Brown, chapter 37)*

**91. (C)** Krabbe disease is a rapidly progressive demyelinating disorder of infants caused by a deficit in the enzyme galactocerebrosidase. The enzyme normally degrades galactocerebroside to ceramide and galactose. The deficiency results in the accumulation of galactocerebroside; a toxic metabolite, psychosine, leads to the early destruction of oligodendrocytes and depletion of lipids in the cerebral white matter. The onset is usually before the sixth month and often before the third month (10% after 1 year). Early manifestations are generalized rigidity, loss of head control, diminished alertness, frequent vomiting, irritability and bouts of inexplicable crying, and spasms induced by stimulation. With increasing muscular tone, opisthotonic recurvation of the neck and trunk develops. Later signs are adduction and extension of the

legs, flexion of the arms, clenching of the fists, hyperactive tendon reflexes, and Babinski signs. Later still, the tendon reflexes are depressed or lost but Babinski signs remain, an indication that neuropathy is added to corticospinal damage. This finding, shared with some of the other leukodystrophies, is of diagnostic value. Blindness and optic atrophy supervene. Convulsions occur but are rare and difficult to distinguish from tonic spasms. Myoclonus in response to auditory stimuli is present in some cases. The head size is normal or, rarely, slightly increased. In the last stage of the disease, which may occur from one to several months after the onset, the child is blind and usually deaf, opisthotonic, irritable, and cachectic. Most patients die by the end of the first year; survival beyond 2 years is unusual, although a considerable number of cases of later onset have been reported. *(Fenichel 132; Ropper and Brown, chapter 37)*

**92. (C)** Leigh disease is a syndrome of progressive dystrophy primarily affecting neurons of the brainstem, thalamus, basal ganglia, and cerebellum. The disease is transmitted by an autosomal recessive or X-linked inheritance. The disease may be caused by an enzyme deficit, either in pyruvate metabolism or in respiratory chain complexes. Onset of the disease occurs in 60% of cases in the first year. The initial symptoms are developmental delay, failure to thrive, hypotonia, and seizures. Intercurrent infection or a heavy carbohydrate meal may worsen symptoms. During infancy the patient may show three typical features: respiratory disturbance, hypotonia, and ocular motility abnormalities. Hypotonia results from a combination of peripheral neuropathy and disturbed cerebellar function. Ocular motility disturbance varies from nystagmus to ophthalmoplegia. Respiratory disturbance can be characterized by Cheyne–Stokes breathing, ataxic breathing, or central hyperventilation. *(Fenichel, 134)*

**93. (D)** Subacute necrotizing encephalomyelopathy (Leigh disease) is a familial or sporadically occurring mitochondrial disorder with a wide range of clinical manifestations. Only some of the cases display a maternal pattern of inheritance. The onset of neurological difficulty in more than half of these patients is in the first year of life, mostly before the sixth month; but late-onset forms, with great heterogeneity of presentation as late as early adulthood, are also known. Neurological symptoms often appear subacutely or abruptly, sometimes precipitated by a febrile illness or a surgical operation. In infants, loss of head control and other recent motor acquisitions, hypotonia, poor sucking, anorexia and vomiting, irritability and continuous crying, generalized seizures, and myoclonic jerks constitute the usual clinical picture. If the onset is in the second year, there is delay in walking, ataxia, dysarthria, psychomotor regression, tonic spasms, characteristic respiratory disturbance (episodic hyperventilation, especially during infections, and periods of apnea, gasping, and quiet sobbing), external ophthalmoplegia, nystagmus, and disorders of gaze (like those of Wernicke disease), paralysis of deglutition, and abnormal movements of the limbs (particularly dystonia but also jerky and choreiform movements). Mild cases, showing mainly developmental delay, have been mistaken for cerebral palsy. Peripheral nerves are involved in some cases (areflexia, weakness, atrophy, and slowed conduction velocities of peripheral nerves); in a few, autonomic failure is the most prominent feature. In some children, the disease is episodic; in others, it is intermittently progressive and quite protracted, with exacerbation of neurological symptoms in association with nonspecific infections. *(Fenichel 134; Ropper and Brown, chapter 37)*.

**94. (C)** Gaucher disease is a lipid storage disease characterized by the deposition of glucocerebroside in cells of the macrophage–monocyte system. The disorder results from the deficiency of a specific lysosomal hydrolase, glucocerebrosidase (also termed acid beta-glucosidase, glucosylceramidase). The disease is characterized by a continuum of phenotypes. The severity is extremely variable; some patients present in childhood with virtually all the complications of Gaucher disease, while others remain asymptomatic into the eighth decade of life. Gaucher disease has traditionally been divided into the following three clinical

subtypes, delineated by the absence or presence of neurologic involvement and its progression: type I, nonneuronopathic form; type II, acute neuronopathic form; and type III, chronic neuronopathic form.

Glucosylceramide, the accumulated glycolipid, is primarily derived from the phagocytosis and degradation of senescent leukocytes and, to a lesser extent, from erythrocyte membranes. The glycolipid storage gives rise to the characteristic Gaucher cells, macrophages engorged with lipid with a crumpled-tissue-paper appearance and displaced nuclei. The factors that contribute to neurological involvement in patients with types II and III disease are still unknown but may be related to the accumulation of a cytotoxic glycolipid, glucosylsphingosine, in the brain due to the severe deficiency of glucocerebrosidase activity.

In type II Gaucher disease, the clinical manifestations are characterized by a rapid neurodegenerative course with extensive visceral involvement and death within the first 2 years of life. Patients with this type may present at birth or during infancy with increased tone, seizures, strabismus, and organomegaly. Disruption of the epidermal layers of the skin, observed on skin biopsy findings, may manifest before the onset of neurological symptoms, but this may not always be clinically apparent. There is a failure to thrive and stridor due to laryngospasm is typical in individuals with type 2 disease. The progressive psychomotor degeneration leads to death, usually caused by respiratory compromise.

The clinical manifestation of type III Gaucher disease varies widely; it can present in infancy or childhood. In addition to organomegaly and bony involvement, individuals with type III disease have neurological involvement. Slowing of the horizontal saccades, an oculomotor finding, is often the sole neurological manifestation. Some patients develop myoclonic epilepsy, exhibit learning disabilities, or develop dementia. *(Fenichel, 128–129; Ropper and Brown, chapter 37)*

**95.** **(A)** Menkes disease is a rare disorder, inherited as a sex-linked recessive trait. The manifestations of this disease are attributable to one of numerous known mutations in a copper-transporting ATPase, ATP7A, that is currently thought to result in a failure of absorption of copper from the gastrointestinal tract and a profound deficiency of tissue copper. Poor feeding and failure to gain weight, instability of temperature (mainly hypothermia), and seizures become apparent in early infancy. *(Fenichel, 137–138; Ropper and Brown, chapter 37)*

**96.** **(E)** Chediak–Higashi syndrome is an autosomal recessive disorder resulting from lack of regulation of the fusion of primary lymphocytes. Recurrent infection during infancy, skin and hair pigmentation defects, peripheral neuropathy, seizures, and developmental retardation may be seen in affected patients. *(Rowland, 1061–1062)*

**97.** **(B)** Niemann–Pick syndrome is a group of disorders grouped together on the basis of the overlapping pathology and biochemistry into four groups. Groups A and B are primary sphingomyelinase deficiencies, whereas groups C and D are allelic disorders, whose primary defect is not deficiency of a lysosomal hydrolase, but is in intracellular lipid trafficking. Patients with types A and B Niemann–Pick disease have deficient activity of the sphingomyelin-cleaving enzyme acid sphingomyelinase. *(Rowland, 629)*

**98.** **(B)** The association of skin lesions and neurological symptoms suggests a neurocutaneous disorder. The association of developmental delay, seizures, and hypopigmented area is highly suggestive of tuberous sclerosis. The disease is transmitted by an autosomal dominant inheritance with a genetic linkage to chromosome 9 and 16. The seizures and mental retardation are caused by disturbed histogenesis in the brain. Leaf-shaped hypochromic nevi are present in only about 18% of patients. Besides the skin, other organs may be affected, such as the retina, kidney, bone, and lungs. Neurofibromatosis type I is unlikely. It is characterized by the presence of at least two of the following: six or more café au lait spots greater than 5 mm (in prepubertal age), two or more neurofibromas, freckling in the axillary or inguinal region, optic glioma, two or more iris hamartomas, bone dyplasia, and a first-degree

relative with neurofibromatosis type I. The patient in the vignette does not correspond to these criteria. *(Fenichel, 135–136)*

**99. (D)** Bilateral acoustic neurinomas are a characteristic of type II neurofibromatosis. The other conditions listed in the question are characteristic of type I neurofibromatosis. Other features of type I neurofibromatosis include a first-degree relative with this diagnosis, neurofibroma, and freckling in the inguinal or axillary region. *(Fenichel, 134–135)*

**100. (B)** Rett syndrome is an X-linked dominant disorder affecting girls almost exclusively (it is lethal to the male fetus). It has a prevalence of 1 to 2 per 20,000. Development proceeds normally until approximately 1 year of age, at which time language and motor development regress and acquired microcephaly becomes apparent. These girls present with midline hand-wringing and unusual sighing. Autistic behaviors are typical. Postmortem examinations have revealed greatly reduced brain size and weight as well as a reduced number of synapses. The Rett syndrome Diagnosis Criteria Work Group has divided the diagnostic criteria into necessary criteria, supportive criteria, and exclusion criteria. Severe progressive dementia is a part of the necessary criteria. Exclusionary criteria include intrauterine growth retardation, microcephaly at birth, organomegaly or sign of storage disease, retinopathy, optic atrophy, and evidence of acquired identifiable neurological disease. *(Behrman, 2034; Fenichel, 13)*

**101. (E)** The association of vomiting, hepatomegaly, cataract, and the presence of reducing substances in the urine, especially after feeding, is highly suggestive of galactosemia. It is a serious disease with an early onset of symptoms. Its incidence is around 1 per 60,000. It results from galactose-1-phosphate uridyl transferase deficiency. The newborn infant normally receives up to 20% of caloric intake as lactose, which consists of glucose and galactose. Without the transferase enzyme, the infant is unable to metabolize galactose-1-phosphate, the accumulation of which results in injury to parenchymal cells of the kidney, liver, and brain. High concentrations of intracellular galactose-1-phosphate can function as a competitive inhibitor of phosphoglucomutase. This inhibition transiently impairs the conversion of glycogen to glucose and produces hypoglycemia. Injury to parenchymal cells may begin prenatally in the affected fetus by transplacental galactose derived from the diet of the heterozygous mother or by endogenous production of galactose in the fetus.

The diagnosis of galactose-1-phosphate uridyl transferase deficiency should be considered in newborns with any of the following features: jaundice, hepatomegaly, vomiting, hypoglycemia, convulsions, lethargy, irritability, feeding difficulties, aminoaciduria, cataracts, or vitreous hemorrhage. The preliminary diagnosis of galactosemia is made by demonstrating a reducing substance in several urine specimens collected while the patient is receiving human milk, cow's milk, or another formula containing lactose. The deficient activity of galactose-1-phosphate uridyl transferase is demonstrable in hemolysates of erythrocytes, which also exhibit increased concentrations of galactose-1-phosphate.

Krabbe disease is a rapidly progressive demyelinating disorder caused by a deficit of the activity of galactosylceramidase. Diffuse demyelination suggests the diagnosis on MRI; prolonged motor nerve conduction velocity and increased cerebrospinal fluid protein content are supportive. The diagnosis is confirmed by showing decreased galactosylceramidase activity in leukocytes.

Gaucher disease is a multisystemic lipidosis characterized by hematological problems, organomegaly, and skeletal involvement. It is the most common lysosomal storage disease and the most prevalent genetic defect among Ashkenazi Jews. There are three clinical subtypes, delineated by the absence or presence and progression of neurological manifestations: type 1 or the adult, nonneuronopathic form; type 2, the infantile or acute neuronopathic form; and type 3, the juvenile form. All subtypes are autosomal recessive traits. Gaucher disease type 2 is much less common and does not have a striking ethnic predilection. It is char-

acterized by a rapid neurodegenerative course with extensive visceral involvement and death, often within the first 2 years of life. It presents in infancy with increased tone, strabismus, and organomegaly. Failure to thrive and stridor due to laryngospasm are typical. After a several-year period of psychomotor regression, death occurs secondary to respiratory complications.

Tay–Sachs disease results from the deficiency of hexosaminidase activity and the lysosomal accumulation of $G_{M2}$ gangliosides, particularly in the central nervous system. Patients with clinical manifestations of the infantile form of Tay–Sachs disease present with loss of motor skills, increased startle reaction, and the presence of macular pallor and a cherry-red spot on retinoscopy. Macrocephaly, not associated with hydrocephalus, may develop. In the second year of life, seizures requiring anticonvulsant therapy develop. Mucopolysaccharidoses result from a deficit of enzymes involved in the catabolism of dermatan sulfate, heparan sulfate, or keratin sulfate. The clinical picture of these diseases is different from the clinical picture presented in the vignette. *(Behrman, 475–476; Fenichel, 13)*

**102. (E)** Zellweger syndrome, or cerebrohepatorenal syndrome, is a rare and lethal disorder. It is inherited as an autosomal recessive trait. It represents the prototype of a group of peroxisomal disorders that have overlapping symptoms, signs, and biochemical abnormalities. Infants with this syndrome have dysmorphic facies consisting of frontal bossing and a large anterior fontanel. The occiput is flattened, and the external ears are abnormal. A high-arched palate, excessive skinfolds of the neck, severe hypotonia, and areflexia are usually evident. Examination of the eyes reveals searching nystagmoid movements, bilateral cataracts, and optic atrophy. Generalized seizures become evident early in life, associated with severe global developmental delay and significant bilateral hearing loss. The cause of the severe neurologic abnormalities is related to an arrest of migrating neuroblasts during early development, resulting in cerebral pachygyria with neuronal heterotopia. Patients with Zellweger syndrome rarely survive beyond 1 year of age. *(Behrman, 439–440)*

**103. (E)** Spinal muscular atrophy is a genetic disorder in which anterior horn cells in the spinal cord and motor nuclei of the brainstem are progressively lost. Two clinical syndromes of infantile spinal muscular atrophy can be distinguished: spinal muscular atrophy type I, which is the acute fulminant form appearing in the first 6 months, and spinal muscular atrophy type II, which is the more chronic form. Affected newborns in spinal muscular atrophy type I have generalized weakness more proximal than distal, hypotonia, and areflexia. Facial expression is relatively well preserved, as are extraocular movements. Despite intrauterine hypotonia, arthrogryposis is not present. Creatine kinase is normal or mildly elevated. The diagnosis is established by a histological examination that shows hypertrophy of type I fibers by the myosin ATPase reaction. Prenatal diagnosis can be accomplished by DNA analysis of chorion villus biopsy. *(Fenichel, 173–174)*

**104. (D)** The association of constipation, poor feeding, and incremental response to repetitive stimulation between 20 and 50 Hz is highly suggestive of infantile botulism. It is an age-limited disorder in which *Clostridium botulinum* is ingested, colonizes the intestinal tract, and produces toxin in situ. The exotoxin prevents the release of acetylcholine, causing a cholinergic blockade of skeletal muscles and the end organs innervated by autonomic nerves. Infected infants at the age of 4 weeks are usually living in a dusty environment adjacent to construction or agricultural soil disruption. The prodromal signs are poor feeding and constipation. Typically, the newborn may present with diffuse hypotonia, ptosis, dysphagia, weak cry, and dilated pupils that react sluggishly to light. Electrophysiology studies show an incremental response to repetitive stimulation at a frequency between 20 and 50 Hz. The diagnosis is confirmed by isolation of organisms or toxin from the stool. Infantile botulism may suggest Guillain–Barré syndrome. The clinical differential diagnosis may be difficult, but electrophysiology testing establishes the diagnosis. Infantile botulism differs from infantile spinal muscular atrophy by the early appearance of facial and pharyngeal weakness,

the presence of ptosis and dilated pupils, and the occurrence of severe constipation. Infants with generalized myasthenia do not have dilated pupils, absent reflexes, or severe constipation. Lowe syndrome, or oculocerebrorenal syndrome, is an X-linked disease characterized by hypotonia and hyporeflexia and sometimes cataracts. Later in infancy mental retardation and defects in urine acidification appear. *(Behrman, 947–995)*

**105. (D)** Myotonic dystrophy is a multisystem disorder transmitted by autosomal dominant inheritance. It is caused by an unstable DNA triplet on chromosome 19 that repeats 50 to several thousand times in successive generations. The number of triplets correlates with the severity of the disease. Repeat size changes from mother to child are greater than from father to child. For this reason, the mother is the most often affected parent when a child has a myotonic dystrophy. The main feature during pregnancy is reduced fetal movements and polyhydramnios. Prominent clinical features in the newborn include facial diplegia, generalized muscular hypotonia with more proximal than distal weakness, and arthrogryposis. Myotonia is not elicited by percussion and may not be demonstrable by EMG. *(Fenichel, 167)*

**106. (A)** Duchenne and Becker muscular dystrophies are variable phenotypic expressions of a gene defect at the Xp21 site. The abnormal gene produces a reduced muscle content of dystrophin, a structural muscle protein. In Duchenne muscular dystrophy, the dystrophin content is less than 3% of normal, whereas in Becker muscular dystrophy, the dystrophin content is between 3% and 20% of normal. The incidence of Duchenne dystrophy is 1 per 3,500 male births. The initial feature of the disease is gait disturbance. Toe-walking and frequent falling before the age of 5 years are typical. The decline in motor function is linear throughout childhood. Motor function appears static between the age of 3 and 6 years because of cerebral maturation. The immediate cause of death may be an arrhythmia, aspiration, and intercurrent infection. Respiratory insufficiency is a contributing factor in most cases. *(Fenichel, 177–178)*

**107. (A)** Myotonic dystrophy (DM) is a complex multisystemic disorder linked to two different genetic loci. Myotonic dystrophy type 1 (DM1) is caused by an expansion of a CTG repeat located in the 3′ untranslated region (UTR) of DMPK (myotonic dystrophy protein kinase) on chromosome 19q13.3. Myotonic dystrophy type 2 (DM2) is caused by an unstable CCTG repeat in intron 1 of ZNF9 (zinc finger protein 9) on chromosome 3q21. Therefore, both DM1 and DM2 are caused by a repeat expansion in a region transcribed into RNA but not translated into protein. The discovery that these two distinct mutations cause largely similar clinical syndromes put emphasis on the molecular properties they have in common, namely, RNA transcripts containing expanded, nontranslated repeats. The mutant RNA transcripts of DM1 and DM2 aberrantly affect the splicing of the same target RNAs, such as chloride channel 1 (ClC-1) and insulin receptor (INSR), resulting in their shared myotonia and insulin resistance. *(Cho, 195–204)*

**108. (C)** Duchenne muscular dystrophy is the most common hereditary neuromuscular disease affecting all races and ethnic groups. This disease is inherited as an X-linked recessive trait. The abnormal gene is on the X chromosome at the Xp21 locus and is one of the largest genes identified. The defected gene product is a reduced muscle content of a the structural protein dystrophin. Muscle dystrophin is found on the plasma membrane surface in skeletal muscle fibers, on the surfaces of plasma membrane and transverse tubules of cardiac muscle fibers, and on smooth muscle membranes. Cortical dystrophin is found in the hippocampus, amygdala, thalamus, hypothalamus, and neocortex, and a Purkinje cell isoform is found in the cerebellum. *(Goetz, 776–778, 787–789; Fenichel, 177–178)*

**109. (A)** Pompe disease, also referred to as glycogen storage disease type II or acid maltase deficiency, is a rare autosomal recessive disorder caused by mutations in the gene that encodes for [alpha]-glucosidase (GAA). GAA cleaves [alpha] 1,4 and 1,6 linkages in glycogen to release glucose. Deficiency of this enzyme

results in the accumulation of glycogen in various tissues. Pompe disease can present in early infancy, childhood, or adulthood. In general, the clinical presentation is related to the amount of functioning enzyme present. Severe cases of Pompe disease in infants are usually associated with less than 1% enzyme activity (which is the limit of assay sensitivity), and most untreated patients die before reaching 1 year of age. In juvenile or adult patients, residual activity can usually be detected and the disease presents with debilitating muscle weakness and respiratory problems. Pompe disease is caused by mutations in the acid GAA gene on chromosome 17q25.2-q25.3. Almost 200 mutations have been identified. The severity of the clinical phenotype is at least in part felt to be related to the residual enzyme activity. However, absent enzyme function has recently been documented in adult-onset cases. In general, nonsense mutations, or insertions or deletions, leading to disruption of the reading frame result in absence of functioning enzyme. Missense and splice site mutations may result in absence of enzyme activity or allow some functioning enzyme to be translated. *(Katzin, 421–431)*

**110.** **(D)** Hyperkalemic periodic paralysis (hyperPP) is an autosomal dominant disorders due in most cases to mutations in the SCN4A (SkM1) adult skeletal muscle sodium channel gene on chromosome 17q23-25. Typical attacks in hyperPP are characterized by generalized or focal muscle weakness, often precipitated by rest after strenuous exercise. The facial and respiratory muscles are usually spared. Attacks vary in frequency and severity but usually last between minutes and an hour. The serum potassium may be normal during an acute attack. Interictally, there may be clinical or electromyography evidence of myotonia. Lid lag (lagging of upper eyelid on downward gaze) may also be seen. Some patients develop a fixed proximal muscle weakness although it remains unclear whether this is related to the number or severity of attacks. *(Hudson, 547–563; Saperstein, 260–269; Fenichel, 194–196)*

**111.** **(B)** Hypokalemic periodic paralysis (hypoPP) is the most frequent form of periodic paralysis, with an estimated prevalence of 1 per 100,000. HypoPP is also autosomal dominant. However, one third of cases are sporadic, and penetrance is only 50% in women. Most patients note that some form of atypical strenuous exercise or exertion followed by rest or sleep usually precipitates an attack. Other aggravating factors include heavy meals rich in carbohydrates and sodium, alcohol consumption, exposure to cold, and emotional stress. During peak weakness, reflexes are absent and the muscle is electrically unexcitable. Myotonia is usually not present but may be found in the eyelids in some patients. The underlying genetic defect in approximately 70% of patients is a mutation in the calcium channel gene CACNA1S on chromosome 1q31. In 12% of cases, sodium channel gene SCN4A mutations has been identified. In approximately 20% of patients, neither mutation will be identified; the cause for these cases remains unknown. *(Hudson, 547–563; Saperstein, 260–269; Fenichel, 194–196)*

**112.** **(B)** Dejerine–Sottas syndrome (DSS) or Charcot–Marie–Tooth 3 was originally described as a severe demyelinating neuropathy of infancy and childhood associated with slow nerve conduction studies, elevated CSF protein, marked clinical weakness, and hypertrophic nerves with onion-bulb formation. Recent progress in genetics demonstrated that DSS includes a group of patients with different gene defects. DSS-A or CMT1A is heterozygous for PMP-22 point mutations located on chromosome 17 with autosmal dominant transmission. DSS-B or CMT1B is caused by P0 point mutations located on chromosome 1q22 with recessive or dominant transmission. In DSS-C, the transmission is autosomal dominant and the gene defect is located on chromosome 8q23-q24. In CMT 4F, the gene defect is located on chromosome 19q13 and in DSS-EGR2, the gene defect is located on chromosome 10q21.1-q22.1. *(Fenichel, 184–185)*

**113.** **(D)** Emery–Dreifuss muscular dystrophy type 1 is characterized by early contractures and cardiomyopathy. Generally, it is transmitted by X-linked inheritance. The gene is located in Xq28. The abnormal gene product is emerin.

The onset of symptoms occurs in patients between 5 and 15 years of age. The earliest feature of the disease is the development of contractures in the flexor of the elbows, the ankle tendon, and the extensors of the hand. Contractures are followed by muscle weakness and wasting first in the biceps and triceps muscles, then in the deltoid and other shoulder muscles. The peroneal muscles are severely affected. The progression of symptoms is slow and the condition usually stabilizes by the age of 20 years. All patients develop cardiomyopathy, which may lead to atrial paralysis, bradycardia, or syncope. *(Fenichel, 190–191)*

**114.** **(A)** The patient described in the vignette has signs of chronic polyneuropathy, cerebellar ataxia, decreased deep tendon reflexes, and night blindness. These signs are highly suggestive of Refsum disease. It is a hereditary motor and sensory polyneuropathy type IV, which is an autosomal recessive disorder caused by an inborn error in the metabolism of phytanic acid. The clinical picture may include, beside the symptoms described in the vignette, progressive hearing loss, cardiomyopathy, ichthyosis, and pes cavus. The diagnosis is confirmed by showing reduced oxidation of phytanic acid in cultured fibroblasts. *(Fenichel, 186–187)*

**115.** **(A)** The patient described in this case has a generalized myotonic syndrome. The association of generalized muscle hypertrophy and myotonic discharges on EMG examination is suggestive of myotonia congenita. Transmission of the disorder is either autosomal dominant or recessive. The abnormal gene is located on chromosome 17q23-35. Clinical features are stereotyped. At rest, muscles are stiff, with difficulty in moving, which improves with activity. The myotonia causes generalized muscle hypertrophy, which gives the infant a Herculean appearance. The diagnosis is established by EMG, which shows repetitive discharges at rates of 20 to 80 Hz when the needle is inserted into the muscle or on voluntary contraction (myotonic discharges). Muscle biopsy shows the absence of type II fibers. The absence of involuntary muscle twitching, excessive sweating, and the improvement of stiffness by exercise make the diagnosis of neuromyotonia unlikely. The absence of skeletal deformities rules out Schwartz–Jampel syndrome. Stiff-person syndrome is an autoimmune condition that is extremely rare in children. It is characterized by involuntary truncal muscle tightness without spinal deformity. Abdominal wall rigidity and contraction of the thoracolumbar paraspinal muscles cause a hyperlordosis that is characteristic of the disease. The patient described in the vignette does not have the features of stiff-person syndrome. *(Fenichel, 154–155)*

**116.** **(C)** The patient described in this case has pain and muscle weakness associated with mild rhabdomyolysis and failure to generate ammonia on an ischemic exercise test. These features are suggestive of myoadenylate deaminase deficiency, an autosomal recessive disease. The defective gene is located on chromosome 1p. Myoadenylate deaminase deficiency most commonly presents with isolated muscle weakness, fatigue, and myalgias following moderate-to-vigorous exercise. Myalgias may be associated with an increased serum creatine kinase level and detectable electromyelographic abnormalities. Muscle wasting or histologic changes on biopsy are absent. The age of onset may be as early as 8 months of life. The enzyme defect has been identified in asymptomatic family members. The disorder may be screened for by performing an exercise test. The normal elevation of venous plasma ammonia following exercise that is seen in normal subjects is absent in myoadenylate deaminase deficiency. The final diagnosis is made by histochemical or biochemical assays of a muscle biopsy. The absence of external ophthalmoplegia, pigmentary degeneration of the retina, and heart block make the diagnosis of Kearns–Sayre syndrome unlikely. Brody disease is caused by a deficiency of calcium-activated ATPase in the sarcoplasmic reticulum. Stiffness becomes worse with exercise. Ischemic exercise results are normal. Muscle biopsy results reveal type II atrophy. Biochemical studies confirm the diagnosis. The age of onset and the absence of myoclonic seizures rule out Menkes syndrome,

a disorder of intestinal copper transport that starts at the age of 3 months. Most patients die before the age of 18 months. Carnitine palmitoyl transferase deficiency causes exercise intolerance and reduced production of ketone bodies in the blood or urine during fasting. *(Behrman, 492; Fenichel, 207)*

**117.** **(A)** The association of limb ataxia with photosensitivity indicates the diagnosis of Hartnup disease. This is a disorder transmitted by autosomal recessive inheritance. It is caused by a defect of neutral amino acid transport in cells of the proximal cell tubules and small intestine. The result is massive aminoaciduria and retention of amino acids in the small intestine, where they may be converted into absorbed toxic products. Clinical features include limb ataxia, nystagmus, decreased tone, and pellagra-like skin lesions after exposure to sunlight because of nicotinamide deficiency. Mental change may occur, ranging from emotional instability to delirium. Administration of nicotinamide may prevent the rash. *(Fenichel, 222)*

**118.** **(E)** Progressive ataxia with an increased blood level of very long chain fatty acids occurs in adrenoleukodystrophy. This is an X-linked disorder associated with the accumulation of saturated very long chain fatty acids and progressive dysfunction of the adrenal cortex and nervous system white matter. Excess hexacosanoic acid is the most striking and characteristic feature. This accumulation of fatty acids is due to genetically determined deficient degradation of fatty acids, which is a normal peroxisomal function. Sulfatide lipidosis is a disorder of central and peripheral myelin metabolism caused by deficient activity of the enzyme arylsulfatase A. Abetalipoproteinemia is a disorder of lipid metabolism transmitted by autosomal recessive inheritance. Apolipoprotein B is essential for the synthesis and integrity of low-density and very low density lipoproteins. Its absence results in fat malabsorption and a progressive deficiency of vitamins A, E, and K. Clinical features include progressive cerebellar ataxia, delayed psychomotor development, and retinitis pigmentosa. Laboratory features include severe anemia, the presence of acanthocytes, low cholesterol, and low triglyceride levels. Ataxia telangiectasia is a multisystem disorder affecting the nervous and immune systems. It is transmitted by autosomal recessive inheritance. The abnormal gene is located on chromosome 11. Clinical features include chronic sinopulmonary infections, truncal ataxia, oculomotor apraxia, and telangiectasias. Ramsay Hunt syndrome is a progressive degeneration of the dentate nucleus and superior cerebellar peduncle characterized by myoclonus and cerebellar ataxia without elevation of very long chain fatty acids. *(Behrman, 2032–2033; Fenichel, 145–146)*

**119.** **(E)** The clinical picture described in this question is suggestive of Harp syndrome. This is a genetic disorder transmitted by autosomal recessive inheritance. Clinical features of the disease include retinitis pigmentosa, mild mental abnormalities, dystonic dysarthria, and decreased facial expression. Head MRI shows an eye-of-the-tiger appearance of the pallidum. Acanthocytes and echinocytes are seen in preparations of washed erythrocytes. *(Behrman, 2020–2023; Ching, 1673–1674; Goetz, 725)*

**120.** **(B)** The patient described in this vignette presents a clinical picture highly suggestive of Hallervorden–Spatz disease. This is a rare degenerative disorder inherited as an autosomal recessive trait. Linkage analysis indicates that the gene is located on chromosome 20p13. The condition usually begins during childhood and is characterized by progressive dystonia, rigidity, and choreoathetosis. Spasticity, extensor plantar responses, dysarthria, and intellectual deterioration become evident during adolescence, and death usually occurs by early adulthood. Head MRI shows lesions of the globus pallidus, including low signal intensity in T2-weighted images (corresponding to iron pigments) and an anteromedial area of high signal intensity or eye-of-the-tiger sign (corresponding to areas of vacuolation). Neuropathological examination indicates excessive accumulation of iron-containing pigments in the globus pallidus and substantia nigra. *(Clement, 26–31; Behrman, 2020–2023; Goetz, 725)*

**121.** **(E)** Sydenham chorea is the most common acquired chorea of childhood and is the sole neurological manifestation of rheumatic fever. The pathogenesis of Sydenham chorea is probably an autoimmune response of the central nervous system to group A streptococcal organisms. The majority of children with Sydenham chorea have antineuronal antibodies, which develop in response to group A beta-hemolytic streptococcal infections. Antineuronal antibodies cross-react with the cytoplasm of subthalamic and caudate nuclei neurons. *(Behrman, 2032–2033; Fenichel, 285–286)*

**122.** **(B)** The combination of encephalopathy and progressive calcification of the basal ganglia is seen in Fahr disease. Affected children may have dwarfism, senile appearance, retinitis pigmentosa, mental retardation, choreoathetotic movements, ataxia, dysarthria, and seizures. Head CT may show calcification that appears first in the dentate nuclei and pons, then in the basal ganglia, and finally in the corpus callosum. *(Behrman, 2032–2033; Fenichel, 284)*

**123.** **(A)** Tardive dyskinesia is characterized by stereotypical facial movements, particularly by lip smacking and protrusion and retraction of the tongue. These are drug-induced choreiform movements. The condition is most often associated with drugs used to modify behavior or with antiemetics. It can occur in children with asthma treated with theophylline. *(Behrman, 2032–2033; Fenichel, 287)*

**124.** **(D)** Neuroacanthocytosis is a rare disorder with autosomal dominant, recessive, or even X-linked inheritance. It is manifested by chorea, tics, dystonia, parkinsonism, self-mutilatory behavior, amyotrophy, areflexia, and elevated creatine phosphokinase. Among the most distinguishing features of neuroacanthocytosis is an eating dysfunction due to orolingual dystonia that is manifested by expulsion of food from the mouth by a protruding tongue. Involuntary vocalizations and parkinsonism also occur. *(Behrman, 2020–2023; Fenichel, 284–285; Goetz, 725)*

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CHAPTER 4

# Neurophysiology, Epilepsy, Evoked Potentials, and Sleep Disorders

## Questions

**1.** What is the frequency of the posterior dominant rhythm at the age of 3 months?

(A) 9 Hz
(B) 7 Hz
(C) 6 Hz
(D) 8 Hz
(E) 4 Hz

**2.** Which of the following statements is true about mu rhythm?

(A) Mu activity is increased with movements of the contralateral arm.
(B) Mu amplitude is usually higher than the amplitude of alpha rhythm.
(C) It is always unilateral.
(D) Mu activity should be considered normal even if it is persistent in a region of focal slowing.
(E) Mu activity may slow gradually with aging.

**3.** Which of the following drugs have the *least* effect on beta rhythm?

(A) Phenobarbital
(B) Valproic acid
(C) Clonazepam
(D) Chloral hydrate
(E) Amitriptyline

**4.** Which of the following cardinal features of stage II sleep is *not* seen in stage I sleep?

(A) Alpha attenuation
(B) Positive occipital sharp transient
(C) Sleep spindles
(D) Vertex sharp transient
(E) Increased frontocentral beta rhythm

**5.** Which of the following statements is true about photomyoclonic response?

(A) It occurs in the occipital area when the flashing light evokes facial muscle contraction.
(B) It is enhanced in case of barbiturate withdrawal.
(C) It is reduced in case of ethanol withdrawal.
(D) Stimulation rate of 2 Hz is most effective in producing a photomyoclonic response.
(E) The amplitude of muscle contraction decreases as the photic stimulation continues.

**6.** Well-formed synchronous sleep spindles appear at the age of

(A) 1 month
(B) 3 months
(C) 4 months
(D) 6 months
(E) 2 years

**7.** During the neonatal period, trace discontinue first appears during the gestational age of

(A) 25 weeks
(B) 30 weeks
(B) 32 weeks
(C) 35 weeks
(D) 37 weeks
(E) 40 weeks

**8.** During the neonatal period, trace alternant first appears during the gestational age of

(A) 32 weeks
(B) 33 weeks
(C) 34 weeks
(D) 35 weeks
(E) 36 weeks

**9.** During the neonatal period, *activité moyenne* first appears during the gestational age of

(A) 32 weeks
(B) 33 weeks
(C) 34 weeks
(D) 35 weeks
(E) 36 weeks

**10.** During the neonatal period, continuous slow-wave sleep first appears during the gestational age of

(A) 40 weeks
(B) 41 weeks
(C) 42 weeks
(D) 43 weeks
(E) 44 weeks

**11.** An asynchronous burst of hemispheric activity is defined as activity in one hemisphere leading the other by more than

(A) 5 seconds
(B) 0.5 second
(C) 1 second
(D) 1.5 seconds
(E) 3 seconds

**12.** Which of the following is true about delta brushes?

(A) They represent the fusion of underlying delta transient with a superimposed rhythmic fast activity.
(B) They occur only during active sleep.
(C) They disappear by the age of 1 year.
(D) Frontal delta brushes are frequent at any age.
(E) They are more common in the occipital area at the conceptional age of 29 weeks.

**13.** Sleep spindles appear for the first time at a conceptional age of

(A) 32 weeks
(B) 36 weeks
(C) 40 weeks
(D) 46 weeks
(E) 50 weeks

**14.** Which of the following is true about active sleep in a full-term neonate?

(A) Eyes are always closed.
(B) There is increased muscle tone.
(C) There is no body or facial movement.
(D) Respiration is irregular.
(E) Active sleep comprises 30% of the time spent in sleep by a full-term neonate.

**15.** Photomyogenic response is

(A) an epileptiform discharge triggered by photic stimulation
(B) a spike-like driving response
(C) of noncerebral origin
(D) less frequent than the flashing stimulus
(E) felt to be an abnormal response to high-intensity light

**16.** Posterior predominant activity during wakefulness blocked by eye opening is suggestive of

(A) alpha activity
(B) alpha rhythm
(C) temporal transient
(D) Bancaud phenomenon
(E) posterior slowing of youth

**17.** Failure of alpha rhythm to block on eye opening is suggestive of

(A) alpha activity
(B) alpha rhythm
(C) temporal transient
(D) Bancaud phenomenon
(E) posterior slowing of youth

**18.** Sail wave is also called

(A alpha activity
(B) alpha rhythm
(C) temporal transient
(D) Bancaud phenomenon
(E) posterior slowing of youth

**19.** Sylvian theta activity that seems to be related to normal aging is suggestive of

(A) alpha activity
(B) alpha rhythm
(C) temporal transient
(D) Bancaud phenomenon
(E) posterior slowing of youth

**20.** Triphasic waves are not seen in

(A) renal failure
(B) hepatic failure
(C) hyponatremia
(D) hypoglycemia
(E) hypoparathyroidism

**21.** Which of the following EEG waves is the *least* likely to be seen in anoxic encephalopathy?

(A) Burst suppression pattern
(B) Periodic spike or sharp waves
(C) Alpha coma pattern
(D) Delta brushes
(E) Bihemispheric epileptiform discharges

**22.** The EEG pattern most commonly seen in dialysis dementia is

(A) the bilateral spike-and-wave complex
(B) triphasic waves
(C) the alpha pattern
(D) bihemispheric lateral epileptiform discharges
(E) the burst suppression pattern

**23.** Benzodiazepine overdose typically shows an EEG pattern of

(A) triphasic waves
(B) widespread high-amplitude beta activity
(C) burst suppression pattern
(D) alpha coma
(E) spontaneous epileptiform spike and wave

**24.** In which stage of Rett syndrome does the EEG show background slowing with focal spike or sharp waves, most commonly over the centroparietal region?

(A) Stage 1
(B) Stage 2
(C) Stage 3
(D) Stage 4
(E) None of the above

**25.** Which of the following is true about EEG guidelines in the determination of brain death in adults?

(A) Minimum of four scalp and two ear electrodes
(B) Electrode impedances between 1,000 and 100 ohms
(C) Instrument sensitivity set at 20 $\mu$V/mm
(D) Interelectrode distance of 8 cm or less
(E) Monitoring for artifact, EMG, and ECG

**26.** Which of the following EEG patterns has the best prognosis in case of anoxic encephalopathy?

(A) Nearly isoelectric record
(B) Dominant alpha rhythm with scattered theta activity
(C) Dominant theta activity with rare alpha activity
(D) Invariant low-amplitude delta activity unresponsive to stimulus
(E) Continuous polymorphic slow delta waves with little activity and fast frequency

**27.** In which of the following conditions does alpha coma cause the abnormal alpha rhythm to have some reactivity and to be more prominent over the posterior head region?

(A) Ventral pons ischemic stroke
(B) Cardiorespiratory arrest
(C) Barbiturate overdose
(D) Benzodiazepine overdose
(E) Methaqualone overdose

**28.** A relatively low voltage mixed (2 Hz to 7 Hz) frequency EEG with episodic rapid eye movements and absent or reduced chin EMG activity are suggestive of which of the following sleep stages?

(A) Stage N1
(B) Stage N2
(C) Stage N3
(D) Wakefulness
(E ) Rapid eye movement (REM) sleep

**29.** Monophasic triangular waves in the occipital region define

(A) mu rhythm
(B) positive occipital sharp transients
(C) lambda waves
(D) wicket spikes
(E) benign epileptiform transients of sleep

**30.** Small sharp spikes seen in adults during drowsiness without distortion of the background activity define

(A) mu rhythm
(B) positive occipital sharp transients
(C) lambda waves
(D) wicket spikes
(E) benign epileptiform transients of sleep

**31.** Arc-like waves typically occur in trains. They are often mistaken for a temporal spike and are suggestive of

(A) mu rhythm
(B) positive occipital sharp transients
(C) lambda waves
(D) wicket spikes
(E) benign epileptiform transients of sleep

**32.** Which of the following is true of lambda waves?

(A) Monophasic triangular waves in the occipital region.
(B) Small sharp spikes seen in adults during drowsiness without distortion of the background activity.
(C) Arc-like waves typically occurring in trains that are often mistaken for a temporal spike.
(D) They may represent an evoked cerebral response to visual stimulus produced from shifts of images across the retina in the course of saccadic eye movements.
(E) Rolandic alpha activity.

**33.** Rolandic alpha activity is also called

(A) mu rhythm
(B) positive occipital sharp transients
(C) lambda waves
(D) wicket spikes
(E) benign epileptiform transients of sleep

**34.** The metabolism of phenytoin slows substantially when its serum concentration reaches

(A) 10 μg/dL
(B) 15 μg/dL
(C) 20 μg/dL
(D) 25 μg/dL
(E) 30 μg/dL

**35.** Which of the following drugs reduces the level of serum phenytoin?

(A) Rifampin
(B) Cimetidine
(C) Chloramphenicol
(D) Isoniazid
(E) Dicumarol

**36.** Which of the following drugs alters the free phenytoin level without altering the total measured serum level?

(A) Sulfonamides
(B) Chlorenphenicol
(C) Disulfiram
(D) Antacids
(E) Salicylates

**37.** Which of the following antiepileptic drugs is a calcium channel blocker?

(A) Phenytoin
(B) Carbamazepine
(C) Ethosuximide
(D) Phenobarbital
(E) Valproic acid

**38.** The addition of valproic acid to a chronic regimen of phenytoin causes immediate

(A) valproic acid toxicity
(B) phenytoin toxicity
(C) a higher serum concentration of phenytoin
(D) a lower serum concentration of phenytoin
(E) a lower serum concentration of valproic acid

**39.** Wave III evoked potential is generated by

(A) the distal part of the auditory nerve
(B) cortical response to visual evoked potentials
(C) trapezoid body
(D) midbrain
(E) Erb's point

**40.** P100 evoked potential is generated by

(A) distal part of the auditory nerve
(B) cortical response to visual evoked potentials
(C) trapezoid body
(D) midbrain
(E) Erb's point

**41.** N9 evoked potential is generated by

(A) Erb's point
(B) caudal medial lemniscus
(C) primary sensory cortex from median nerve stimulation
(D) lumbar cord
(E) cortical response from posterior tibial nerve stimulation

**42.** N22 evoked potential is generated by

(A) Erb's point
(B) caudal medial lemniscus
(C) primary sensory cortex from median nerve stimulation
(D) lumbar cord
(E) cortical response from posterior tibial nerve stimulation

**43.** Breach rhythm is linked to which of the following EEG variety?

(A) Sleep spindle
(B) Skull defect causes enhanced beta activity
(C) Presence of occipital sharp transient
(D) Delta slowing in 20% to 50% of its record
(E) Unilateral failure of alpha wave blocking on eye opening

**44.** Which of the following is not a side effect of valproic acid?

(A) Hair loss
(B) Weight gain
(C) Essential tremor
(D) Acute pancreatitis
(E) Aplastic anemia

**45.** Which of the following is true of carbamazepine?

(A) It is highly soluble in water.
(B) In the naive patient, the half-life of the drug is about 30 hours; it decreases to 10 hours within a few weeks.
(C) Skin rash is seen less with carbamazepine than with phenytoin.
(D) Hypernatremia may complicate the chronic use of carbamazepine.
(E) It may cause elevation of hepatic enzymes that predispose to hepatitis.

**46.** Which of the following antiseizure medications is *not* metabolized by the liver?

(A) Zonisamide
(B) Levetiracetam
(C) Topiramate
(D) Lamotrigine
(E) Tiagabine

**47.** A 45-year-old man with a history of seizure disorder and ethanol abuse is admitted to the neurology floor because of phenytoin intoxication. His admission phenytoin level is 45 μg/mL. On the second and third days of admission, his levels drop to 35 and 25 μg/mL, respectively. What would be his level on the fourth day of admission?

(A) 15 μg/mL
(B) 10 μg/mL
(C) Unpredictable because phenytoin follows zero-order kinetics
(D) Unpredictable because phenytoin follows first-order kinetics
(E) Unpredictable because the patient is an ethanol abuser

**48.** A 25-year-old man is diagnosed with a complex partial seizure and started on carbamazepine 200 mg PO qid. In the first week of treatment, he developesd blurred vision, nystagmus, dizziness, fatigue, and headache that progressively improve. He asks about these symptoms 2 weeks later. His carbamazepine level was 8 μg/mL. The initial symptoms were due to

(A) a physiological effect of carbamazepine
(B) carbamazepine intoxication
(C) an idiosyncratic reaction to carbamazepine
(D) psychogenic symptoms not related to carbamazepine administration
(E) none of the above

**49.** Which of the following is true of lamotrigine?

(A) The half-life of the drug is not affected by other antiepileptic drugs.
(B) It acts by prolonging inactivation of voltage-sensitive calcium channels.
(C) Cutaneous rash may occur in 10% of cases.
(D) Its antiseizure activity correlates with its ability to inhibit dihydrofolate reductase activity.
(E) It is about 95% protein-bound.

**50.** In case of renal failure, which of the following drugs needs the *least* adjustment?

(A) Ethosuximide
(B) Carbamazepine
(C) Phenytoin
(D) Phenobarbital
(E) Topiramate

**51.** Which of the following antiepileptic drugs is *not* removed by dialysis?

(A) Ethosuximide
(B) Phenobarbital
(C) Gabapentin
(D) Phenytoin
(E) Lamotrigine

**52.** Which of the following drugs is the treatment of choice for infantile spasm?

(A) Carbamazepine
(B) Adrenocorticotropic hormone (ACTH)
(C) Phenobarbital
(D) Topiramate
(E) Phenytoin

**53**. As a side effect, phenytoin may cause

(A) somnolence, headaches, and ataxia
(B) poor memory, cognitive impairment, and Dupuytren contracture with chronic use
(C) cutaneous rash in up to 10% of cases, especially with concomitant administration of valproic acid
(D) weight gain in 50% of cases
(E) cerebellar atrophy and gum hypertrophy with long-term use

**54**. As a side effect, lamotrigine may cause

(A) somnolence, headaches, and ataxia
(B) poor memory, cognitive impairment, and Dupuytren contracture with chronic use
(C) cutaneous rash in up to 10% of cases, especially with concomitant administration of valproic acid
(D) weight gain in 50% of cases
(E) cerebellar atrophy and gum hypertrophy with long-term use

**55**. As a side effect, phenobarbital may cause

(A) somnolence, headaches, and ataxia
(B) poor memory, cognitive impairment, and Dupuytren contracture with chronic use
(C) cutaneous rash in up to 10% of cases, especially with concomitant administration of valproic acid
(D) weight gain in 50% of cases
(E) cerebellar atrophy and gum hypertrophy with long-term use

**56**. As a side effect, carbamazepine may cause

(A) somnolence, headaches, and ataxia
(B) aplastic anemia
(C) cutaneous rash in up to 10% of cases, especially with concomitant administration of valproic acid
(D) weight gain in 50% of cases
(E) hyponatremia

**57**. As a side effect, felbamate may cause

(A) somnolence, headaches, and ataxia
(B) aplastic anemia
(C) cutaneous rash in up to 10% of cases, especially with concomitant administration of valproic acid
(D) weight gain in 50% of cases
(E) hyponatremia

**58**. As a side effect, zonisamide may cause

(A) somnolence, headaches, and ataxia
(B) aplastic anemia
(C) hyponatremia
(D) weight gain in 50% of cases
(E) renal stones

**59.** As a side effect, gabapentin may cause

(A) somnolence, headaches, and ataxia
(B) poor memory, cognitive impairment, and Dupuytren contracture with chronic use
(C) cutaneous rash in up to 10% of cases, especially with concomitant administration of valproic acid
(D) weight gain in 50% of cases
(E) cerebellar atrophy and gum hypertrophy with long-term use

**60**. As side effect, valproic acid may cause

(A) somnolence, headaches, and ataxia
(B) poor memory, cognitive impairment, and Dupuytren contracture with chronic use
(C) cutaneous rash in up to 10% of cases, especially with concomitant administration of valproic acid
(D) weight gain in 50% of cases
(E) cerebellar atrophy and gum hypertrophy with long-term use

**61.** Which of the following drugs is removed by dialysis?

(A) Carbamazepine
(B) Topiramate
(C) Valproic acid
(D) Phenytoin
(E) None of the above

**62.** Which of the following antiepileptic drugs does not inhibit voltage-dependent sodium channels?

(A) Tiagabine
(B) Phenytoin
(C) Carbamazepine
(D) Valproic acid
(E) Zonisamide

**63.** The overall risk of having a baby with a major malformation from a mother taking a single antiepileptic drug is

(A) 2%
(B) 5%
(C) 10%
(D) 15%
(E) 20%

**64.** Which of the following drugs increases the level of phenytoin?

(A) Reserpine
(B) Sucralfate
(C) Amiodarone
(D) Verapamil
(E) Erythromycin

**65.** Which of the following drugs decreases the level of carbamazepine?

(A) Cimetidine
(B) Fluoxetine
(C) Isoniazid
(D) Theophylline
(E) Propoxyphene

**66.** Which of the following drugs may increase EEG beta activity?

(A) Olanzapine
(B) Phenytoin
(C) Carbamazepine
(D) Topiramate
(E) Lorazepam

**67.** What is the most likely EEG pattern seen in a 56-year-old man with acute left parietal ischemic stroke?

(A) Left triphasic wave
(B) Beta asymmetry
(C) Generalized temporal theta
(D) Hypsarrhythmia
(E) PLEDs (periodic lateralizing epileptiform discharges)

**68.** Which of the following is an inhibitor neurotransmitter?

(A) Aspartic acid
(B) Cysteic acid
(C) Glutamic acid
(D) GABA
(E) Homocystic acid

**69.** Hyperventilation is most helpful in which of the following?

(A) A 65-year-old man with recurrence of stroke
(B) An 8-year-old girl with staring spells
(C) A 40-year-old woman with history of depression
(D) A 53-year-old woman with history of cerebral aneurysm
(E) A 10-year-old boy with history of attention deficit–hyperactivity disorder

**70.** Which of the following is true of REM parasomnia?

(A) It shows marked female predominance.
(B) It usually occurs in preschool children.
(C) It often occurs in the first portion of sleep.
(D) It results from lack of normal atonia of REM sleep.
(E) It responds well to treatment with a tricyclic antidepressant.

**71.** Which of the following is more characteristic of complex partial seizure rather than absence seizure?

(A) 3-Hz spike and wave on EEG
(B) Photic stimulation inducing seizure activity in 10% to 30% of cases
(C) Brief period of confusion, emotional disturbance, and headache in the postictal phase.
(D) Hyperventilation most likely increasing the seizure activity in the EEG
(E) Most likely age of onset in childhood or early adulthood

**72.** Which of the following is more suggestive of lateral temporal seizure than medial temporal seizure?

(A) A history of febrile seizure
(B) Autonomic signs or symptoms
(C) Motionless stare
(D) Structured hallucination of visual type during the aura period
(E) Postictal confusion

**73.** Which of the following is *not* characteristic of frontal seizure?

(A) Frequent attacks with clustering
(B) Presence of psychiatric aura
(C) Absence of postictal confusion
(D) Frequent secondary generalization
(E) EEG showing no focal abnormalities ictally or interictally

**74.** The incidence of epilepsy is greater in which of the following degenerative diseases?

(A) Alzheimer disease
(B) Pick disease
(C) Huntington disease
(D) Wilson disease
(E) Amyotrophic lateral sclerosis

**75.** The most frequent inducing factor for reflex epilepsy is

(A) menstruation
(B) visual stimuli
(C) music
(D) eating
(E) bathing in hot water

**76.** Which of the following is true about West syndrome?

(A) Phenobarbital is the treatment of choice.
(B) EEG typically shows burst suppression pattern.
(C) Seizures remit only on antiepileptic medications.
(D) Patients typically show spasms that take the form of sudden brief contractions of the head, neck or trunk, usually in flexion but sometimes in extension.
(E) Long-term prognosis is good, with improvement of mental retardation after the spasms cease.

**77.** In a benign rolandic epilepsy

(A) seizures have a strong tendency to occur during wakefulness
(B) typical seizures are primarily generalized
(C) typical EEG shows focal high-amplitude midtemporal spikes
(D) cognitive function is usually mildly affected
(E) seizures may persist for 5 years after their onset in 90% of cases

**78.** Lennox–Gastaut syndrome is characterized by

(A) onset after the age of 10 years
(B) multiple seizures
(C) absence of mental retardation
(D) seizures precipitated by hyperventilation
(E) a good response to antiepileptic drugs

**79.** Which of the following is true about childhood absence epilepsy?

(A) Monozygotic twins develop absence as frequently as dizygotic twins.
(B) Hyperventilation may precipitate absence more than photic stimulation.
(C) Ten percent of patients with childhood absence epilepsy develop generalized tonic–clonic seizures within 5 to 10 years after the onset of absence seizures.
(D) Typical EEG in childhood absence epilepsy shows generalized bilateral synchronous, symmetric 3-Hz spikes and slow-wave discharges with abnormal background.
(E) By adulthood, remission occurs in only 20% of cases.

**80.** Which of the following is *not* a progressive myoclonic epilepsy?

(A) Juvenile myoclonic epilepsy
(B) Lafora disease
(C) Unverricht–Lundborg disease
(D) Juvenile neuronal ceroid lipofuscinosis
(E) Myoclonic epilepsy with ragged-red fibers

**81.** What is the appropriate EEG pattern of idiopathic generalized epilepsy?

(A) Generalized epileptiform discharges of 3 Hz maximum in the parasagittal region. Normal background. Photic stimulation often induces occipital spikes.
(B) Bitemporal spikes are usually maximal over the temporal frontal region. Ictal EEG shows rhythmic theta at onset.
(C) Posterior 1.5 to 3 spikes and slow waves per second discharges that usually attenuate with eye opening.
(D) Hypsarrhythmia.
(E) Triphasic large-amplitude spikes maximum in the centrotemporal area.

**82.** What is the appropriate EEG pattern of temporal lobe epilepsy?

(A) Generalized epileptiform discharges of 3 Hz maximum in the parasagittal region. Normal background. Photic stimulation often induces occipital spikes.
(B) Bitemporal spikes are usually maximal over the temporal frontal region. Ictal EEG shows rhythmic theta at onset.
(C) Posterior 1.5 to 3 spikes and slow waves per second discharges that usually attenuate with eye opening.
(D) Hypsarrhythmia.
(E) Triphasic large-amplitude spikes maximum in the centrotemporal area.

**83.** What is the appropriate EEG pattern of infantile spasm?

(A) Slow disorganized background. EEG with superadded 1- to 2.5-Hz generalized interiorly predominant and slow-wave discharges.
(B) Bitemporal spikes are usually maximal over the temporal frontal region. Ictal EEG shows rhythmic theta at onset.
(C) Posterior 1.5 to 3 spikes and slow waves per second discharges that usually attenuate with eye opening.
(D) Hypsarrhythmia.
(E) Triphasic large-amplitude spikes maximum in the centrotemporal area.

**84.** What is the appropriate EEG pattern of benign rolandic epilepsy?

(A) Slow, disorganized background. EEG with superadded 1- to 2.5-Hz generalized interiorly predominant and slow-wave discharges.
(B) Bitemporal spikes are usually maximal over the temporal frontal region. Ictal EEG shows rhythmic theta at onset.
(C) Posterior 1.5 to 3 spikes and slow waves per second discharges that usually attenuate with eye opening.
(D) Hypsarrhythmia.
(E) Triphasic large-amplitude spikes maximum in the centrotemporal area.

**85.** What is the appropriate EEG pattern of benign occipital epilepsy?

(A) Slow, disorganized background. EEG with superadded 1- to 2.5-Hz generalized interiorly predominant and slow-wave discharges.
(B) Bitemporal spikes are usually maximal over the temporal frontal region. Ictal EEG shows rhythmic theta at onset.
(C) Posterior 1.5 to 3 spikes and slow waves per second discharges that usually attenuate with eye opening.
(D) Hypsarrhythmia.
(E) Triphasic large-amplitude spikes maximum in the centrotemporal area.

**86.** What is the appropriate EEG pattern of Lennox–Gastaut syndrome?

(A) Slow, disorganized background. EEG with superadded 1- to 2.5-Hz generalized interiorly predominant and slow-wave discharges.
(B) Bitemporal spikes are usually maximal over the temporal frontal region. Ictal EEG shows rhythmic theta at onset.
(C) Posterior 1.5 to 3 spikes and slow waves per second discharges that usually attenuate with eye opening.
(D) Hypsarrhythmia.
(E) Triphasic large-amplitude spikes maximum in the centrotemporal area.

**87.** Seizure and impaired cognitive function occurs in $G_{M2}$ gangliosidosis. The disorder is characterized by

(A) reduced N-acetylneuraminidase activity in leukocytes
(B) spongiform leukodystrophy with deficiency in aspartoacylase
(C) polyglucosans found in the peripheral muscle and liver
(D) sphingomyelinase activity is decreased in leukocytes
(E) reduced hexosaminidase activity in leukocytes

**88.** Seizure and impaired cognitive function occurs in $G_{M1}$ gangliosidosis. The disorder is characterized by

(A) reduced N-acetylneuraminidase activity in leukocytes
(B) spongiform leukodystrophy with deficiency in aspartoacylase
(C) polyglucosans found in the peripheral muscle and liver
(D) sphingomyelinase activity is decreased in leukocytes
(E) reduced beta galactosidase activity in leukocytes

**89.** Seizure and impaired cognitive function occurs in Niemann–Pick disease. The disorder is characterized by

(A) reduced N-acetylneuraminidase activity in leukocytes
(B) spongiform leukodystrophy with deficiency in aspartoacylase
(C) polyglucosans found in the peripheral muscle and liver
(D) sphingomyelinase activity decreased in leukocytes
(E) reduced beta galactosidase activity in leukocytes

**90.** Seizure and impaired cognitive function occurs in Gaucher disease. The disorder is characterized by

(A) reduced N-acetylneuraminidase activity in leukocytes
(B) spongiform leukodystrophy with deficiency in aspartoacylase
(C) reduced beta glucocerebrosidase activity in leukocytes
(D) sphingomyelinase activity decreased in leukocytes
(E) reduced beta galactosidase activity in leukocytes

**91.** Seizure and impaired cognitive function occurs sialidosis. The disorder is characterized by

(A) reduced N-acetylneuraminidase activity in leukocytes
(B) spongiform leukodystrophy with deficiency in aspartoacylase
(C) reduced beta glucocerebrosidase activity in leukocytes
(D) sphingomyelinase activity decreased in leukocytes
(E) reduced beta galactosidase activity in leukocytes

**92.** Seizure and impaired cognitive function occurs in the presence of Lafora bodies. The disorder is characterized by

(A) reduced N-acetylneuraminidase activity in leukocytes
(B) spongiform leukodystrophy with deficiency in aspartoacylase
(C) reduced beta glucocerebrosidase activity in leukocytes
(D) sphingomyelinase activity decreased in leukocytes
(E) polyglucosans found in the peripheral muscle and liver

**93.** Seizure and impaired cognitive function occurs in metachromatic leukodystrophy. The disorder is characterized by

(A) reduced N-acetylneuraminidase activity in leukocytes
(B) spongiform leukodystrophy with deficiency in aspartoacylase
(C) reduced beta glucocerebrosidase activity in leukocytes
(D) sphingomyelinase activity is decreased in leukocytes
(E) reduced arylsulfatase activity

**94.** Seizure and impaired cognitive function occurs in adrenoleukodystrophy. The disorder is characterized by

(A) defective lignoceroyl CoA
(B) spongiform leukodystrophy with deficiency in aspartoacylase
(C) reduced hexosaminidase activity in leukocytes
(D) sphingomyelinase activity decreased in leukocytes
(E) polyglucosans found in the peripheral muscle and liver

**95.** Seizure and impaired cognitive function occurs in globoid leukodystrophy. The disorder is characterized by

(A) defective lignoceroyl CoA
(B) spongiform leukodystrophy with deficiency in aspartoacylase
(C) reduced hexosaminidase activity in leukocytes
(D) sphingomyelinase activity decreased in leukocytes
(E) reduced galactocerebroside beta-galactosidase in leukocytes

**96.** Seizure and impaired cognitive function occurs in Canavan disease. The disorder is characterized by

(A) defective lignoceroyl CoA
(B) spongiform leukodystrophy with deficiency in aspartoacylase
(C) reduced hexosaminidase activity in leukocytes
(D) sphingomyelinase activity decreased in leukocytes
(E) reduced galactocerebroside beta-galactosidase in leukocytes

**97.** Which of the following is an X-linked disorder characterized by abnormal copper metabolism?

(A) MELAS syndrome (myopathy, encephalopathy, lactic acidosis, stroke)
(B) Nonketotic hyperglycinemia
(C) Wilson disease
(D) Porphyria
(E) Menkes disease

**98.** Which of the following disorders is characterized by the formation of Kayser–Fleischer rings?

(A) MELAS syndrome (myopathy, encephalopathy, lactic acidosis, stroke)
(B) Nonketotic hyperglycinemia
(C) Wilson disease
(D) Porphyria
(E) Menkes disease

**99.** Which of the following is characterized by reduced activity of glycine cleavage enzyme?

(A) MELAS syndrome (myopathy, encephalopathy, lactic acidosis, stroke)
(B) Nonketotic hyperglycinemia
(C) Wilson's disease
(D) Porphyria
(E) Menkes disease

**100.** Which of the following is characterized by a respiratory chain enzymes defect?

(A) MELAS syndrome (myopathy, encephalopathy, lactic acidosis, stroke)
(B) Nonketotic hyperglycinemia
(C) Wilson disease
(D) Porphyria
(E) Menkes disease

**101.** Which of the following is characterized by exacerbation of seizures when carbamazepine is used?

(A) MELAS syndrome (myopathy, encephalopathy, lactic acidosis, stroke)
(B) Nonketotic hyperglycinemia
(C) Wilson disease
(D) Porphyria
(E) Menkes disease

**102.** Failure of oral contraception may be caused by which of the following antiepileptic drugs?

(A) Vigabatrin
(B) Carbamazepine
(C) Valproate
(D) Gabapentin
(E) Benzodiazepine

**103.** Which of the following causes of seizure carries the best prognosis after surgical resection?

(A) Hippocampal sclerosis
(B) Large arteriovenous malformation
(C) Gross cortical dysplasia
(D) Small low-grade glioma
(E) Trauma

**104.** Which of the following polysomnographic patterns is observed in REM sleep behavior disorder?

(A) Short sleep latency, excessive disruption of sleep with frequent arousals, reduced total sleep time, excessive body movement, and reduced slow-wave sleep
(B) Reduction of slow-wave sleep, reduced REM and total sleep time, increased sleep latency, and increased number of awakenings during sleep
(C) Reduced total sleep time, decreased REM and slow-wave sleep, reduction of sleep spindle and K complexes, and increased sleep fragmentation
(D) Absence of muscle atonia during REM sleep, with increased muscle tone activity in upper and lower limbs
(E) Periodic limb movements

**105.** Which of the following polysomnographic patterns is observed in multiple system atrophy?

(A) Short sleep latency, excessive disruption of sleep with frequent arousals, reduced total sleep time, excessive body movement, and reduced slow-wave sleep
(B) Reduction of slow-wave sleep, reduced REM and total sleep time, increased sleep latency, and increased number of awakenings during sleep
(C) Reduced total sleep time, decreased REM and slow-wave sleep, reduction of sleep spindle and K complexes, and increased sleep fragmentation
(D) Absence of muscle atonia during REM sleep, with increased muscle tone activity in upper and lower limbs
(E) Periodic limb movements

**106.** Which of the following polysomnographic patterns is observed in restless leg syndrome?

(A) Short sleep latency, excessive disruption of sleep with frequent arousals, reduced total sleep time, excessive body movement, and reduced slow-wave sleep
(B) Reduction of slow-wave sleep, reduced REM and total sleep time, increased sleep latency, and increased number of awakenings during sleep
(C) Reduced total sleep time, decreased REM and slow-wave sleep, reduction of sleep spindle and K complexes, and increased sleep fragmentation
(D) Absence of muscle atonia during REM sleep, with increased muscle tone activity in upper and lower limbs
(E) Periodic limb movements

**107.** Which of the following polysomnographic patterns is observed in narcolepsy?

(A) Short sleep latency, excessive disruption of sleep with frequent arousals, reduced total sleep time, excessive body movement, and reduced slow-wave sleep
(B) Reduction of slow-wave sleep, reduced REM and total sleep time, increased sleep latency, and increased number of awakenings during sleep
(C) Reduced total sleep time, decreased REM and slow-wave sleep, reduction of sleep spindle and K complexes, and increased sleep fragmentation
(D) Absence of muscle atonia during REM sleep, with increased muscle tone activity in upper and lower limbs
(E) Periodic limb movements

**108.** Which of the following polysomnographic patterns is observed in Alzheimer disease?

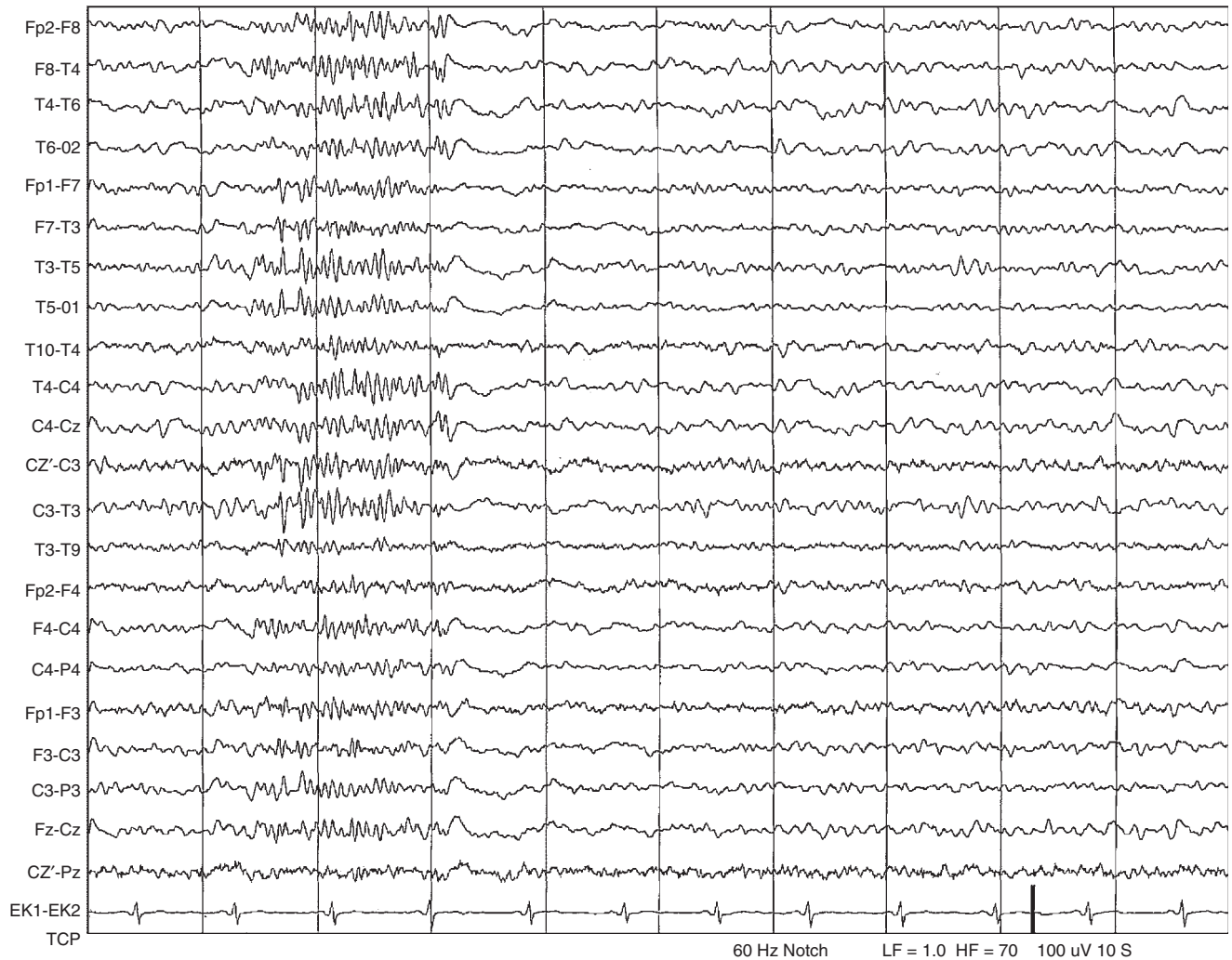
(A) Short sleep latency, excessive disruption of sleep with frequent arousals, reduced total sleep time, excessive body movement, and reduced slow-wave sleep
(B) Reduction of slow-wave sleep, reduced REM and total sleep time, increased sleep latency, and increased number of awakenings during sleep
(C) Reduced total sleep time, decreased REM and slow-wave sleep, reduction of sleep spindle and K complexes, and increased sleep fragmentation
(D) Absence of muscle atonia during REM sleep, with increased muscle tone activity in upper and lower limbs
(E) Periodic limb movements

**Questions 109 through 115**

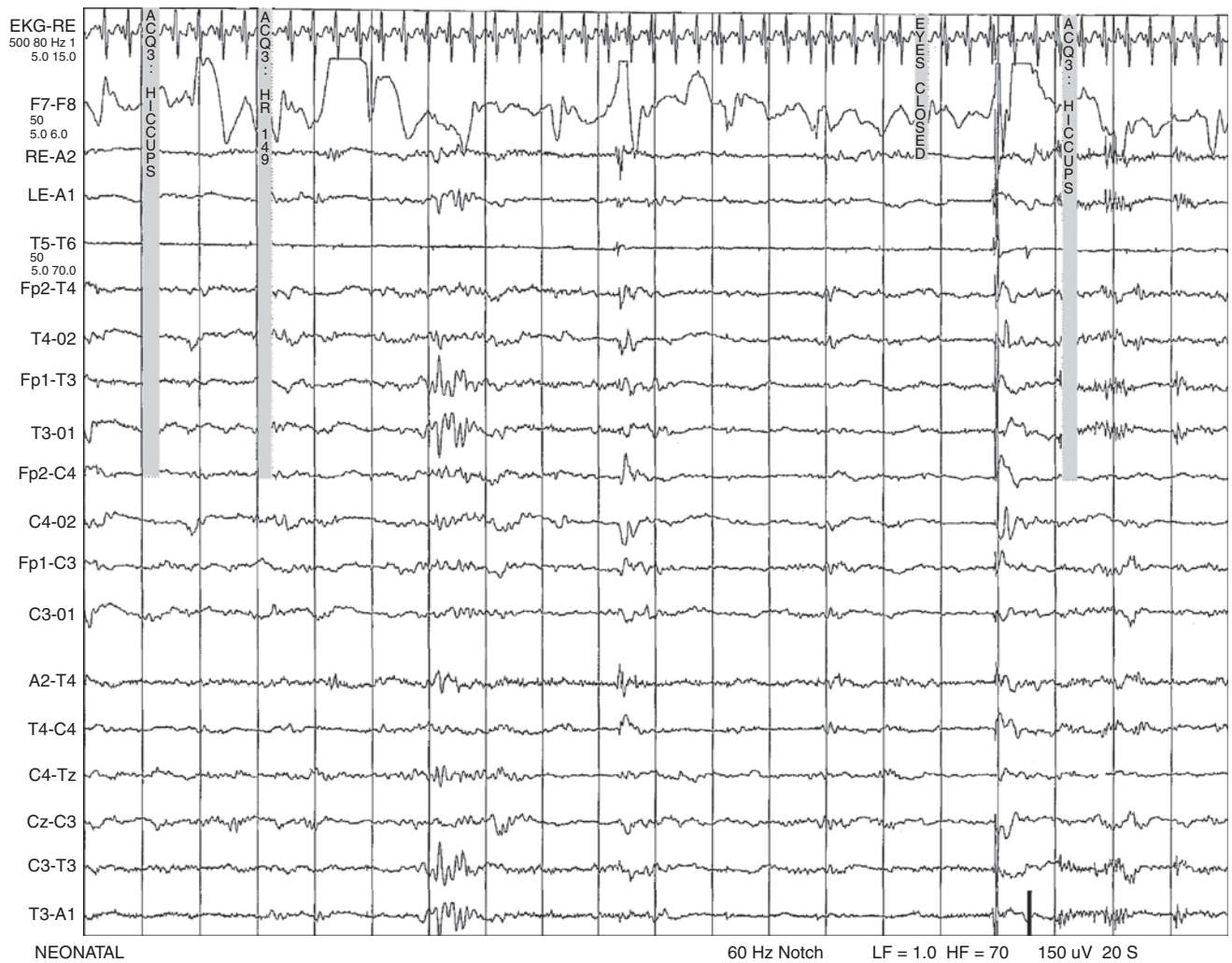
Link each EEG pattern to the appropriate description.

(A) Hepatic failure
(B) Hypsarrhythmia
(C) K complexes
(D) Stage I of sleep
(E) Absence seizures
(F) Porencephaly
(G) Normal EEG pattern at the conceptional age of 29 weeks

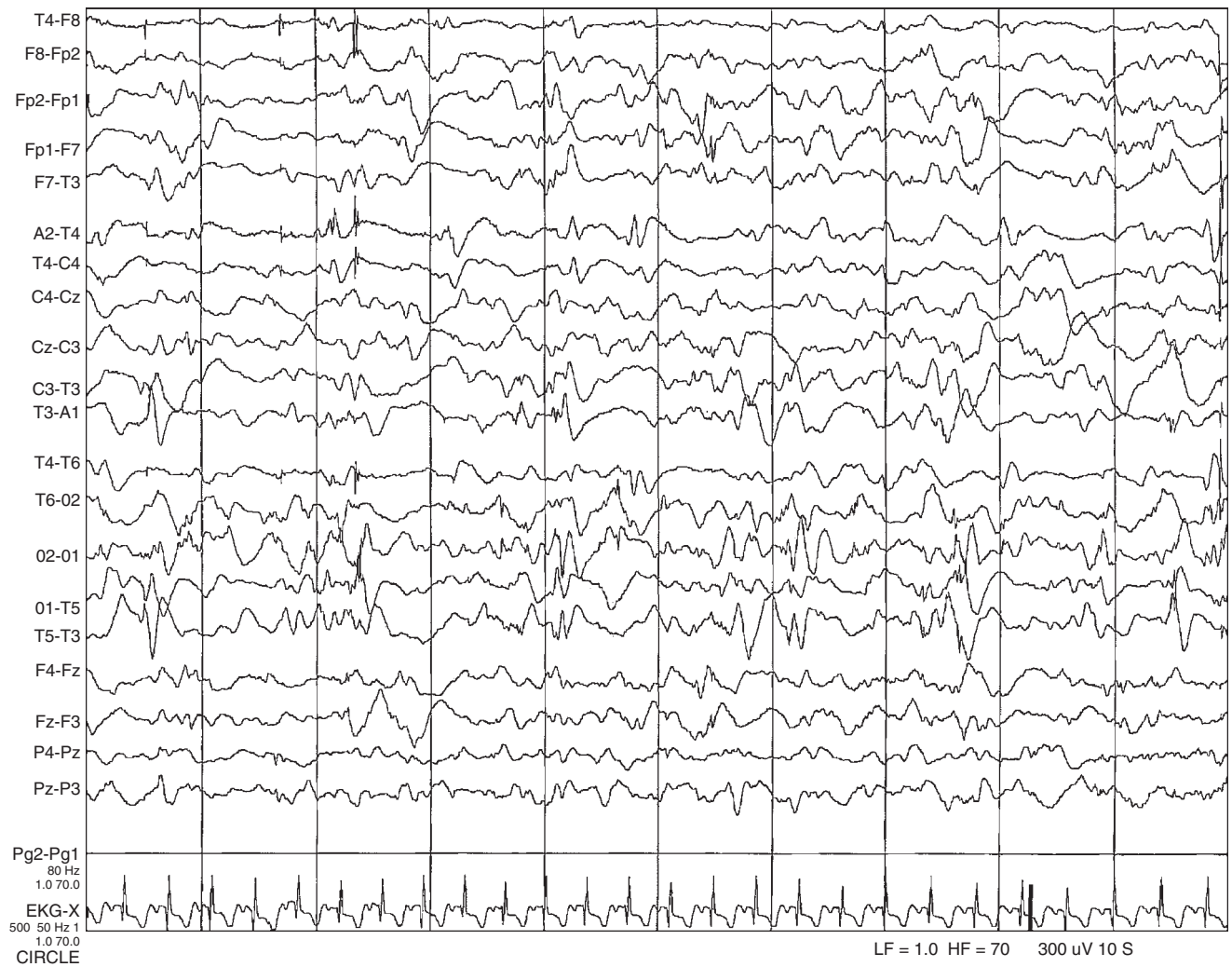
**109.** Fig. 4-1; EEG 1



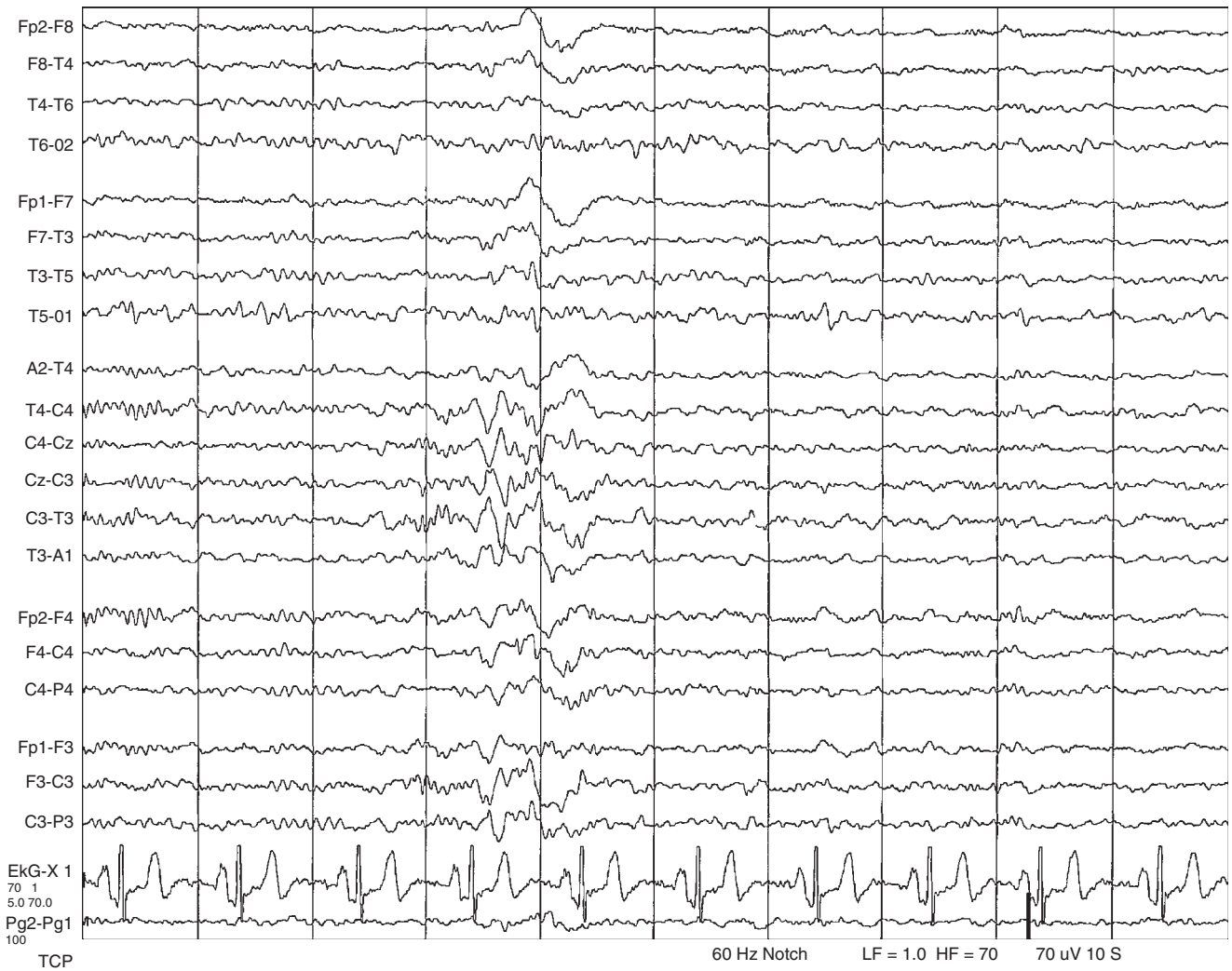
**110.** Fig. 4-2; EEG 2



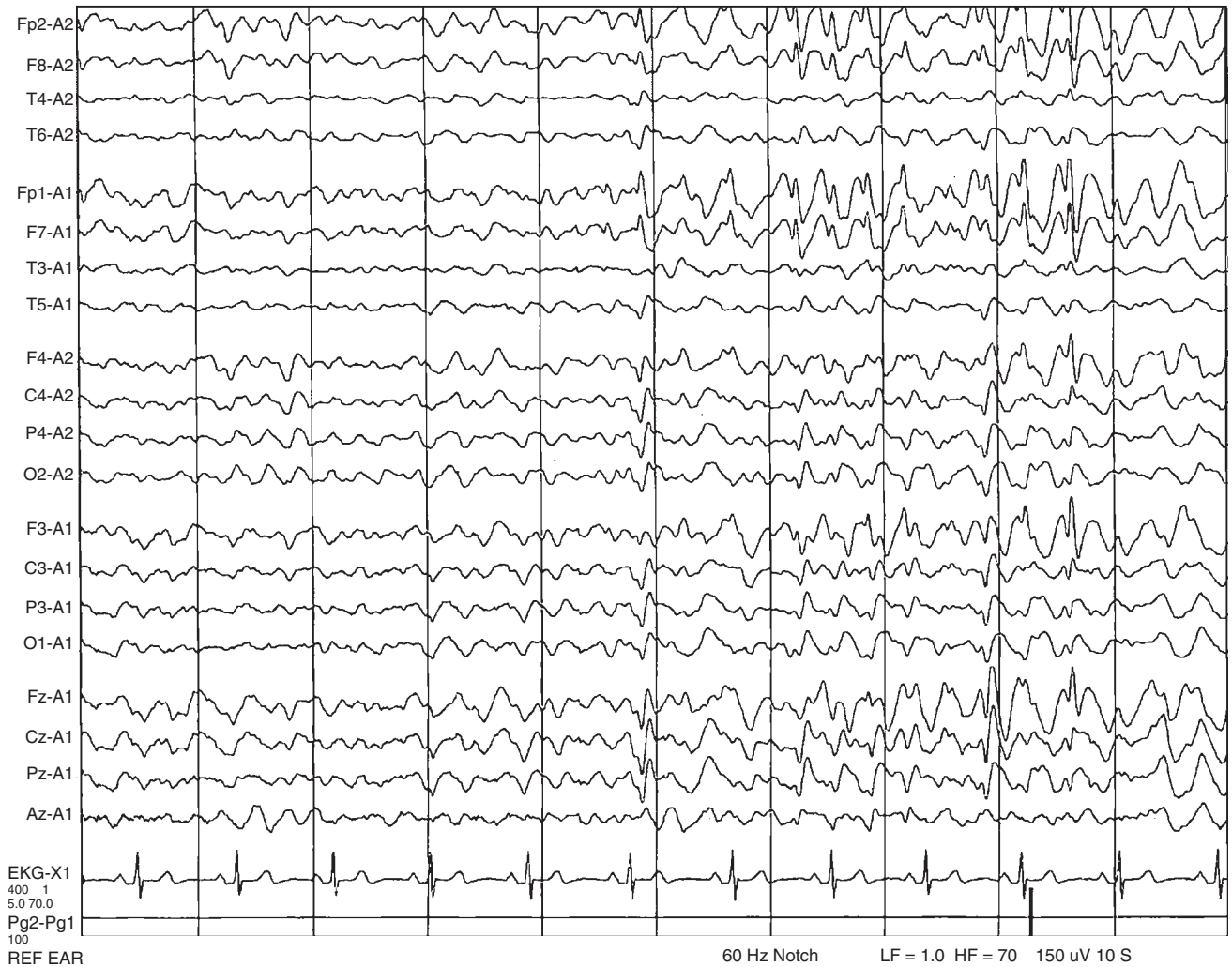
**111.** Fig. 4-3; EEG 3



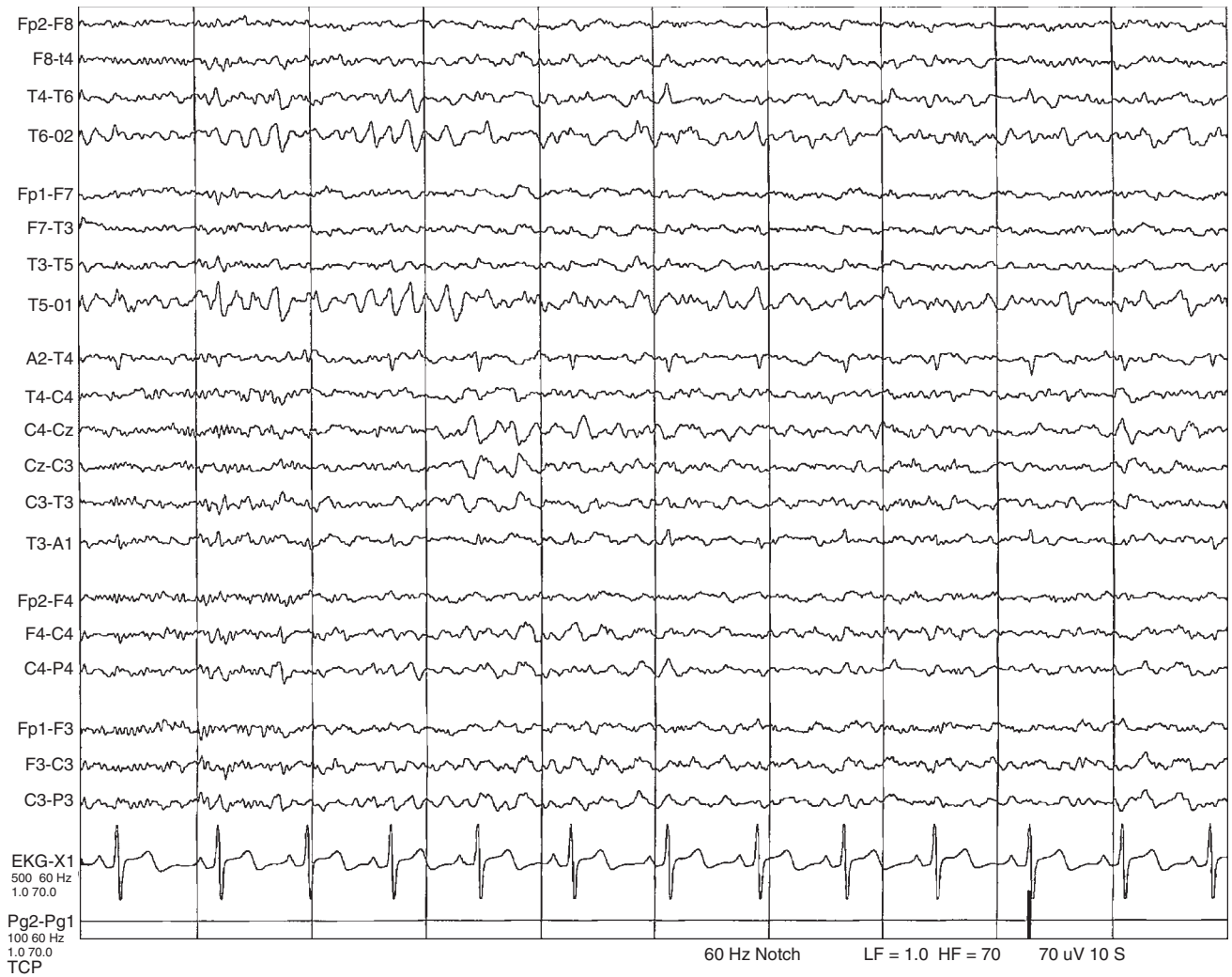
**112.** Fig. 4-4; EEG 4



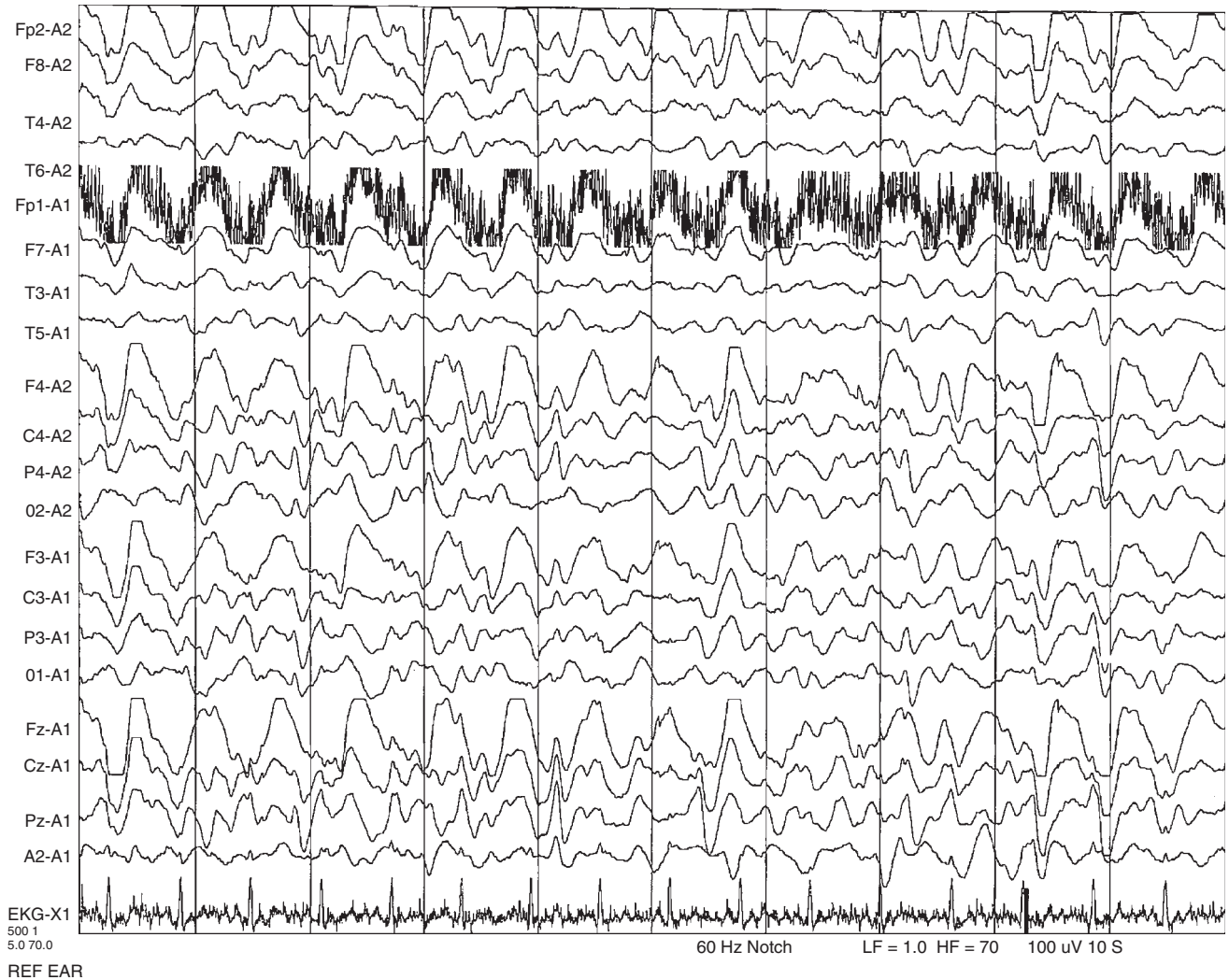
**113.** Fig. 4-5; EEG 5



**114.** Fig. 4-6; EEG 6



**115.** Fig. 4-7; EEG 7



**116.** Tetrodotoxin

(A) blocks the opening of voltage-gated sodium channels
(B) inactivates voltage-gated potassium channels
(C) prolongs the duration of action potential
(D) prolongs the opening of voltage-gated potassium channels
(E) prolongs the opening of voltage-gated sodium channels

**117.** Retrograde axonal transport

(A) occurs at a speed rate of 1 mm/day
(B) is based on the action of kinesin
(C) carries actin from the cell body toward axonal terminals
(D) is used by the rabies virus to reach the neural cell body
(E) is used by radioactively labeled amino acids when injected into neuronal cells body to be transported to the corresponding axons

**118.** Astrocyte cells

(A) propagate action potential
(B) are derived from the mesoderm
(C) are responsible for neuron myelination in the central nervous system
(D) are able to become phagocytic scavengers in the central nervous system
(E) provide a pathway for neuronal migration

**119**. Merkel cells

(A) are activated by motion
(B) are crucial to reading Braille
(C) are rapidly adapting receptors
(D) Ia fibers are the corresponding afferent fibers
(E) respond to joint position

**120.** Which of the following receptors is a proprioceptive receptor?

(A) Meissner corpuscule
(B) Pacinian corpuscle
(C) Hair follicle
(D) Nuclear bag fiber
(E) Merkel cell

**121.** Gap junction channels

(A) provide high-resistance synaptic transmission
(B) provide the ultrastructural components of electrical synapses
(C) are usually involved in a unidirectional synapse
(D) cause significant delay in synaptic transmission
(E) activate chemical transmitters in the synaptic transmission

**122.** The process by which photons are detected and the information is transduced into an electrochemical signal is performed by

(A) rods
(B) ganglion cells
(C) bipolar cells
(D) horizontal cells
(E) amacrine cells

**123.** Rods

(A) have a resting potential of $-70$ mV
(B) are hyperpolarized in response to light stimulus
(C) release epinephrine in response to light
(D) are responsible for color vision
(E) are the only photoreceptors present in the fovea

**124.** Slow-twitching fibers

(A) contract with a higher level of force than fast-twitching fibers
(B) are resistant to fatigue
(C) contain large stores of glycogen
(D) are the predominant muscle fibers in the gastrocnemius muscle
(E) use exclusively anaerobic metabolism

**125.** Nerve cooling may cause

(A) an increase in nerve conduction velocity
(B) a dispersion of sensory nerve action potential
(C) a reduction in distal motor latency
(D) an increase in sensory nerve action potential amplitude
(E) a reduction in the amplitude of the compound muscle action potential

**126.** What is the effect of increasing a low-frequency (high-pass) filter from 10 to 300 Hz on the response of the sensory nerve action potential?

(A) Prolonged onset distal latency of sensory nerve action potential response
(B) Reduction of sensory nerve action potential amplitude
(C) Prolongation of sensory nerve action potential response peak latency
(D) An increase in the negative spike duration of sensory nerve action potential response
(E) No effect on the morphology, duration, and latencies of the sensory nerve action potential response

**127.** In recording a compound muscle action potential, the increase of low-frequency (high-pass) filter from 1 to 100 Hz results in

(A) reduction of onset latency of compound muscle action potential
(B) prolongation of onset latency of compound muscle action potential
(C) reduction of compound muscle action potential amplitude
(D) prolongation of compound muscle action potential peak latency
(E) no effect on compound muscle action potential amplitude or latencies

**128.** In recording a sensory nerve action potential, the reduction of high-frequency (low-pass) filter from 10,000 to 500 Hz results in

(A) reduction of sensory nerve action potential onset latency
(B) reduction of sensory nerve action potential amplitude
(C) reduction of sensory nerve action potential peak latency
(D) reduction of sensory nerve action potential duration
(E) no effect on sensory nerve action potential response

**129.** In recording a compound muscle action potential, the reduction of high-frequency (low-pass) filter from 10,000 to 500 Hz results in

(A) reduction in compound muscle action potential amplitude
(B) an increase in compound muscle action potential amplitude
(C) reduction in compound muscle action potential onset latency
(D) prolongation of compound muscle action potential onset latency
(E) no effect on compound muscle action potential response

**130.** F latency response depends on the patient's

(A) age
(B) gender
(C) weight
(D) height
(E) temperature

**131.** The cooling of a single myelinated fiber results in

(A) increased nerve fiber excitability
(B) reduced nerve fiber excitability
(C) increased nerve fiber transmembrane resistance
(D) reduced nerve fiber transmembrane resistance
(E) no effect on nerve fiber excitability and transmembrane resistance

**132.** As the nerve's temperature declines,

(A) action potential amplitude increases
(B) action potential's rise and fall times declines
(C) nerve conduction velocity is reduced
(D) absolute refractory period decreases
(E) relative refractory period decreases

**133.** In mammalian nerves, decreasing temperature

(A) significantly alters sodium channel activation
(B) significantly slows sodium channel inactivation
(C) significantly alters potassium channel activation
(D) significantly slows potassium channel inactivation
(E) significantly alters calcium channel activation

**134.** Which of the following is true about the waves illustrated in Figure 4-8?

(A) They are obtained by submaximal long-duration (1-ms) nerve stimulation.
(B) Sensory nerve fibers constitute the afferent pathway that generates these waves.
(C) Their latencies are specifically affected in S1 radiculopathy.
(D) They may be absent or have prolonged latency in acute inflammatory demyelinating polyneuropathy.
(E) They are the electrical correlate of ankle jerk.

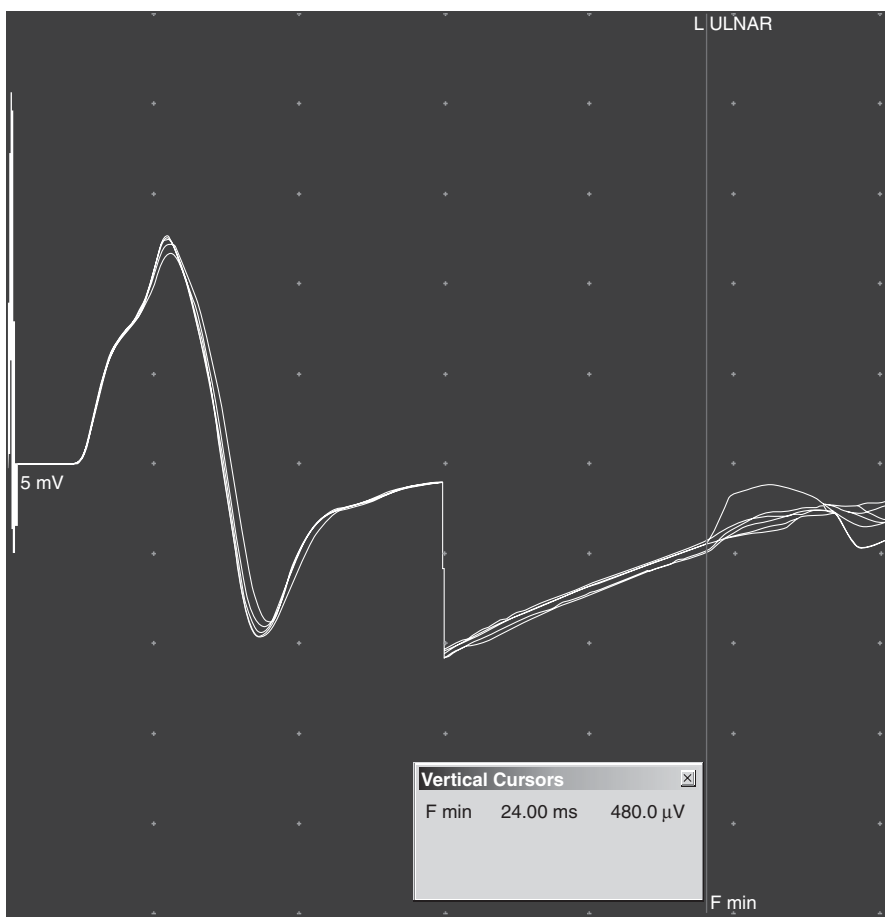



**FIG. 4-8**

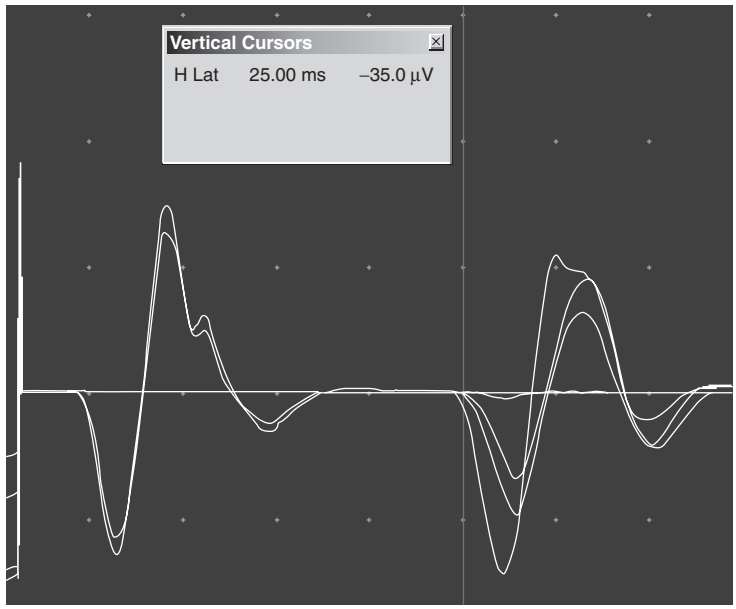


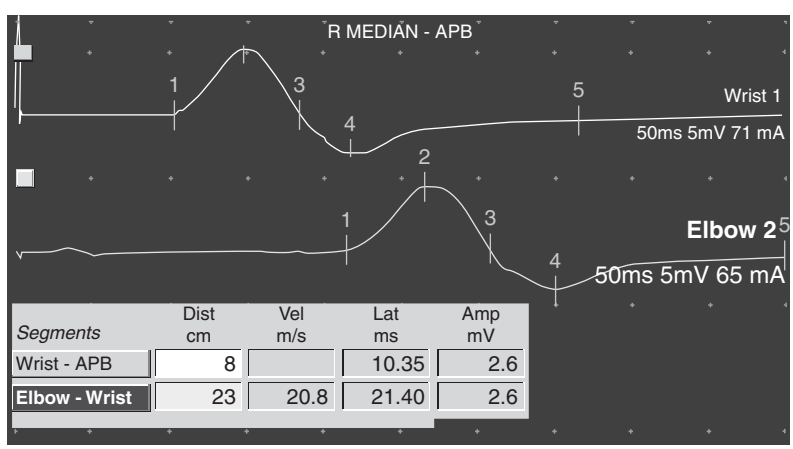

FIG. 4-9

**135.** Which of the following is true about the waves illustrated in Figure 4-9?

(A) They are obtained by supramaximal nerve stimulation.
(B) Motor nerve fibers are the afferent pathway that generate these waves.
(C) They can be obtained from sensory nerves.
(D) They are usually preserved in S1 radiculopathy.
(E) They are the electrical correlate of ankle jerk.

**136.** Figure 4-10 illustrates a motor nerve conduction study of a median nerve, stimulating at the wrist and the elbow and recording at the abductor pollicis brevis. The most likely diagnosis suggested by Figure 4-10 is

(A) carpal tunnel syndrome
(B) congenital demyelinating polyneuropathy
(C) acquired demyelinating polyneuropathy
(D) axonal polyneuropathy
(E) myasthenia gravis




| Segments | Dist cm | Vel m/s | Lat ms | Amp mV |
|---|---|---|---|---|
| Wrist - APB | 8 | | 10.35 | 2.6 |
| Elbow - Wrist | 23 | 20.8 | 21.40 | 2.6 |

FIG. 4-10

**137.** Figure 4-11 illustrates a motor nerve conduction study of a ulnar nerve, stimulating at the wrist and the elbow and recording at the abductor digiti minimi. The most likely diagnosis suggested by Figure 4-11 is

(A) carpal tunnel syndrome
(B) congenital demyelinating polyneuropathy
(C) acquired demyelinating polyneuropathy
(D) axonal polyneuropathy
(E) myasthenia gravis

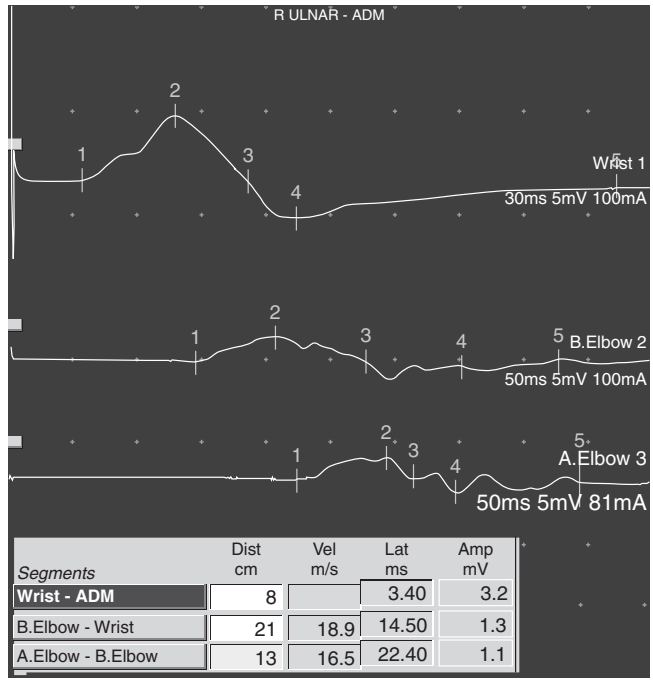



FIG. 4-11

**138.** Figure 4-12 illustrates a motor nerve conduction study of a median nerve, stimulating at the wrist and the elbow and recording at the abductor pollicis brevis. The most likely diagnosis suggested by Figure 4-12 is

(A) carpal tunnel syndrome
(B) congenital demyelinating polyneuropathy
(C) acquired demyelinating polyneuropathy
(D) axonal polyneuropathy
(E) myasthenia gravis

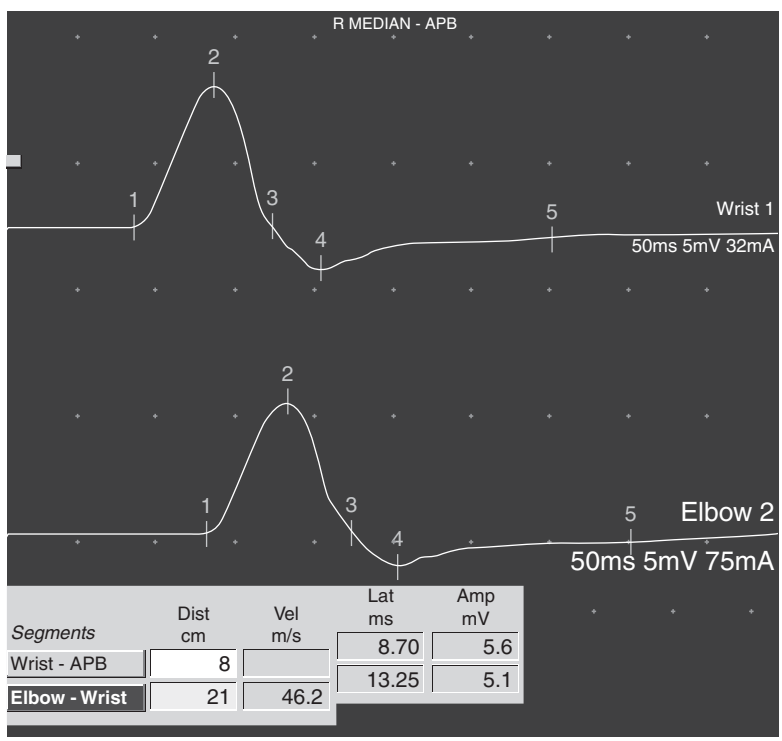



FIG. 4-12

# Answers and Explanations

**1. (E)** The posterior dominant rhythm is located over the occipital, parietal, and posterior temporal regions of both hemispheres. The typical alpha frequency is 8 to 13 Hz, usually 9 to 11 Hz in adults. Age affects alpha frequency. A reactive posterior dominant rhythm first appears at the age of 3 to 4 months. The typical frequency at that age is 3.5 to 4.5 Hz.

**Frequency of Posterior Dominant Rhythm by Age**

| Age | Frequency in Hz |
|---|---|
| 3–4 months | 3.5–4.5 |
| 1 year | 5–7 |
| 2 years | 6–8 |
| 3 years | 7–9 |
| 7–9 years | 9 |
| Midteens | 10 |

(Spehlman, 170–173)

**2. (E)** Mu rhythm is a centrally located alpha frequency activity that diminishes with movement of the contralateral arm or body. Tactile stimuli and the thought of movement can also attenuate mu activity. Its morphology is often arch-shaped and the rhythm can be unilateral or bilateral. Mu activity may slow with aging. It should be considered abnormal if it is persistent or nonreactive in a region of focal slowing. *(Spehlman, 191–192)*

**3. (B)** Beta rhythm is defined by a frequency greater than 13 Hz. It is best seen when the subject is relaxed or drowsy. Beta activity can increase with cognition or stage I sleep, especially in children. Beta activity is enhanced by the use of barbiturates, benzodiazepines, and chloral hydrate. Occasionally, antidepressants, antihistamines, and neuroleptics may enhance beta activity in routine EEG. Valproic acid does not modify beta activity. *(Aminoff, 43)*

**4. (C)** Stage II sleep has all the features of stage I sleep with the addition of sleep spindles and K complexes. Sleep spindles can be located centrally at a frequency of 14 to 15 Hz. They can be frontally located, especially in younger individuals, often at a frequency of 12 Hz. Spindles first appear at the age of 2 months at a frequency of 8 to 12 Hz. They are asynchronous before the age of 18 months. They later become symmetric in amplitude and frequency. They become less frequent with aging. They are seen in stages II and III of sleep.

K complexes are diphasic waves, which consist of an initial sharply contoured transient followed by high-amplitude slow waves, usually of delta frequency, maximal in the frontocentral region. They are seen in sleep stages II to IV. They appear at the age of 5 months. Vertex sharp transients can be seen in the deeper portion of stage I of sleep and in stages II and III of sleep. They are diphasic sharp transients maximal centrally at C3 and C4 with prominent negative phase reversal at the midline in the coronal bipolar montages. They are first seen at the age of 2 months with a synchronous and symmetric appearance. A consistent lateralization of vertex waves is abnormal. Positive occipital sharp transients are surface-positive, bisynchronous sharp transients occasionally followed by low-amplitude surface negativity. They occur in stages I or II, predominantly in the occipital region singly or in runs. Alpha attenuation and increased frontocentral beta are features of stages I and II. *(Spehlman, 203–204)*

**5.** **(B)** Intermittent photic stimulation is used as an activating procedure in the diagnostic evaluation of epilepsy. A photomyoclonic response occurs frontally when the flashing light evokes muscle contraction of the facial musculature about 50 to 60 ms after each flash. The amplitude of this muscle artifact increases as photic stimulation continues. The response can be enhanced in case of barbiturate or ethanol withdrawal. Photic stimulation rates from about 12 to 18 Hz are most effective in producing a photomyoclonic response. *(Spehlman, 448–449)*

**6.** **(E)** Sleep spindles consist of sinusoidal waves, from 12 to 15 Hz, which develop in the central regions during the first few weeks of life and are well established by the age of 6 to 8 weeks. Spindle bursts are commonly asynchronous in the two hemispheres until the age of 2 years. *(Aminoff, 108)*

**7.** **(A)** The neonatal EEG is characterized by an age-specific bioelectric rhythm. Between 24 and 28 weeks of conceptional age, the entire EEG is essentially discontinuous. Whether the child is clinically awake or asleep, active or quiet, the EEG itself is composed of discontinuous background. Stimulation of the newborn or changes in spontaneous state provoke minor qualitative changes in the discontinuity of the background. *(Spehlman, 159–170)*

**8.** **(E)** After 32 weeks of age, EEG discontinuity is mostly confined to quiet sleep. The voltage of the interburst activity remains less than 25 μV. With advancing maturity, the voltage of the interburst period exceeds 25 μV. The label assigned to this more mature discontinuous quiet sleep activity is trace alternant. It is seen by the age of 36 weeks. The distinction between trace discontinue and trace alternant is arbitrary except for the higher interburst voltage. *(Spehlman, 159–170)*

**9.** **(E)** *Activité moyenne* appears during wakefulness, by 36 to 40 weeks of gestational age. It is formed by a continuous low- to medium-voltage mixed-frequency signal. *(Spehlman, 159–170)*

**10.** **(E)** By 44 to 46 weeks of conceptional age, the trace discontinue and trace alternant gradually yield to more mature and continuous slow-wave sleep during which nonstop high voltage and activity dominate the tracing. *(Spehlman, 159–170)*

**11.** **(D)** Lombroso proposed an operational definition of interhemispheric synchrony that has been widely adopted. In a synchronous burst, the signal begins in both hemispheres within 1.5 seconds. Excessive interhemispheric asynchrony of burst activity may be seen in prematurity, diffuse encephalopathy, and cerebral dysgenesis. *(Lombroso, 460–474)*

**12.** **(A)** Delta brushes are the quintessential waveforms of prematurity. The brush represents a pattern of the simultaneous fusion of two subunits, the underlying delta transient and the superimposed rhythmic fast activity. Brushes occur during wakefulness, active sleep, and quiet sleep. At a very premature age, brushes are more common in the rolandic region. When they achieve their highest expression, between 32 and 34 weeks of conceptional age, brushes are seen in the occipital, temporal, and rolandic regions. Frontal brushes are rare at any age. By the age of 1 month after term, brushes largely disappear as greater maturity emerges. *(Aminoff, 86)*

**13.** **(D)** By 44 to 46 weeks of conceptional age, quiet sleep sheds its immature trace alternant pattern and establishes its mature foundation as continuous slow-wave sleep. Sleep spindles appear from the midline or the central region. They are asynchronous between the two hemispheres and remain so until the age of 2 years. *(Spehlman, 175)*

**14.** **(D)** A full-term neonate expresses the following behavioral sleep states:

1. Waking state: the full-term neonate spends one-third of the time in this state. It is characterized by eye opening, body and facial movements, muscle activity, and irregular breathing.
2. Active sleep: the full-term neonate spends 50% to 60% of the time in this state. It is

characterized by closed eyes, most of the time with occasional opening, slower facial and body movements, decreased muscle tone, and irregular respiration.
3. Quiet sleep represents 30% to 40% of sleep time with regular respiration, few body and facial movements, and muscle tone similar to that of the waking state.
4. Transitional sleep.

*(Spehlman, 165–170)*

**15. (C)** The photomyogenic response is a noncerebral response characterized by brief repetitive muscle spikes in the frontal leads with the same frequency as the flash stimulus. This may be associated with fluttering and twitching movements of the forehead and eyelid muscles. The photomyogenic response shows recruitment and ceases when the photic stimulus stops. It is most prominent when the eyes are closed but can occur when the eyes are open. It is believed by some to represent a physiological response to high-intensity light. *(Aminoff, 53–54)*

**16. (B)** Alpha activity is an activity in the range of 8 to 13 Hz, whereas alpha rhythm is activity in the same range occurring during wakefulness over the posterior head region; it is present when the eyes are closed and the patient relaxed and is blocked by eye opening or alerting the patient. *(Spehlman, 215; Aminoff, 42–43, 109)*

**17. (D)** The Bancaud phenomenon results from failure of alpha rhythm to block on one side of the brain. It indicates an abnormality on the side that fails to attenuate. *(Spehlman, 215; Aminoff, 42–43, 109)*

**18. (E)** Posterior slowing of youth consists of single 2- to 4-Hz triangular-contoured slow waves (also called sail waves) interspersed with alpha activity over the posterior head regions and occurring maximally over the occipital head regions. *(Spehlman, 215; Aminoff, 42–43, 109)*

**19. (C)** Temporal transients consist of episodic slow-wave components ranging from 2 to 5 Hz that occur singly or in brief trains over the temporal region. Temporal transients are usually maximal over the mid-Sylvian area. They are seen in normal subjects after the age of 40, with left-side preponderance, and occur in about 35% of individuals between the fifth and sixth decades. They appear to be related to a normal aging process, although some studies suggest cerebrovascular ischemia as the origin of this activity. *(Spehlman, 215; Aminoff, 42–43, 109)*

**20. (E)** Triphasic waves are 100- to 300-μV positive sharp waves preceded and followed by lower-amplitude negative waves. They are bilaterally synchronous, generalized in distribution, and usually predominant in the frontal region. Triphasic waves occur more commonly from hepatic encephalopathy than from other causes. They may occur in hypoglycemia, renal failure, hyponatremia, hypercalcemia, hyperthyroidism, drug intoxication, and anoxia. There is no specific EEG finding in hypoparathyroidism. EEG may show irregular high-voltage delta activity that is increased on hyperventilation. Paroxysmal abnormalities may also occur during wakefulness and sleep. *(Spehlman, 327)*

**21. (D)** Patients with anoxic encephalopathy exhibiting the following EEG patterns are gravely ill and may have a poor prognosis.

- The burst suppression pattern consists of generalized high-voltage, mixed-frequency waveforms of variable duration, usually with admixed spike and sharp waves.
- The periodic spikes or sharp waves are usually seen at a rate of 0.5 to 2 Hz. They are often associated with multifocal or bilateral myoclonus.
- The alpha coma pattern in cerebral anoxia consists of monotonous unreactive alpha activity with diffuse frontal predominance. This pattern carries a poor prognosis in anoxic encephalopathy.
- A pattern of bihemispheric periodic lateralized epileptiform discharges also carries a poor prognosis. About 60% of patients showing this pattern do not recover.
- Delta brushes are seen in prematurity.

*(Spehlman, 389–392; Prior, 770)*

**22.** **(A)** Dialysis dementia is a progressive condition that develops in patients on chronic hemodialysis. Characterized by confusion, progressive dementia, dysarthria, myoclonus, and seizure, it is caused by the toxic accumulation of aluminum in the brain. Hughes and colleagues found bilateral spike-and-wave complexes in 77% of patients with dialysis dementia. Based on the presence or absence of that pattern, 91% of the patients, along with 91% of their EEGs, were correctly placed by Hughes and coworkers into the clinical category of dialysis dementia either with or without chronic encephalopathy. *(Hughes and Schreeder, 1148–1154)*

**23.** **(B)** Benzodiazepines acutely induce widespread fast activity with a maximum in the central and frontal regions. This persists during wakefulness until stages I and II of sleep and becomes more conspicuous when the alpha rhythm disappears. *(Spehlman, 428)*

**24.** **(B)** Rett syndrome, a neurodegenerative disorder of unknown cause, occurs exclusively in girls and has a prevalence of approximately 1 per 15,000 to 22,000. The hallmarks of Rett syndrome are repetitive hand-wringing movements and loss of purposeful and spontaneous use of the hands; these may not appear until 2 to 3 years of age. Autistic behavior is a typical finding in all patients. Generalized tonic–clonic convulsions occur in the majority and are usually well controlled by anticonvulsants. The EEG in Rett syndrome has been extensively studied. In stage 1 of the disease, the corresponding EEG is normal or may show minimal slowing of the background. In stage 2, a rapidly destructive stage, background slowing of the EEG is evident. Focal spikes or sharp waves appear, most commonly over the centroparietal regions but sometimes bilateral, multifocal, or diffuse. By stage 3, or the plateau stage, diffuse intermittent 2- to 4-Hz slow waves are superimposed on background slowing. In stage 4, the motor deterioration stage, the EEG is dominated by monorhythmic 4- to 5-Hz activity; there are frequent multifocal and generalized slow spike wave discharges during both waking and sleep. *(Behrman, 2034; Verma et al., 395–401)*

**25.** **(E)** Electrocerebral inactivity or electrocerebral silence is defined as no EEG activity of more than 2 μV in recording from scalp electrode pairs 10 cm or more apart with interelectrode impedances less than 10,000 but more than 100 ohms. Ten guidelines for EEG recordings are recommended:

1. A minimum of eight scalp electrodes should be utilized.
2. Interelectrode impedances should be less than 10,000 but more than 100 ohms.
3. The integrity of the entire recording system should be tested.
4. Interelectrode distances should be at least 10 cm.
5. Sensitivity must be increased from 7 μV/mm to at least 2 μV/mm for at least 30 minutes of the recording, with inclusion of appropriate calibrations.
6. Filter settings should be appropriate for the assessment of electrocerebral silence.
7. Additional monitoring techniques should be employed when necessary.
8. There should be no EEG reactivity to intense somatosensory, auditory, or visual stimuli.
9. Recordings should be made only by a qualified technologist.
10. A repeat EEG should be performed if there is doubt about electrocerebral silence.

*(Aminoff, 688)*

**26.** **(B)** Hockaday and coworkers studied the EEG of patients with anoxic encephalopathy and classified the abnormalities into five grades according to the final outcome. The prognosis for patients belonging to grade 1 was favorable. Severity increases and prognosis worsens from grade 1 to grade 5. In grade 1, the EEG shows reactive alpha rhythm with scattered theta activity. In grade 2, the EEG shows dominant theta activity with rare alpha activity. In stage 3, there are continuous polymorphic slow delta waves with little activity and faster frequency. In stage 4, there is invariant low-amplitude delta activity unresponsive to stimulus or any activity with a suppression interval of 1 second or more. Stage 5 shows a nearly or completely isoelectric record. *(Hockaday et al., 575)*

**27.** **(A)** Alpha coma in patients with brainstem lesions is most commonly seen in vascular disease, with lesions noted in the ventral pons, sparing the brainstem tegmentum. This abnormal alpha rhythm tends to be more reactive than that seen after hypoxia or drug overdose and is most prominently seen over the posterior head region. *(Spehlman, 438)*

**28.** **(E)** Five stages of sleep, representative of two alternating physiological mechanisms, have been defined. In each stage, the electrical activity of the brain occurs in organized and recurring cycles, referred to as the architecture of sleep. As the electrophysiological stages of sleep progress, sleep becomes deeper, meaning that arousal requires a more intense stimulus. Relaxed wakefulness with the eyes closed is accompanied in the EEG by posterior alpha waves of 9 to 11 Hz (cycles per second) and intermixed low-voltage fast activity of mixed frequency. Except for the facial muscles, the EMG is silent when the patient is sitting or lying quietly. With drowsiness, as the first stage of sleep sets in, the eyelids begin to droop, the eyes may rove slowly from side to side, and the pupils become smaller. As the early stage of sleep evolves, the muscles relax and the EEG pattern changes to one of progressively lower voltage and mixed frequency with a loss of alpha waves; this is associated with slow, rolling eye movements and is called stage 1 sleep. As this changes into stage 2 sleep, 0.5- to 2-s bursts of biparietal 12- to 14-Hz waves (sleep spindles) and intermittent high-amplitude, central-parietal sharp slow-wave complexes appear (vertex waves). The American Academy of Sleep Medicine (AASM) recommends the following staging: stage W (wakefulness); stage N1 (non–rapid eye movements [NREM sleep] or NREM 1, formerly stage 1); stage N2 (NREM 2, formerly stage 2); stage N3 (NREM 3, combining former stages 3 and 4, or slow-wave sleep); and stage R (REM sleep). The essential difference between this new nomenclature and the one familiar to most neurologists is that stage N3 now represents slow-wave sleep, replacing stage 3 and stage 4 sleep, composed of an increasing proportion of high-amplitude delta waves (0.75-μV, 0.5- to 2-Hz in the EEG). If the eyelids are raised gently, the globes are usually seen to be exotropic and the pupils are even smaller than before, but with retained responses to light. An additional stage of the sleep cycle, which follows the others intermittently throughout the night, is associated with further reduction in muscle tone except in the extraocular muscles and with bursts of REMs; thus the term *REM sleep* designates this stage. The EEG becomes desynchronized (i.e., it has a low-voltage, high-frequency discharge pattern). The first three stages of sleep are called NREM sleep or synchronized sleep; the last stage, in addition to REM sleep, is variously designated as fast-wave, nonsynchronized, or desynchronized sleep. *(Ropper and Samuels, Chapter 19)*

**29.** **(B)** Positive occipital sharp transients of sleep are monophasic triangular waves in the occipital regions. They may appear at the end of stage 1 of sleep in many subjects. *(Spehlman, 191–197)*

**30.** **(E)** Benign epileptiform transients of sleep are small sharp spikes seen mainly in adults during drowsiness. Unlike true epileptiform discharges, they do not distort the background activity. They disappear in deeper levels of sleep. *(Spehlman, 191–197)*

**31.** **(D)** Wicket spikes are arc-like waves that typically occur in train. When they occur as a single waveform, they are often mistaken for a temporal spike. They are not associated with a subsequent slow wave and do not disrupt the background. *(Spehlman, 191–197)*

**32.** **(D)** Lambda waves occur over the occipital head regions when the subject is engaged actively at something that arouses his or her interest. These waves appear to represent an evoked cerebral response to a visual stimulus produced from shifts of images across the retina in the course of saccadic eye movements. *(Spehlman, 191–197)*

**33.** **(A)** Mu rhythm has been called rolandic alpha activity and consists of 7- to 11-Hz arc-shaped waveforms, usually unilateral, present over the central region. It seems to be related to

functions of the sensorimotor cortex. It is not attenuated by eye opening but by active movement or the thought of movement of the contralateral extremity. *(Spehlman, 191–197)*

**34.** **(B)** Phenytoin toxicity may occur unexpectedly because its metabolism slows substantially when a serum concentration of approximately 15 μg/dL is reached due to zero-order kinetics. In this state of slow metabolism, even small adjustments in dosage may lead to very large increases in serum concentration. *(Pollard et al., 91–105)*

**35.** **(A)** Phenytoin, because of its properties of hepatic enzyme induction and also its own metabolism via cytochrome P450, may produce drug–drug interactions. Some examples of clinically significant interactions include the ability of dicumarol, chloramphenicol, sulfonamides, isoniazid, disulfiram, and cimetidine to produce competitive or noncompetitive inhibition of hepatic metabolism and to increase serum phenytoin levels, whereas rifampin and antacids may decrease them. Phenytoin, in turn, may increase clearance of oral contraceptives, quinidine, chloramphenicol, and dicumarol. *(Pollard et al., 91–105)*

**36.** **(E)** Salicylates may alter protein binding, causing an increase in free (active) phenytoin without altering the total measured serum level. *(Pollard et al., 91–105)*

**37.** **(C)** Ethosuximide (Zarontin), a T-type calcium channel blocker, is an antiepileptic agent with a very narrow therapeutic indication. It is effective only as a first-line agent for absence seizures occurring in isolation, a condition seen primarily in childhood. Occasionally, in primary generalized epilepsy with seizure types other than absence where valproate acid is ineffective, the addition of ethosuximide improves seizure control. It is in this setting that most adult use of ethosuximide occurs. Ethosuximide is primarily cleared through hepatic metabolism, although a small portion (less than 20%) is renally eliminated. The most common side effects noted with ethosuximide use include nausea and abdominal discomfort, drowsiness, anorexia, and headache. In rare cases, behavioral changes may be seen, including psychosis. Drug–drug interactions are minimal. *(Pollard et al., 91–105)*

**38.** **(B)** Some antiepileptic drugs are bound substantially to serum proteins. Bound drug is not relevant to drug effect and is thus considered "inactive," as it cannot cross the blood–brain barrier. An interaction that displaces the drug from its binding site immediately increases the active fraction of the drug. This can cause transient toxicity. However, the free fraction is also available for metabolism, which, therefore, will occur at a higher rate. After several days of equilibration, the total concentration of the displaced drug, as measured by serum levels, is typically lower, but the free fraction is the same as before the drug was displaced. The most frequently encountered example is the displacement of phenytoin from serum proteins by valproate. The addition of valproate to a chronic regimen of phenytoin will result in an immediately higher free fraction of phenytoin. The patient therefore can experience symptoms of phenytoin toxicity without a higher total serum concentration of phenytoin. *(Pollard et al., 91–105)*

**39.** **(C)** The brainstem evoked potentials are signals generated in the auditory nerve and brainstem following an acoustic stimulus. A normal brainstem evoked response has five waves. Waves I and II correspond to the activation of the distal and proximal parts of the auditory nerve, respectively. Wave III corresponds to the activation of the superior olive and trapezoid body. The generators of wave IV and V are located in the upper pons and midbrain. *(Aminoff, 421–536)*

**40.** **(B)** The clinical interpretation of the pattern reversal visual evoked potential is based on measurement of the latency of the cortical response from the P100 component, the major positive wave having a nominal latency of 100 ms in normal subjects. *(Aminoff, 421–536)*

**41.** **(A)** Median nerve somatosensory evoked potentials show, in normal cases, N9 generated

at Erb's point; N14 generated in the cervicomedullary region, probably in the caudal medial lemniscus; and N20 in the cortical area processing the stimulus. *(Aminoff, 421–536)*

**42. (D)** Somatosensory evoked potential obtained from stimulation of the posterior tibial nerve shows N22 potential generated in the gray matter of the lumbar cord and P38 generated in the cortical area close to the leg representation. *(Aminoff, 421–536)*

**43. (B)** Sleep spindles and K complexes are seen in stage II or III of sleep. K complexes consist simply of a sharp vertex wave associated with a sleep spindle. Positive occipital transients of sleep are seen in the deep stage I of sleep. In stage III of sleep, delta slowing is seen in 20% to 50% of sleep. The enhancement of the amplitude of beta activity in the presence of a skull defect is called a breach rhythm. The Bancaud phenomenon results from failure of the alpha rhythm to attenuate by eye opening. *(Aminoff, 45–46, 54)*

**44. (E)** Nausea, vomiting, and gastrointestinal distress are among the most frequent adverse effects of valproic acid. Other common side effects include weight gain in 50% of cases, hair loss, and a tremor in 10% of cases. Hyperammonemia may occur; it is usually asymptomatic but can cause encephalopathy in the absence of hepatic dysfunction. Mild to moderate hepatic dysfunction may occur in 40% of cases. It is dose-related and reversible. Fatal hepatitis may occur as an idiosyncratic reaction, especially in children under the age of 2 years who are on multiple antiseizure medications. Acute pancreatitis can be induced by valproic acid in children more than adults. Aplastic anemia is seen after treatment with felbamate. *(Bazil and Pedley, 1998, 135–162; Dichter and Brodie, 1531–1590)*

**45. (B)** Carbamazepine has poor solubility in water, a factor that has inhibited the development of a parenteral form for clinical use. Carbamazepine is metabolized by the liver. Its pharmacokinetics are characterized by the phenomenon of autoinduction of hepatic microsomal enzymes. In naive patients, introduction of the drug is associated with a half-life of 30 hours, decreasing within days to weeks to 10 to 20 hours. A low dose of the drug should be introduced first, when starting the treatment; then it should be increased slowly to avoid toxicity. Skin rash occurs in 15% of patients treated with carbamazepine, whereas it occurs in only 10% of those treated with phenytoin. Carbamazepine has a slight antidiuretic effect, which may result in mild to moderate hyponatremia. Mild elevation of hepatic enzymes may occur with carbamazepine use in 5% to 10% of cases. This elevation neither predicts nor predisposes to hepatitis, which is presumed to be an immune hypersensitivity reaction. *(Bazil and Pedley,1998, 135–162)*

**46. (B)** Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite (24%) and is not dependent on any of the liver cytochrome P450 isoenzymes. The major metabolite is inactive in animal seizure models. Its plasma half-life in adults is $7 \pm 1$ hour and is unaffected by either dose or repeated administration. It is eliminated from the systemic circulation by renal excretion as unchanged drug, which represents 66% of the administered dose. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. Levetiracetam elimination is correlated with creatinine clearance. Levetiracetam clearance is reduced in patients with impaired renal function.

Zonisamide is 70% metabolized by the liver. Topiramite is 30% metabolized by the liver, whereas lamotrigine and tiagabine are more than 90% metabolized by the liver. *(Patsalos, 123–129)*

**47. (C)** Phenytoin has zero-order kinetics. This means that its process of utilization is not linear. The plasma drug concentration and clearance are independent of drug dose. Furthermore, in this case, one cannot reliably predict the time that will be required for phenytoin concentration to fall into the therapeutic range. *(Bazil and Pedley, 1998, 135–162)*

**48.** **(B)** The patient described in the vignette has early symptoms of carbamazepine intoxication. The therapeutic level of carbamazepine is explained by the phenomenon of autoinduction of the drug from its own metabolism by hepatic microsomal enzymes. The patient was started initially on a full dose of the drug, which caused signs of carbamazepine intoxication. Autoinduction of the drug decreases its serum level to a therapeutic range and improves the clinical symptoms. It is recommended that carbamazepine be started at a low dose (100 mg PO bid) and increased progressively. *(Bazil and Pedley, 2003, 38–52)*

**49.** **(C)** Lamotrigine was originally developed because of an observation that some anticonvulsants have antifolate properties. Although lamotrigine weakly inhibits dihydrofolate reductase, there is no correlation between this activity and its anticonvulsant action. Lamotrigine is about 55% bound to protein. It undergoes extensive liver metabolism. Its rate of elimination is influenced by concomitant administration of hepatic inhibitors or inducers. When lamotrigine is given in monotherapy, the elimination half-life is about 25 hours. When it is given with enzyme inducers (carbamazepine, phenytoin, phenobarbital), its half-life is reduced to 15 hours. When given with an enzyme inhibitor (valproic acid), the half-life increases to 60 hours. Rash may complicate lamotrigine administration in 10% of cases. It acts through prolonging inactivation of voltage-sensitive sodium channels. *(Bazil and Pedley, 2003, 38–52)*

**50.** **(C)** Phenytoin has minimal renal excretion and does not require adjustment in case of renal failure. Ethosuximide has renal excretion of 10% to 20%. A decrease of 25% of the regular dose is needed if the glomerular filtration is less than 10 mL/min. Phenobarbital has a renal excretion of 25% to 30%. The dosing interval must be increased by 50% to 100% in cases of renal failure. Carbamazepine has minimal renal excretion, but its dose must be decreased by 25% in cases of renal failure with glomerular filtration less than 10 mL/min. Topiramate has renal excretion of 70%. A decrease in the regular dose by 50% is needed in cases of renal failure or dialysis. *(Bazil and Pedley 2003, 38–52)*

**51.** **(D)** All these drugs are removed by dialysis except phenytoin. In case of phenytoin overdose, forced fluid diuresis, peritoneal dialysis, exchange transfusion, hemodialysis, and plasmapheresis are ineffective. They produce little renal elimination and pose a danger of fluid overload. *(Bazil and Pedley 2003, 38–52)*

**52.** **(B)** West syndrome is an age-dependent epilepsy with a characteristic EEG pattern known as hypsarrhythmia; it is also accompanied by infantile spasms and psychomotor retardation. Infantile spasms occur in 24 to 42 of 100,000 births. Spasms and psychomotor retardation appear in the first year of life in 85% of cases, the majority between 3 and 7 months. Associated abnormalities include generalized hypotonicity, microcephaly, paralysis, ataxia, blindness, and deafness. The typical EEG reveals hypsarrhythmia, a chaotic pattern of high-amplitude slow waves with multifocal epileptiform discharges and poor interhemispheric synchrony. ACTH is the treatment of choice for infantile spasm. The dose and duration of steroid therapy has not been standardized. The most common treatment is ACTH 40 IU/day administered intramuscularly. Approximately 75% of patients achieve initial seizure control with this regimen. The response rate tends to increase with duration of therapy. Within 2 months of remission, however, approximately 30% to 50% of patients suffer relapse after the first course of steroids. *(Goetz, 1070–1072)*

**53.** **(E)** Phenytoin can cause a range of dose-related and idiosyncratic adverse effects. Reversible cosmetic changes (gum hypertrophy, acne, hirsutism, and facial coarsening), although often mild, can be troublesome. Neurotoxic symptoms (drowsiness, dysarthria, tremor, ataxia, and cognitive difficulties) may occur when the plasma drug concentration exceeds 20 μg/mL. Cerebellar atrophy may occur with chronic use. *(Brodie and Dichter, 168–175; Dichter and Brodie, 1583–1590)*

**54.** **(C)** The most common side effects of lamotrigine use are headache, nausea and vomiting, dizziness, diplopia, and ataxia. Tremor can be troublesome at high dosages. In up to 10% of patients in add-on trials, a rash may develop, which subsequently disappears in some patients despite continued therapy. In a few patients, however, the rash is more serious, and fever, arthralgias, and eosinophilia occur. In rare cases (less than 1%), Stevens–Johnson syndrome develops. The concomitant administration of valproic acid with lamotrigine may increase the likelihood of a serious rash; the gradual introduction of lamotrigine may lower the likelihood of skin reactions. *(Brodie and Dichter, 168–175; Dichter and Brodie, 1583–1590)*

**55.** **(B)** The main limitation of phenobarbital use is its propensity to alter cognition, mood, and behavior. The drug can cause fatigue in adults, and insomnia, hyperactivity, and aggression in children (and sometimes in the elderly). Memory, mood, and learning capacity may be subtly impaired. Depression, arthritic changes, and Dupuytren's contracture can be associated problems. *(Brodie and Dichter, 168–175; Dichter and Brodie, 1583–1590)*

**56.** **(E)** Carbamazepine can cause a range of idiosyncratic reactions; the most common is a morbilliform rash, which develops in about 10% of patients. Less common skin eruptions include erythema multiforme and Stevens–Johnson syndrome. Reversible mild leukopenia is common but does not generally require discontinuation of therapy. Blood dyscrasias and toxic hepatitis are rare. At high plasma concentrations, carbamazepine has an antidiuretic hormone–like action; the resulting hyponatremia is usually mild and asymptomatic. But if the plasma sodium concentration falls below 125 mmol/L, there may be confusion, peripheral edema, and decreasing control of seizures. Orofacial dyskinesias and cardiac arrhythmias are additional rare side effects. *(Brodie and Dichter, 168–175; Dichter and Brodie, 1583–1590)*

**57.** **(B)** Felbamate may cause aplastic anemia and hepatic toxicity. *(Brodie and Dichter, 168–175; Dichter and Brodie, 1583–1590)*

**58.** **(E)** Zonisamide is a weak carbonic anhydrase inhibitor that is probably responsible for an increased incidences of symptomatic renal stones, although the rate was similar to placebo in clinical trials. *(Brodie and Dichter, 168–175; Dichter and Brodie, 1583–1590)*

**59.** **(A)** Gabapentin is typically well tolerated. The most common side effects are headache, fatigue, ataxia, and somnolence. *(Brodie and Dichter, 168–175; Dichter and Brodie, 1583–1590)*

**60.** **(D)** The common side effects of valproic acid are dose-related tremor, weight gain due to appetite stimulation, thinning or loss of hair (usually temporary), and menstrual irregularities, including amenorrhea. Sedation is unusual, although stupor and encephalopathy occur in rare cases. The incidence of hepatotoxic effects, histologically evident as a microvesicular steatosis, is less than 1 in 20,000 patients, but such effects are of concern in children under 3 years of age who are receiving multiple antiepileptic drugs. Approximately 20% of all patients receiving the drug have hyperammonemia without hepatic damage. This effect is usually asymptomatic but occasionally can cause confusion, nausea, and vomiting. *(Brodie and Dichter, 168–175; Dichter and Brodie, 1583–1590)*

**61.** **(B)** Carbamazepine, valproic acid, and phenytoin are not removed by dialysis. *(Bazil and Pedley, 2003, 38–52)*

**62.** **(A)** Tiagabine acts as an inhibitor of GABA reuptake into presynaptic nerve terminals. Because GABA is a major inhibitory neurotransmitter in the central nervous system, the increase of available GABA through this mechanism may be responsible for tiagabine's anticonvulsant action. *(Bazil and Pedley, 2003, 38–52)*

**63.** **(B)** The overall risk of having a baby with a major malformation is about 2% to 3% in healthy populations. This is increased to 5% to 6% in women with epilepsy taking a single antiepileptic drug, perhaps to 6% to 7% if the drug is carbamazepine or valproic acid. This rate may be doubled by the use of two or more

drugs or by a very high plasma level of antiepileptic drugs. *(Bazil and Pedley, 2003, 38–52)*

**64. (C)** Many drugs may increase phenytoin levels. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected. Drugs that may increase phenytoin serum levels include alcohol (acute intake), amiodarone, chloramphenicol, chlordiazepoxide, diazepam, dicumarol, disulfiram, estrogens, H2-antagonists, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, and trazodone. *(Bazil and Pedley, 2003, 38–52)*

**65. (D)** Theophylline, a CYP3A4 inducer, can increase carbamazepine metabolism, resulting in the potential for decreased plasma carbamazepine levels. *(Bazil and Pedley, 2003, 38–52)*

**66. (E)** Barbiturates and benzodiazepines are potent beta activators. Chloral hydrate is another activator of beta activity. Occasionally, neuroleptics, antidepressants, and antihistamines can increase beta activity in routine EEG. Drug-induced beta activity is usually slower than physiological beta. *(Spehlman, 428–429)*

**67. (E)** Periodic lateralizing epileptiform discharges (PLEDs) are EEG patterns showing complexes consisting of di- or polyphasic spike or sharp waves. They commonly appear in a wide distribution on one side of the head. They are uni- or bilateral but with a clear maximum on one side. Clinical conditions causing PLEDs are mainly acute cerebral infarcts but they also include encephalitis, cerebral tumors, meningitis, cerebral abscess, and other conditions causing acute destruction of an area of the brain. PLEDs usually disappear after days or weeks from the acute phase of the damage. *(Spehlman, 321)*

**68. (D)** Amino acids have been separated into two general classes: excitatory and inhibitory. The former group depolarizes neurons in mammalian cells and is formed by aspartic acid, cysteic acid, glutamic acid, and homocystic acid. The latter group hyperpolarizes neurons in mammals and is formed by GABA, glycine, taurine, and beta-alanine. *(Cooper, 126)*

**69. (B)** Hyperventilation is an activation procedure used to bring out focal slowing or epileptiform abnormalities. The incidence and intensity of the hyperventilation response depend on age, blood sugar level, and cerebral oxygen supply. Hyperventilation responses are most common and extensive in children and teenagers. In children, spike and wave discharges of 3 Hz are particularly seen in absence seizures and are particularly sensitive to hyperventilation; in many cases, they appear only during this procedure. The 8-year-old boy with episodes of staring most likely has absence seizures. Hyperventilation may be the only procedure to induce spike and wave discharges, considering this patient's age and the type of seizure that he is most likely to have. *(Spehlman, 219–222)*

**70. (D)** REM parasomnias usually occur in middle-aged or elderly patients and show a marked male predominance. They are due to a lack of normal atonia of REM sleep. Consequently, they occur more often in the later portion of sleep. During REM sleep, patients may have an increase in the severity or frequency of fragmentary myoclonus. Although REM sleep behavior disorders may occur in healthy elderly subjects, they are also seen with tricyclics, alcohol abuse, or central nervous system diseases affecting the pathways controlling REM atonia, such as multisystem atrophy. REM parasomnias, like other REM sleep disorders, respond well to clonazepam. *(Duncan, 21)*

**71. (C)** Absence seizures usually occur in childhood or early adulthood, whereas complex partial seizures occur at any age. Absence seizures are idiopathic and generalized, while complex partial seizures can be cryptogenic or caused by focal pathology. The duration of attacks is short in absence seizures, less than 30 seconds, while it is longer in cases of complex partial seizures. There is no postictal state in absence seizures, whereas in complex partial seizures confusion, emotional disturbance, or headache usually occurs in the postictal state. The EEG may show

spikes and slow waves induced by hyperventilation or, less frequently, by photic stimulation in absence seizures. Photosensitivity induces spikes and waves in only 10% to 30% of patients with absence seizures. In complex partial seizures, photic stimulation does not induce seizure activity on EEG, while hyperventilation has a modest effect. *(Duncan, 35)*

**72. (D)** There is a considerable overlap between the clinical and EEG features of mesiobasal and lateral temporal lobe epilepsy. In lateral temporal seizures, there is usually a detectable underlying structural pathology like glioma, angioma, hamartoma, neural migration defect, and posttraumatic changes. There is no association with a history of febrile seizure. Consciousness may be preserved longer than in mesial temporal epilepsy. Typical aura includes structured hallucination of visual, auditory, gustatory, or olfactory forms. Illusions of size, shape, weight, distance, or sound may occur. Automatisms may occur unilaterally and have more motor manifestations than does mesial temporal epilepsy. Motor arrest or absence is most often seen in mesial temporal epilepsy. Postictal phenomena and autonomic changes may occur in both mesial and lateral temporal epilepsy. *(Duncan, 44–46)*

**73. (B)** The clinical and EEG features of frontal lobe seizures overlap with those of complex partial seizures of temporal lobe origin. Nevertheless, there are a number of core features that are strongly suggestive of frontal lobe origin. Typically, the seizures are frequent, with a marked tendency to cluster. A brief nonspecific cephalic aura may occur, which is a vague sensation of dizziness, strangeness, and headache. Automatisms are present. They are typically gestural, highly excited, violent, or bizarre, leading to the misdiagnosis of nonepileptic attacks. Postictal recovery is rapid, with a shorter period of postictal confusion than in temporal epilepsy. Frontal lobe seizures are more likely to generalize secondarily than are partial seizures of temporal lobe origin. The EEG in frontal lobe epilepsy may be normal ictally or interictally, partly because of the large area of frontal cortex covered by the relatively few scalp electrodes and the inaccessibility of scalp electrodes to the medial and inferior frontal lobe surfaces. *(Duncan, 47)*

**74. (A)** Epilepsy, although a relatively common symptom of cerebral degenerative diseases, is seldom the predominant clinical problem. Seizures develop in up to 33% of cases of Alzheimer disease late in the course of the illness. Pick disease rarely causes seizures. Epilepsy occurs in 5% of cases of Huntington disease, especially in late stages and the juvenile rigid form. Epilepsy occurs in 6% of cases of Wilson disease and may be the presenting feature. *(Duncan, 55–56)*

**75. (B)** Reflex seizures are attacks precipitated by a specific stimulus, such as touch, musical tune, a particular movement, reading, stroboscopic light patterns, or complex visual images. The most common reflex epilepsies are those induced by visual stimuli such as flashing lights and moving patterns. The other answers mentioned cause seizures less frequently. *(Duncan, 66–67)*

**76. (D)** West syndrome is defined by the clinical triad of infantile spasms, arrest of psychomotor development, and hypsarrhythmia on EEG. Its incidence is estimated to be 1 per 4,000 to 6,000 live births. The identified causes of infantile spasms are divided into prenatal (cerebral dysgenesis, genetic disorders, intrauterine infection), perinatal (anoxic injury, head trauma, infection), and postnatal (metabolic disorders, trauma, infection). No etiology (cryptogenic) can be identified in as many as 40% of cases. The onset of almost all cases occurs before age 1 year, with peak onset between 3 and 7 months of age. The spasms occur in clusters and are characterized by sudden flexor or extensor movements of the trunk. They have a myoclonic quality but are somewhat longer in duration. Developmental arrest and regression begins with or before the spasms. EEG shows hypsarrhythmia on interictal EEG recordings. In the waking record, hypsarrhythmia consists of disorganized high-voltage slow waves, spikes, and sharp waves that occur diffusely with a somewhat posterior predominance.

The prognosis for children with infantile spasms is extremely poor. Although the spasms cease, 70% to 90% of infants develop mental retardation and 35% to 60% have chronic epilepsy. However, the major determinant of outcome is the underlying cause of the spasms. Only 5% of children develop normally, and these are mainly from the cryptogenic group. Corticosteroids, in the form of adrenocorticotropic hormone (ACTH), prednisone, or prednisolone, are the treatment of choice for infantile spasms. Benzodiazepines, in the form of clonazepam, provide some benefit but are not as effective as corticosteroids. Valproic acid is also effective, but the risk of hepatotoxicity in this age group must be considered. Vigabatrin has been used to treat infantile spasms effectively. *(Bradley, 1757–1758; Duncan, 73–74)*

**77. (C)** Rolandic epilepsy is a well-defined childhood syndrome accounting for up to 15% of all childhood epilepsies. The age of onset is between 3 and 13 years with a peak incidence between 5 and 10 years. The seizures are typically focal, involving the face and oropharynx, often with secondary generalization, and have a strong tendency to occur during sleep. The motor phenomena are usually associated with sensory disturbances and clonic unilateral jerking of the upper limb. In about two thirds of patients, secondarily generalized tonic–clonic seizures occur, almost always during sleep. There is generally no associated neurological abnormality, and intellect is usually normal. The diagnosis of rolandic epilepsy can be made by the typical clinical features and confirmed by characteristic EEG findings. These consist of remarkably focal high-amplitude midtemporal spikes or spike-wave discharges. There is a striking contrast between the active EEG and the benign clinical picture. The prognosis of rolandic epilepsy is good. Only 10% of patients will continue to have seizures 5 years after onset of the disease. *(Duncan, 78–79)*

**78. (B)** Lennox–Gastaut syndrome is responsible for 2% to 3% of childhood epilepsies. The syndrome is characterized by multiple seizure types, slow spike-wave complexes, and diffuse cognitive dysfunction. Seizure onset ranges from 1 to 8 years of age, with a peak incidence between 3 and 5 years of age. Fifty percent of cases have severe mental retardation, preceding the onset of seizures 20% to 60% of the time. In addition, disturbances of behavior and personality are common. The EEG reveals 2.0- to 2.5-Hz slow spike-wave complexes and multifocal spikes superimposed on abnormal background activity. The complexes are rarely induced by hyperventilation or photic stimulation. Seizures may be precipitated by drowsiness or stimulation. In general, seizures respond poorly to anticonvulsant treatment, and polytherapy is usually required. Benzodiazepines and valproic acid are the most effective agents, although the former may precipitate tonic status. Sedation should be minimized because of the tendency for seizures to increase in sleep. Phenytoin and rectal diazepam are effective for serial tonic seizures and status epilepticus. Refractory cases may benefit from the ketogenic diet or corpus callosotomy, which reduces tonic and atonic seizures in some cases. *(Goetz, 1072–1073)*

**79. (B)** Absence seizures begin between the ages of 3 and 12 years. Patients are more commonly female than male and there is a strong genetic predisposition. Monozygotic twins develop absences in 75% of pairs, as do 5% of dizygotic twins. Typical absence seizure is characterized by sudden behavioral arrest and unresponsiveness that may be accompanied by eyelid or facial clonus; automatisms; and autonomic, tonic, or atonic features. The interictal EEG in patients with typical absence seizures reveals generalized 3.0-Hz spike-wave complexes superimposed on normal background activity. Bursts of generalized 3.0- to 4.0-Hz spike-wave complexes slowing to 2.5 to 3.0 Hz are observed during seizures. Typical absence seizures are commonly precipitated by hyperventilation and infrequently by photic stimulation. The prognosis of absence seizure is good. Absences become less frequent through adolescence and about 80% remit by adulthood. *(Duncan, 84–85; Goetz, 1063–1064)*

**80. (A)** Progressive myoclonic epilepsies represent a group of disorders of various etiology that

collectively account for 1% of all epilepsy syndromes. The natural history varies with the specific disorder from mild neurological impairment to severe disability progressing to death in early childhood.

The disorders comprising the progressive myoclonic epilepsies may be classified into the following categories: (1) those with well-defined biochemical defects such as sialidosis; (2) those with a known pathological or biochemical marker yet poorly defined mechanism, such as Lafora disease and myoclonic epilepsy with ragged-red fibers; (3) the degenerative diseases such as Unverricht–Lundborg disease (Baltic myoclonus) and dentatorubropallidoluysian atrophy.

Juvenile myoclonic epilepsy is distinct from progressive myoclonic epilepsy. It usually appears around puberty and is characterized by seizures with bilateral single or repetitive arrhythmic, irregular myoclonic jerks, predominantly in the arms. Jerks may cause some patients to fall suddenly. No disturbance of consciousness is noticeable. The disorder may be inherited and sex distribution is equal. Often there are generalized tonic–clonic seizures and, less often, infrequent absences. The seizures usually occur after awakening and are often precipitated by sleep deprivation. Interictal and ictal EEGs have rapid, generalized, often irregular spike waves and polyspike waves; there is no close phase correlation between EEG spikes and jerks. Frequently, the patients are photosensitive. Response to appropriate drugs is good. *(Duncan, 90–92; Goetz, 1073–1074)*

**81.** **(A)** The key EEG features of idiopathic generalized epilepsy are generalized epileptiform discharges that often have a 3-Hz frequency; usually maximum in the anterior parasagitall regions, normal background, and often photosensitive. Photic stimulation may induce occipital spikes, occipital spikes and slow waves with frontal or parietooccipital regions, and generalized spike and slow-wave discharges. *(Duncan, 115–119)*

**82.** **(B)** Temporal lobe epilepsy is characterized in the EEG interictally by spikes that are usually maximal over the temporal or frontotemporal regions. The ictal scalp EEG often shows rhythmic theta at the onset that may be bilateral or localized in the affected temporal lobe. *(Duncan, 115–119)*

**83.** **(D)** In infantile spasms, the resting EEG shows a characteristic disorganized high-voltage pattern, with generalized attenuation during spasms. This pattern may be seen unilaterally or bilaterally. *(Duncan, 115–119)*

**84.** **(E)** Benign rolandic epilepsy is characterized by unilateral or bilateral triphasic, large-amplitude spikes that are maximum in the central or centrotemporal region without background abnormalities. *(Duncan, 115–119)*

**85.** **(C)** In benign occipital epilepsy, the EEG shows posterior 1.5- to 3-Hz spike and slow-wave discharges, singly or in long runs. These may be lateralized and usually attenuate with eye opening. *(Duncan, 115–119)*

**86.** **(A)** In Lennox–Gastaut syndrome, the background EEG is usually slow and disorganized, with superimposed 1- to 2.5-Hz generalized, anteriorly predominant spike and slow-wave discharges. *(Duncan, 115–119)*

**87.** **(E)** GM2 gangliosidosis is an autosomal recessive condition caused by a deficit in the activity of hexosaminidase A. Its clinical picture includes seizures, dementia, blindness, and a cherry-red spot in the retina. *(Behrman, 2030–2932; Duncan, 160–164; Goetz, 1074)*

**88.** **(E)** $G_{M1}$ gangliosidosis usually presents with failure to thrive in infants, hepatosplenomegaly, mental regression, and seizures. Later onset forms result in seizures, cognitive decline, spasticity, extrapyramidal rigidity, and ataxia. The key diagnostic test is reduced leukocyte beta-galactosidase activity. *(Behrman, 2030–2932; Duncan, 160–164; Goetz, 1074)*

**89.** **(D)** Niemann–Pick disease is characterized in type A by infant hepatosplenomegaly, slow development, loss of skills, spasticity, and seizures. In type C, Niemann–Pick disease is characterized by tonic–clonic seizures, ataxia,

and dementia. Sphyngomyelinase activity in both types is deficient. *(Behrman, 2030–2932; Duncan, 160–164; Goetz, 1074)*

**90. (C)** In Gaucher disease, beta-galactocerebrosidase activity is reduced in leukocytes. Infantile Gaucher disease is an autosomal recessive condition. The onset of the neuronopathic form is usually before 6 months and frequently before 3 months. Oculomotor apraxia and bilateral strabismus are early signs and are accompanied by rapid loss of head control, ability to roll over and sit, and purposeful movements of the limbs—along with apathy, irritability, frequent crying, and difficulty in sucking and swallowing. In some cases, progression is slower, with acquisition of single words by the first year, bilateral corticospinal signs, persistent retroflexion of the neck, and strabismus. Laryngeal stridor and trismus, diminished reaction to stimuli, smallness of the head, rare seizures, normal optic fundi, enlarged spleen and slightly enlarged liver, poor nutrition, yellowish skin and scleral pigmentation, osteoporosis, vertebral collapse and kyphoscoliosis, and sometimes lymphadenopathy complete the clinical picture. The important laboratory findings are an increase in serum acid phosphatase and characteristic histiocytes (Gaucher cells) in marrow smears and liver and spleen biopsies. A deficiency of glucocerebrosidase in leukocytes and hepatocytes is diagnostic; glucocerebroside accumulates in the involved tissues. The characteristic pathological feature is the Gaucher cell, 20 to 60 μm in diameter, with a wrinkled appearance of the cytoplasm and eccentricity of the nucleus. These cells are found in the marrow, lungs, and other viscera; neuronal storage is seldom evident. In the brain, the main abnormality is a loss of nerve cells—particularly in the bulbar nuclei but also in the basal ganglia, cortex, and cerebellum—and a reactive gliosis that extends into the white matter. *(Behrman, 2030–2932; Duncan, 160–164; Goetz, 1074; Ropper and Samuels, Chapter 37)*

**91. (A)** Sialidosis is a complex of two types of autosomal recessive disorders associated with deficiencies of N-acetylneuraminidase. The clinical picture includes myoclonic and generalized tonic–clonic seizures, dementia, and visual failure. *(Behrman, 2030–2932; Duncan, 160–164; Goetz, 1074)*

**92. (E)** Lafora disease usually presents with the phenotype of progressive myoclonic epilepsy with cerebellar ataxia, dementia, and personality changes. Death occurs within 10 to 15 years from the onset. Lafora bodies consist of polyglucosans and are found in peripheral nerve, liver, and muscle. *(Behrman, 2030–2932; Duncan, 160–164; Goetz, 1074)*

**93. (E)** Metachromatic leukodystrophy is transmitted in an autosomal recessive pattern and results from a deficiency of arylsulfatase A. Enzyme deficiency leads to an accumulation of the sulfatides, especially cerebroside sulfate. The gene for arylsulfatase A has been localized to chromosome 22q, and a wide range of mutations has been described. *(Behrman, 2030–2932; Duncan, 160–164; Goetz, 1074)*

**94. (A)** Adrenoleukodystrophy is a disorder with several clinically and genetically distinct forms. It is a progressive disease with symptoms referable to myelin loss from the central nervous system and peripheral nerves as well as adrenal insufficiency. In general, forms with earlier onset have a more rapid course. The X-linked form usually presents in the early school years with neurological symptoms and adrenal insufficiency. The disease is rapidly progressive and fatal. In individuals with later onset, the course is more protracted; when it develops in adults, it is usually a slowly progressive disorder with predominantly peripheral nerve involvement developing for a period of decades. The adrenoleukodystrophy gene encodes a member of the ATP-binding transporter family of proteins. The disease is characterized by the inability to properly catabolize very long chain fatty acids within peroxisomes because of a deficit of lignoceroyl CoA, with elevation of levels of very long chain fatty acids in serum. *(Behrman, 2030–2932; Duncan, 160–164; Goetz, 1074)*

**95. (E)** Krabbe disease or globoid cell leukodystrophy is a rare autosomal recessive neurodegenerative disorder characterized by severe

myelin loss and the presence of globoid bodies in the white matter. The gene for Krabbe disease is located on chromosome 14q24.3-q32.1. The disease results from a marked deficiency of the lysosomal enzyme galactocerebroside beta-galactosidase. The onset of the disorder is usually before the sixth month and often before the third month (10% after 1 year). Early manifestations are generalized rigidity, loss of head control, diminished alertness, frequent vomiting, irritability and bouts of inexplicable crying, and spasms induced by stimulation. With increasing muscular tone, opisthotonic recurvation of the neck and trunk develops. Later signs are adduction and extension of the legs, flexion of the arms, clenching of the fists, hyperactive tendon reflexes, and Babinski signs. Later still, the tendon reflexes are depressed or lost but Babinski signs remain, an indication that neuropathy is added to corticospinal damage. Blindness and optic atrophy supervene. Convulsions occur but are rare and difficult to distinguish from tonic spasms. Myoclonus in response to auditory stimuli is present in some cases. The head size is normal or, rarely, slightly increased. In the last stage of the disease, which may occur up to several months after the onset, the child is blind and usually deaf, opisthotonic, irritable, and cachectic. Most patients die by the end of the first year and survival beyond 2 years is unusual, although a considerable number of cases of later onset have been reported (see below). The deficient lysosomal enzyme in Krabbe disease is galactocerebrosidase (GALC; also called galactosylceramide beta-galactosidase); it normally degrades galactocerebroside to ceramide and galactose. The deficiency results in the accumulation of galactocerebroside; a toxic metabolite, psychosine, leads to the early destruction of oligodendrocytes and depletion of lipids in the cerebral white matter. The globoid cell reaction, however, indicates that impaired catabolism of galactosylceramide is also important. *(Behrman, 2030–2932; Duncan, 160–164; Goetz, 1074; Ropper and Samuels, Chapter 37)*

**96.** **(B)** Canavan disease, an autosomal recessive disorder characterized by spongy degeneration of the white matter of the brain, leads to a severe form of leukodystrophy. The cause of the disease is a deficit of the enzyme aspartoacylase, which leads to the accumulation of N-acetylaspartic acid in the brain. The onset is early, usually recognizable in the first 3 months of life and sometimes in the first neonatal weeks. There is either a lack of development or rapid regression of psychomotor function, loss of sight and optic atrophy, lethargy, difficulty in sucking, irritability, reduced motor activity, hypotonia followed by spasticity of the limbs with corticospinal signs, and an enlarged head. There are no visceral or skeletal abnormalities but a variable sensorineural hearing loss has been found. Seizures occur in some cases. The CSF is usually normal but the protein is slightly elevated in some cases. The disease is characterized by the increased urinary excretion of N -acetyl-L-aspartic acid (NAA), which may be used as a biochemical marker. It reflects the basic enzyme abnormality, a deficiency of aminoacylase II, which catalyzes the breakdown of NAA. On computed tomography (CT) scans there is attenuation of cerebral and cerebellar white matter in an enlarged brain with relatively normal-size ventricles. The characteristic pathological changes are an increase in brain volume and weight, spongy degeneration in the deep layers of the cerebral cortex and subcortical white matter, widespread depletion of myelin involving the convolutional more than the central white matter, loss of Purkinje cells, and hyperplasia of Alzheimer type II astrocytes throughout the cerebral cortex and basal ganglia. Adachi and coworkers have demonstrated an abnormal vacuolar accumulation of fluid in astrocytes and between split myelin lamellae; they have suggested that the loss of myelin is secondary to these changes. *(Behrman, 2030–2932; Duncan, 160–164; Goetz, 1074; Ropper and Samuels, Chapter 37)*

**97.** **(E)** Menkes disease is an X-linked disorder of copper metabolism. This rare disorder is inherited as a sex-linked recessive trait. Poor feeding and failure to gain weight, instability of temperature (mainly hypothermia), and seizures become apparent in early infancy. The manifestations of this disease are attributable to one of numerous known mutations in a copper-transporting adenosine triphosphatase (ATPase),

ATP7A, that is attributed to a failure of absorption of copper from the gastrointestinal tract and a profound deficiency of tissue copper. Furthermore, because copper fails to cross the placenta, a severe reduction of copper in the brain and liver is evident from birth. In this sense, the abnormality of copper metabolism is the opposite of that in Wilson disease. *Ropper and Samuels, Chapter 37)*

**98. (C)** In Wilson's disease, seizures occur in about 6% of cases and may be associated with disorders of movement, psychiatric and behavioral derangements, and impaired cognition. A slit-lamp examination of the cornea shows a Kayser–Fleischer ring, which is a peripheral corneal deposition of copper involving Descemet's membrane. *(Duncan, 165–166)*

**99. (B)** In nonketotic hyperglycinemia, severe epilepsy and mental retardation with abnormal EEG are the key features. Glycine concentration is very high in plasma and urine without ketosis or acidosis. Reduced glycine cleavage enzyme activity is demonstrated in liver biopsy. *(Duncan, 165–166)*

**100. (A)** MELAS syndrome is a mitochondrial disease caused by a defect in respiratory chain enzyme deficiencies. Patients with this syndrome have normal early development followed by poor growth, focal or generalized seizures, and recurrent acute episodes that resemble strokes or prolonged transient ischemic attacks. The stroke deficits often improve but in some cases lead to a progressive encephalopathy. Some have hemicranial headaches that cannot be distinguished from migraine, and others suffer repetitive vomiting or episodic lactic acidosis. If there is a characteristic feature it is the unusual clinical pattern of focal seizures, sometimes prolonged, which herald a stroke and produce an unusual radiographic pattern of infarction involving the cortex and immediate subcortical white matter. The CT scan may also show numerous low-density regions that have no clinical correlates. Most patients have ragged red fibers in muscle but only rarely is there weakness or exercise intolerance. Approximately 80% of MELAS cases are related to a mitochondrial mutation occurring at the 3243 site of the mitochondrial gene or, in a few instances, at an alternative locus that also codes for a segment of transfer RNA. Maternal inheritance is common but sporadic cases are well known. *(Ropper and Samuels, Chapter 37)*

**101. (D)** Carbamazepine inhibits uroporphyrinogen-1 synthase, which increases the frequency of seizures in case of porphyria, a condition caused by a defect in uroporphyrinogen-1 synthase, coproporphyrinogen oxidase, and protoporphyrine oxydase in erythrocytes. *(Duncan, 165–166)*

**102. (B)** Carbamazepine increases the rate of metabolism of steroid hormones by inducing the activity of hepatic microsomal enzymes. This will reduce the plasma estrogen level in women taking carbamazepine and birth control pills. As a consequence, there is a reduction of contraceptive efficacy. Vigabatrin, valproate, benzodiazepines, and gabapentin do not induce hepatic enzymes. *(Duncan, 268)*

**103. (D)** The nature of the underlying pathology is a key determinant of outcome of epilepsy surgery. Small low-grade glioma, dysembryolastic neuroepithelial tumors, and small cryptic vascular malformations carry the best prognosis for epilepsy surgery, with about 70% to 80% of cases being rendered seizure-free following adequate resection. In an MRI-based study, 62% of patients with hippocampal sclerosis became seizure-free after surgery. Large or complex vascular malformations, particularly if they have bled and resulted in deposition of hemosiderin or traumatic injuries, have a poorer prognosis after epilepsy surgery, with less than 50% of patients rendered seizure-free. Cortical dyplasia carries a poor prognosis for surgery, presumably because such abnormalities represent a more diffuse process than is usually apparent. Only a small percent of patients with gross cortical dysplasia become seizure-free following epilepsy surgery. *(Duncan, 359–360)*

**104. (D)** The characteristic polysomnographic findings in REM behavior disorder (RBD) consists

of the absence of muscle atonia and the presence of increased EMG activity in the upper and lower limbs. *(Bradley, 1807–1814)*

**105. (B)** In multiple system atrophy, polysomnography shows a reduction of slow-wave, REM, and total sleep time, increased sleep latency, and increased number of awakenings during sleep. *(Bradley, 1807–1814)*

**106. (E)** In restless leg syndrome, polysomnography documents sleep disturbance and periodic limb movements in sleep, which is found in at least 80% of patients. Diagnosis of periodic limb movements in sleep is based on an index gauging this (the number of periodic limb movements in sleep per hour of sleep); periodic limb movements in sleep of up to five is considered normal. High periodic limb movements in sleep with arousal are considered more significant than movements without arousal. *(Bradley, 1807–1814)*

**107. (A)** Narcolepsy rarely begins before adolescence and is characterized by paroxysmal attacks of irrepressible daytime sleep, which is sometimes associated with transient loss of muscle tone. Overnight polysomnography findings include short sleep latency, excessive disruption of sleep with frequent arousals, reduced total sleep time, excessive body movements, and reduced slow-wave sleep. *(Bradley, 1807–1814)*

**108. (C)** In Alzheimer disease (AD), the essential features of sleep architectural alterations are reduced total sleep time, decreased REM and slow-wave sleep, reduction of sleep spindles and K complexes, increased nighttime awakenings, and sleep fragmentation. There is a high frequency of sleep apnea in those with AD compared with age-matched controls. *(Bradley, 1807–1814)*

**109. (F)**

**110. (G)**

**111. (B)**

**112. (C)**

**113. (E)**

**114. (D)**

**115. (A)**

**Explanations 109 through 115**

EEG 1 shows generalized paroxysmal fast activity that may be seen in porencephaly. Reduced EEG amplitude, focal slow waves, and focal epileptiform activity over areas of atrophic brain may be also seen. EEG 2 shows a pattern of discontinuous background activity with a series of bursts separated by lower voltage interburst periods. This is characteristic of trace discontinue, a normal EEG pattern for a 29-week-old premature baby.

Hypsarrhythmia corresponds to the EEG pattern seen in EEG 3. It is a disorganized EEG background seen in West syndrome. EEG 4 shows K complexes, which are diphasic waves consisting of an initial sharply contoured transient followed by a high-amplitude slow wave, usually of delta frequency. EEG 5 shows 3-Hz burst of spikes and waves that may be seen in typical absence seizure. EEG 6 shows a pattern of positive occipital transients, which are surface-positive bisynchronous sharp transients. They occur in stage I of sleep. EEG 7 shows triphasic waves, a pattern seen in hepatic failure, renal failure, and drug intoxication. *(Spehlman, 327, 31, 175, 201–205, 254–255)*

**116. (A)** Tetrodotoxin clogs the sodium-permeable pore by binding tightly to a specific site on the outside of the channel. It blocks all sodium-dependent action potentials and therefore is usually fatal when ingested. *(Bear, 89)*

**117. (D)** Axonal transport from the nerve terminals to the cell body is called retrograde transport, whereas axonal transport occurring from the cell body to terminals is called anterograde transport and is dependent on a protein called kinesin. Retrograde transport allows the neuron to respond to molecules such as growth factors, which are taken up near the axon

terminal by either pinocytosis or receptor-mediated endocytosis. Retrograde transport along axonal microtubules is driven by the protein dynein rather than by kinesin. After replicating in muscle tissue, at a site of a bite, the rabies virus is then transported in a retrograde direction to the cell bodies of neurons innervating muscles. Anterograde transport is used by radioactively labeled amino acids when injected into neuronal cell bodies. They will be incorporated into neuronal proteins and transported in an anterograde direction. The axons containing the radiolabeled proteins can then be detected by autoradiography. *(Haines, 19–20)*

**118.** **(E)** Unlike neurons, astrocytes do not propagate action potentials. However, they provide neurons with structural support and maintain the appropriate microenvironment essential for neuronal function. Astrocytes associated to oligodendrocytes and microglia form the major types of glial cells in the central nervous system. Astrocytes and oligodendrocytes are derived from the neuroectoderm, whereas microglial cells are derived from the mesoderm. Oligodendrocytes are responsible for central nervous system myelination. During development, astrocytes, in the form of radial glial cells, provide a pathway for neuronal migration. Microglial cells are the immune effector cells of the central nervous system. They are able to become phagocytic scavenger of the central nervous system when it suffers injury. Activated migroglial cells migrate to the site of damage, where they proliferate and phagocytose cell debris. *(Haines, 259–228)*

**119.** **(C)** The first step in evoking somatic sensations is the activation of peripheral mechanoreceptors. Cutaneous tactile receptors are located in the basal epidermis and dermis of the glabrous and hairy skin. Merkel cells are low threshold unencapsulated mechanoreceptors signal tonic events such as discrete small indentation in the skin. They provide input to type II afferent sensory fibers related to both displacement and velocity of a stimulus. They produce sensation to touch and pressure. They have small receptive field size. They are also capable of encoding stimulus intensity or duration because they are slow adapting and are active so long as the stimulus is present. For that reason they are crucial to reading Braille. Receptors such as Meissner corpuscles respond to each initial application or removal of a stimulus but fail to respond during maintained stimulation. They are called a rapidly adapting receptors. *(Haines, 264–265)*

**120.** **(D)** Muscle spindles such as nuclear bag fibers are small encapsulated sensory receptors that have a spindle-like or fusiform shape and are located within the fleshy part of the muscle. Their main function is to signal changes of the length of the muscle within which they reside. Changes in the length of muscles are closely associated with changes in the angles of the joint that the muscles cross. Thus, muscle spindles can be used by the central nervous system to sense relative positions of the body segments. *(Kandel, 718)*

**121.** **(B)** Gap junction channels provide the ultrastructural components of electrical synapse. At electrical synapses, the gap junction channels that connect the pre- and postsynaptic cells provide a low-resistance (high-conductance) pathway for electrical current to flow between the two cells. Electrical synapse provides a cytoplasmic continuity between a pre- and postsynaptic cells, and a synaptic transmission is usually bidirectional and without any delay. At chemical synapses, there is no direct continuity or direct low-resistance pathway between pre- and postsynaptic cells. The synaptic transmission is unidirectional, using a chemical transmitter that is released from presynaptic vesicles to activate postsynaptic receptors. *(Kandel, 176–177)*

**122.** **(A)** The rods and cones of the retina are responsible for photoreception, a process by which photons are detected and the information is transduced into an electrochemical signal. *(Haines, 314)*

**123.** **(B)** Rod cells are photoreceptor cells in the retina responsible for night vision. Named for their cylindrical shape, rods are concentrated at the outer edges of the retina and are used in peripheral vision. There are about 120 million

rod cells in the human retina. At rest, in the dark, sodium ions flow into the rod's outer segment. This high resting level of sodium permeability results in a relatively high resting potential for rod cells, about −40 mV. These sodium channels of the outer segment membrane, which are normally open, close in response to increased calcium or a reduction in cyclic guanosine monophosphate. This drives the membrane potential away from the sodium equilibrium potential and toward the potassium equilibrium potential, and the rod cell is hyperpolarized in response to light stimulus. In the absence of light, the photoreceptor terminals constantly release the transmitter glutamate at these synapses. The arrival of a light-induced wave of hyperpolarization causes a transient reduction in this tonic release of glutamate. The perception of color is achieved in humans through color receptors containing pigments carried by cone cells. *(Haines, 314–315)*

**124. (B)** Motor units can be divided into two categories (slow-twitch and fast-twitch) based on the metabolic and physiological properties of the muscle fibers and their innervations. Type I, slow-oxidative, slow-twitch, or "red" muscle is dense with capillaries and is rich in mitochondria and myoglobin, giving the muscle tissue its characteristic red color. It can carry more oxygen and sustain aerobic activity. Because of the ability of type I muscle fibers to utilize glucose and oxygen from the bloodstream, these fibers can generate abundant adenosine triphosphate (aerobic metabolism) and fuel the contractile apparatus for long periods of contraction time, making these motor units resistant to fatigue. The trade-off, however, is that these muscle fibers can generate only relatively small levels of force or tension. The postural muscles, such as deep back muscles, are composed predominantly of this fiber type. These muscles may contract at low level of tension but for exceedingly long periods of time. In contrast, the type II or fast-twitch muscle fibers generate much higher levels of force but for comparatively brief periods of time. Muscles used during strenuous exercise are examples of type II muscle fibers: they contract with greater force than postural muscles but for shorter period of time. The fast-twitch muscle fibers are divided into two types: the first type, the fast fatigable type IIB muscle fibers, contain large stores of glycogen that provide the energy necessary to produce relatively greater amount of force compared with slow-twitch muscle fibers. The second type is type IIA, which is an intermediate between the type I slow-twitch and type II fast-twitch muscle fiber. Muscles generally contain a mixture of motor units; the proportions vary according to the demands placed on the muscle. The gastrocnemius muscle is a dynamic, powerful muscle used in running and jumping. It is considered a fast-twitch muscle and contains type IIB muscle fibers innervated by large-diameter, rapidly conduction axons. *(Haines, 381–382)*

**125. (D)** Nerve cooling significantly slows sodium channel inactivation, which causes prolongation of the absolute refractory period. This results in a reduction in nerve conduction velocity, a prolongation of motor nerve distal latency, and an increase in the amplitude of sensory nerve action potentials. *(Dumitru, 188–189)*

**126. (B)** Most commercially available instruments for nerve conduction studies have variable low- and high-frequency filter systems that can be adjusted by the clinician to optimize the frequency content of the signal under investigation and limit undesirable noise. This low- and high-frequency filter combination constitutes a window through which to observe a relatively limited frequency domain, referred to as a *handwidth*. The frequencies above and below the handwidth's limitations are severely attenuated by the low- and high-frequency filters, respectively. Increasing the low-frequency (high-pass) filter from 10 to 300 Hz reduces the amplitude of sensory nerve's action potential, shortens its peak latency, and reduces the duration of the negative spike. The onset latency remains unchanged; however, the morphology of the sensory nerve's action potential become triphasic. The waveform's initial departure from the baseline occurs over a relatively short period of time. This portion of the waveform

has a minimal amplitude contribution from the low frequencies contained in the potential. Because elevating the low-frequency filter does not affect high frequencies, the onset latency remains unchanged. *(Dumitru, 82–83)*

**127.** **(C)** The biological waveforms of the compound muscle action potential have both low- and high-frequency subcomponents. The high frequencies of most waveforms are contained in the portions of the potential that change rapidly, as during the rise time or inflection points. Increasing the low-frequency (high-pass) filter from 1 to 100 Hz removes more low frequencies from the motor waveform. This reduces the amplitude of the compound nerve's action potential, shortens its peak latency, reduces the duration of the negative spike, and increases the number of phases of motor response. However, the onset latency is not significantly affected. *(Dumitru, 83)*

**128.** **(B)** Lowering the high-frequency filter results in the removal of some high-frequency components from the sensory response waveform, leaving it with a relatively lower-frequency content below the upper cutoff limit, which is 500 Hz in this question. This delays distal and peak latencies, reduces the amplitude of the sensory nerve action potential, and prolongs the duration of the negative spike. *(Dumitru, 83)*

**129.** **(D)** In recording compound muscle action potentials, a reduction in the high-frequency (low filter) component from 10,000 to 500 Hz causes a delay in the onset and peak latency, mild amplitude reduction, and longer negative spike duration. *(Dumitru, 83–84)*

**130.** **(D**) The F response is generated by supramaximal stimulation of a motor nerve. It is produced by an antidromic action potential traveling centripetally toward the spinal cord. At the level of the corresponding anterior cells, this antidromic action potential establishes a persistent or second action potential at the level of either the perikaryon or its axon hillock. The action potential produced at this location is carried in a centrifugal or orthodromic direction along the entire length of one or more of the same motor axons back to the original target muscle. F response latency is shorter in the arms than in the legs because the length of nerve traveled is less. Taller patients have longer F responses than do shorter patients. Thus, F latency depends on the distal motor latency, the conduction velocity, and the height of patient. *(Dumitru, 238–241)*

**131.** **(B)** One of the most profound factors influencing nerve conduction studies is temperature. The cooling of a single myelinated fiber results is reduction of its excitability without any effect on transmembrane resistance. *(Dumitru, 188–189)*

**132.** **(C)** The action potential's amplitude increases as the nerve's temperature declines. In addition to amplitude, the action potential's rise and fall times are also increased. The conduction velocity is reduced with nerve temperature decline. *(Dumitru, 188–189)*

**133.** **(B)** The reduction of nerve temperature causes a prolongation of the absolute refractory period mainly through a slowing of sodium channels inactivation. *(Dumitru, 188–189)*

**134.** **(D)** Figure 4-8 illustrates the F wave response. The afferent and efferent pathways are carried by the stimulated motor nerve. The response is obtained by supramaximal stimulation of a motor nerve. F latency depends on the distal motor latency, the conduction velocity, and the height of the tested patient. In acute inflammatory demyelinating polyneuropathy, motor nerve demyelination dramatically reduces the nerve conduction velocity, which results in absence or prolonged latency of the F response. *(Preston, 48–50)*

**135.** **(E)** Figure 4-9 illustrates the H reflex. It is elicited by stimulating the tibial nerve in the popliteal fossa, recording the gastrocsoleus muscle. The circuit of H reflex involves Ia muscle spindles as sensory afferents and the motor neurons and their axons as efferents. It is obtained by submaximal stimulation of the tibial nerve. It is the electrical correlate of ankle jerk. H reflex may be absent or have prolonged

latency in case of S1 radiculopathy and generalized neuropathy. *(Preston, 53–56)*

**136. (B)** Figure 4-10 illustrates a motor median nerve conduction study recording from the abductor pollicis brevis. The median nerve distal latency (normally 4.5 ms or less) was prolonged in the demylination range. The median nerve conduction velocity (normally 49 m/s) was reduced in the demyelination range. The absence of compound muscle action potential dispersion or conduction block is suggestive of congenital demylinating polyneuropathy. *(Dumitru, 904–905)*

**137. (C)** Figure 4-11 illustrates a motor nerve conduction study of a ulnar nerve, stimulating at the wrist and the elbow and recording at the abductor digiti minimi. There is a dramatic reduction of the nerve conduction velocity in the demyelinating range with conduction block and dispersion of the compound muscle action potential. These findings are suggestive of acquired demyelinating polyneuropathy. *(Dumitru, 951–952)*

**138. (A)** Figure 4-12 illustrates a motor nerve conduction study of a median nerve, stimulating at the wrist and the elbow and recording at the abductor pollicis brevis. The median nerve distal latency is prolonged (normal 4.5 ms or less), suggesting a median nerve dysfunction at the wrist consistent with the diagnosis of carpal tunnel syndrome. *(Dumitru, 1061–1063)*

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CHAPTER 5

# Neuromuscular Diseases
## Questions

**1.** Vasculitic neuropathy may occur following

(A) hepatitis C infection
(B) botulism
(C) neomycin administration
(D) *Campylobacter jejuni* infection
(E) amiodarone administration

**2.** Human immunodeficiency virus (HIV)–associated Guillain–Barré syndrome (GBS) occurs most often

(A) when retroviral therapy is withdrawn
(B) when the CD4+ cell count is less than $100/mm^3$
(C) when the CD4+ cell count is less than $50/mm^3$
(D) early in the course of the disease or at the time of seroconversion
(E) following immune reconstitution

**3.** The most frequent HIV neuropathy is

(A) mononeuritis multiplex
(B) distal sensory polyneuropathy
(C) motor polyneuropathy
(D) acute inflammatory demyelinating polyneuropathy
(E) chronic inflammatory demyelinating polyneuropathy

**4.** The most reported vaccine associated with Guillain–Barré syndrome is

(A) rabies vaccine
(B) hepatitis vaccine
(C) influenza virus vaccine
(D) tetanus and diphtheria toxoids
(E) rubella virus vaccine

**5.** Respiratory failure in myotonic dystrophy type 1 (DM1)

(A) does not parallel the muscular manifestations of DM1
(B) is usually triggered by pulmonary embolus
(C) may be the first manifestation of DM1
(D) correlates in occurrence with the severity of the genetic defect
(E) causes nocturnal dyspnea and hypoventilation correlating with the severity of limb weakness

**6.** Mutation in which of the following myelin proteins genes causes predominantly axonal neuropathy?

(A) Myelin-oligodendrocyte glycoprotein
(B) Myelin-associated glycoprotein
(C) PMP-22 protein
(D) Myelin protein zero (MPZ)
(E) Early growth response-2

**7.** Which of the following is the first step in activation of botulinum toxin (BTX)?

(A) A release of a zinc endopeptidase into the cytoplasm
(B) A proteolytic cleavage of the BTX polypeptide chain into a 100-kDa heavy chain (H) and a 50-kDa light chain (L) linked by a disulfide bond (S-S)
(C) Internalization of the BTX by energy-dependent endocytosis
(D) Enzymatic cleavage by the light chain of BTX of selected proteins that are critical for fusion of the presynaptic acetylcholine vesicle with the presynaptic membrane
(E) Binding of the light chain of the toxin to the presynaptic plasma membrane of the motor axon terminal

**8.** The classic neurophysiological finding in botulism is

(A) reduction of the compound muscle action potential (CMAP), which increases after repetitive high-frequency nerve stimulation
(B) reduction of the compound muscle action potential (CMAP), which increases after repetitive low-frequency nerve stimulation
(C) absence of sensory responses on nerve conduction studies
(D) absence of motor response after repetitive high-frequency nerve stimulation
(E) reduction of the conduction velocity in motor nerves in the demyelinating range

**9.** In which of the following disorders does electrical myotonia occur (on EMG testing) without clinical myotonia?

(A) Hyperkalemic periodic paralysis
(B) Schwartz–Jampel syndrome
(C) Paramyotonia congenita
(D) Acid maltase deficiency
(E) Myotonic dystrophy type 2 (proximal myotonic myopathy)

**10.** In traumatic nerve injury, neuropraxia is defined by

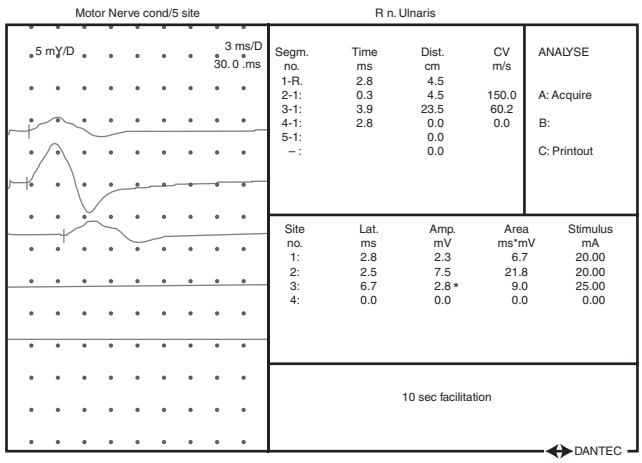
(A) complete axonal degeneration; disruption of all connective tissue elements
(B) focal demyelination; block of nerve conduction without axonal degeneration
(C) axonal degeneration with intact endoneurium
(D) axonal degeneration and endoneurial disruption with intact perineurium
(E) axonal degeneration and endoneurial and perineurial disruption with intact epineurium

**11.** Which of the following is true of neuropraxia?

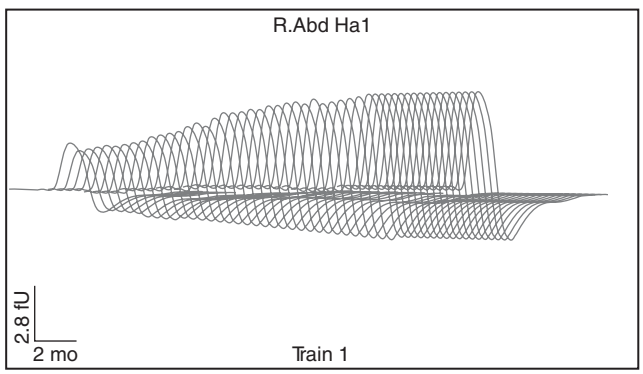
(A) At least 6 months is needed for some recovery.
(B) Remyelination is the main mechanism of recovery.
(C) Collateral sprouting is the main mechanism of recovery.
(D) Regeneration from the proximal site of injury is the main mechanism of recovery.
(E) It commonly results from axonal lacerations.

**12.** A 50-year-old man developed progressive proximal lower extremities weakness, dry month, and easy fatigability over several months. His weakness is worsened by hot weather. The result of 20-Hz repetitive nerve stimulation of the right abductor digiti minimi is shown in Figure 5-1. This suggests

(A) a normal response
(B) Lambert–Eaton myasthenic syndrome
(C) botulism
(D) myotonic dystrophy
(E) myasthenia gravis




A




B

**FIG. 5-1.** (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders.* New York: McGraw-Hill; 2008.)

**13.** Figure 5-2 is consistent with the diagnosis of

(A) motor neuron disease
(B) diabetic neuropathy
(C) chronic inflammatory demyelinating polyneuropathy
(D) hereditary neuropathy with liability to pressure palsies
(E) schwannoma

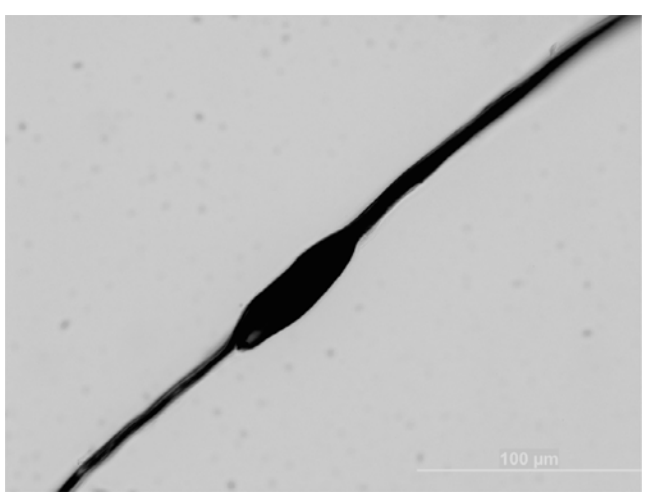



**FIG. 5-2.** (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders.* New York: McGraw-Hill; 2008.)

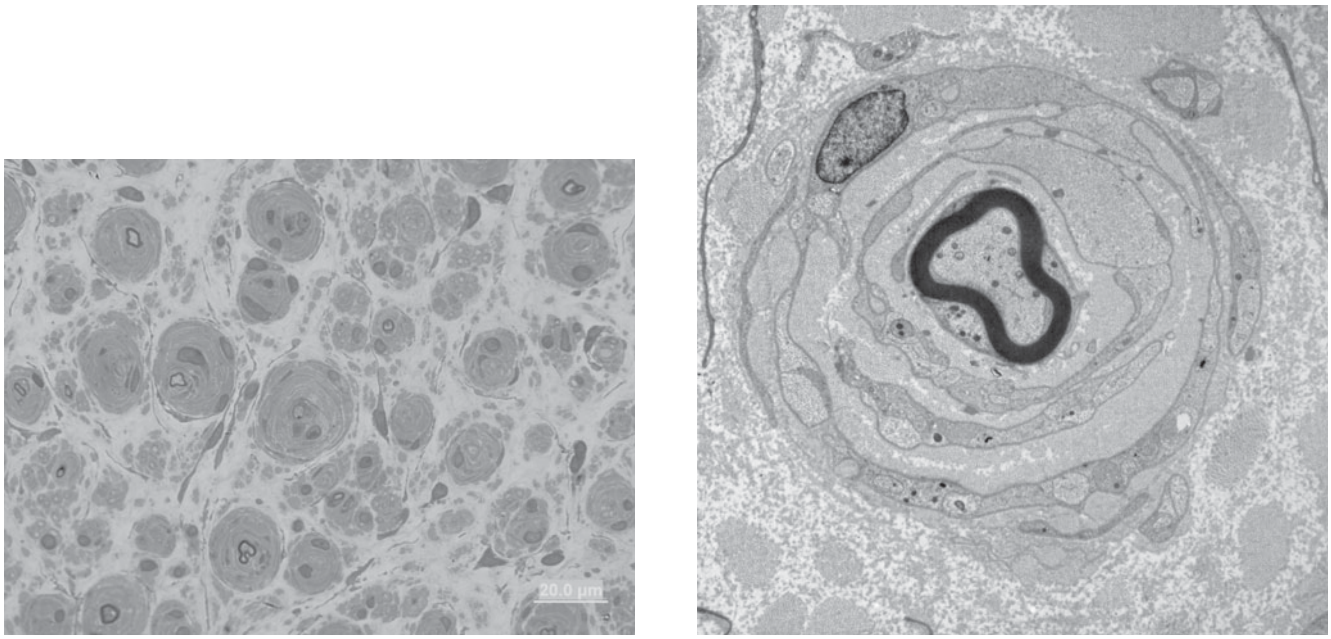
**14.** The most likely diagnosis suggested by Figure 5-3 is

(A) normal peripheral nerve structure
(B) Wallerian degeneration
(C) segmental peripheral nerve demyelination
(D) amyloid polyneuropathy
(E) necrotizing vaculitis

**FIG. 5-3.** (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders.* New York: McGraw-Hill; 2008.)

**15.** Figure 5-4 is suggestive of

(A) acute inflammatory demyelinating polyneuropathy
(B) Charcot–Marie–Tooth disease type 1
(C) amyloidosis
(D) polyarteritis nodosa
(E) diabetic neuropathy




A B

**FIG. 5-4.** See color insert. (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders.* New York: McGraw-Hill; 2008.)

**16.** Primary lateral sclerosis (PLS) is characterized by

(A) asymmetric leg weakness, which is frequently the initial manifestation of the disease
(B) the fact that genitourinary symptoms never occur in PLS
(C) a life expectancy similar to that of patients with amyotrophic lateral sclerosis (ALS)
(D) the fact that PLS never progresses to ALS
(E) the fact that bulbar muscles are initially affected in PLS in 80% of cases

**17.** Hereditary spastic paraplegia is caused by a mutation in the gene coding for

(A) superoxide dismutase
(B) hexominidase A deficiency
(C) senataxin
(D) microtubule associated tau
(E) atlastin

**18.** Hereditary spastic paraplegia may have a clinical presentation similar to that of

(A) Guillain–Barré syndrome
(B) copper deficiency
(C) multifocal motor neuropathy
(D) chronic inflammatory demylinating polyneuropathy
(E) Charcot–Marie–Tooth neuropathy type 1

**19.** Spinal muscular atrophy type I (Werdnig–Hoffman disease) is characterized by

(A) severe weakness of facial muscles
(B) preservation of deep tendon reflexes
(C) abdominal breathing
(D) severe mental retardation
(E) delay in the capability of sitting independently

**20.** A 35-year-old man consults the neurologist because of muscle cramping and fatigue. His physical examination is significant for limb fasciculations and gynecomastia. His CPK level is at 450 UI/L (normal is less than 170 UI/L). The most likely diagnosis is

(A) bulbospinal muscular atrophy
(B) inflammatory myopathy
(C) adult-onset spinal muscular atrophy
(D) ALS
(E) multifocal motor neuropathy

**21.** Duplication of the peripheral myelin protein (PMP-22) gene causes

(A) Charcot–Marie–Tooth type 1A disease
(B) Charcot–Marie–Tooth type 1B disease
(C) Charcot–Marie–Tooth type 1C disease
(D) Charcot–Marie–Tooth type 1E disease
(E) Charcot–Marie–Tooth type 2B1 disease

**22.** De novo deletion of the gene coding for PMP-22 causes

(A) Charcot–Marie–Tooth type 3 disease (Dejerine–Sottas disease)
(B) Charcot–Marie–Tooth type 2A1 disease
(C) Charcot–Marie–Tooth type 1A disease
(D) hereditary neuropathy with liability to pressure palsies
(E) Charcot–Marie–Tooth type 1C disease

**23.** Charcot–Marie–Tooth type 1B disease is caused by a mutation in the gene coding for

(A) myelin protein zero (MPZ)
(B) connexin 32
(C) neurofilament light chain
(D) heat-shock 27-kDa protein-1
(E) early growth response-2 protein (ERG2)

**24.** A 27-year-old man developed a progressively worsening unsteady gait and a visual deficit most prominent at night. Neurological examination demonstrated cerebellar ataxia, reduced pinprick and vibration sensation in all extremities, and the absence of deep tendon reflexes throughout. Ophthalmological examination revealed retinitis pigmentosa. Cerebrospinal fluid examination was significant for an elevated concentration of protein. These finding are associated with

(A) reduced α galactosidase activity
(B) reduced β galactosidase activity
(C) reduced arylsulfatase A activity
(D) deficiency of high-density lipoprotein
(E) impaired α-oxidation of phytanic acid

**25.** Acute motor axonal neuropathy is characterized by

(A) the lengthy recovery time, which is usually longer than for acute inflammatory demyelinating polyneuropathy
(B) the mortality rate, which is close to 20%
(C) respiratory failure requiring mechanical ventilation, which may be seen in up to one third of patients
(D) the fact that proximal muscles are often more severely affected than distal muscles
(E) the fact that there is no autonomic dysfunction

**26.** Anti-GM1 antibodies are most frequently seen in

(A) chronic inflammatory demyelinating polyneuropathy
(B) multifocal motor neuropathy
(C) Miller–Fisher syndrome
(D) acute inflammatory demyelinating polyneuropathy
(E) acute sensory neuropathy affecting small fibers

**27.** The most likely diagnosis suggested by Figure 5-5 is

(A) a dorsal scapular nerve lesion
(B) a long thoracic nerve lesion
(C) an axillary nerve lesion
(D) a thoracodorsal nerve lesion
(E) a musculocutaneous nerve lesion

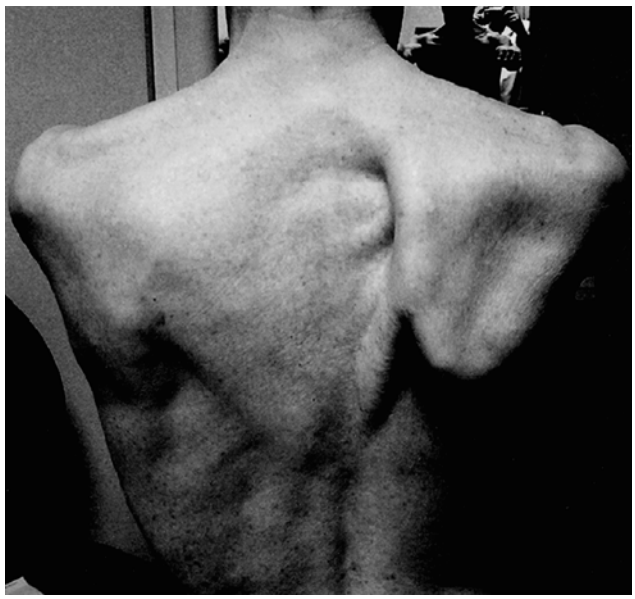


**FIG. 5-5.** (Photo courtesy of Steven A. Greenberg, MD. Reproduced with permission from Greenberg SA, Amato AA. *EMG Pearls.* Philadelphia: Hanley & Belfus; 2004.)

**28.** Figure 5-6 is suggestive of

(A) inclusion body myositis
(B) dermatomyositis
(C) congenital muscular dystrophy
(D) mitochondrial myopathy
(E) metabolic myopathy

**29.** The molecular abnormality associated with the neurophysiological findings illustrated in Figure 5-7 is

(A) expansion of unstable polymorphic cytosine–thymine–guanine (CTG) trinucleotide repeats
(B) mutation in the gene coding for superoxide dismutase
(C) de novo deletion of the gene coding for PMP-22
(D) hexominidase A deficiency
(E) duplication of the PMP-22 gene

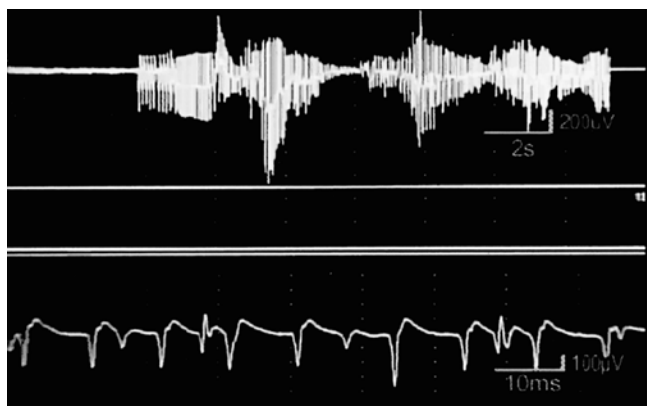



**FIG. 5-7.** (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders.* New York: McGraw-Hill; 2008.)

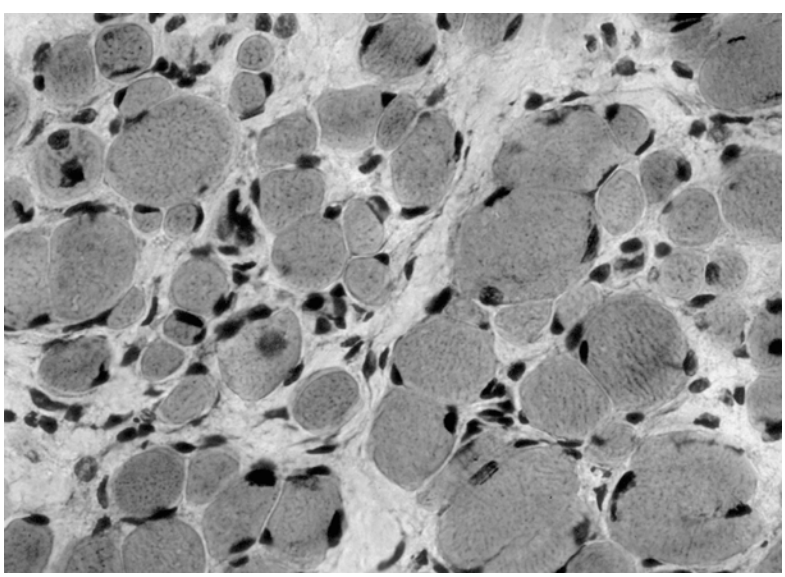
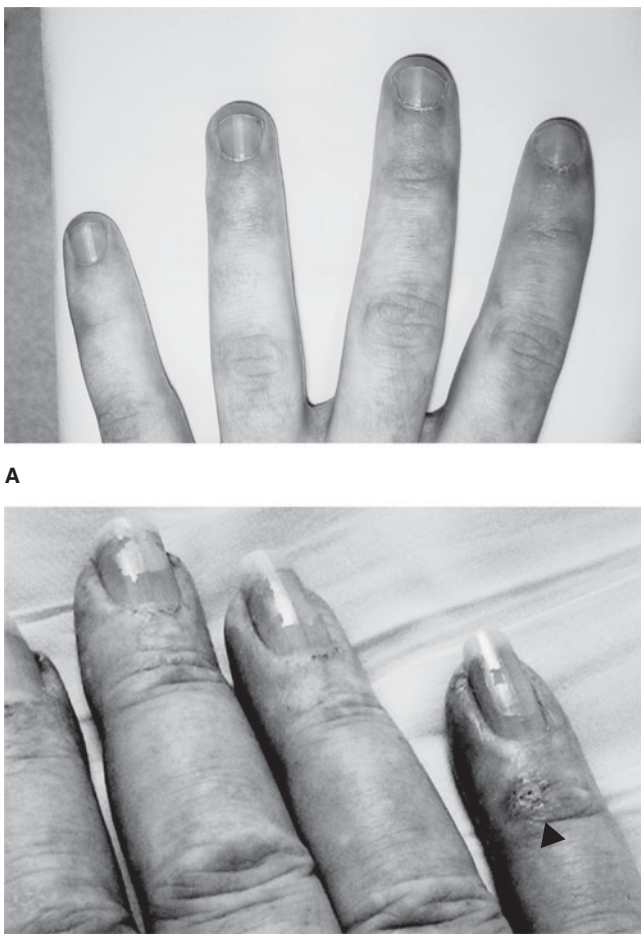


**FIG. 5-6.** See color insert. (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders.* New York: McGraw-Hill Medical; 2008.)

**30.** The most likely diagnosis suggested by Figure 5-8 is

(A) vasculitic neuropathy
(B) hereditary neuropathy
(C) dermatomyositis
(D) amyloid myopathy
(E) inclusion body myositis



**A**

**B**

**FIG. 5-8.** See color insert. (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders.* New York: McGraw-Hill; 2008.)

**31.** Figure 5-9 is an ATPase 4.5 staining of a muscle biopsy. The most likely diagnosis is

(A) mitochondrial myopathy
(B) steroid myopathy
(C) myotonic dystrophy
(D) nemaline myopathy
(E) dermatomyositis

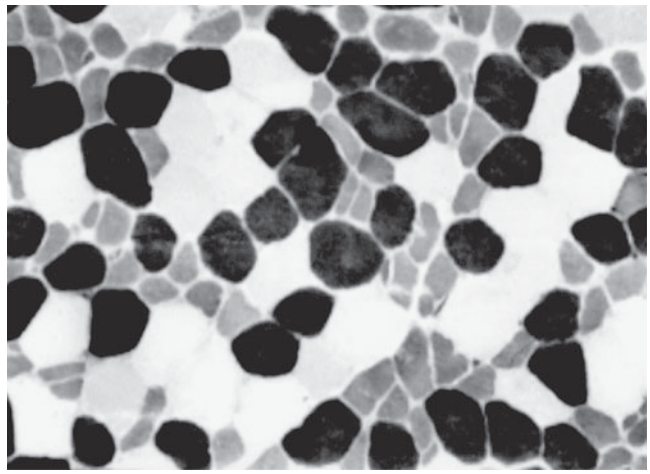


**FIG. 5-9.** See color insert. (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders.* New York: McGraw-Hill Medical, 2008.)

**32.** Mutation of the ryanodine receptor 1 (RYR1) gene is responsible for

(A) myotonic dystrophy
(B) Charcot–Marie–Tooth type 1A disease
(C) motor neuron disease
(D) spinal muscular atrophy
(E) malignant hyperthermia

**33.** A 10-year-old boy had difficulties with walking since the age of 1 year. His CPK level is 20 times the upper limit of normal and his muscle biopsy showed the presence of staining with antidystrophin antibodies. The most likely diagnosis is

(A) Becker muscular dystrophy
(B) Duchenne muscular dystrophy
(C) myotonic dystrophy
(D) nemaline myopathy
(E) inclusion body myositis

**34.** A 35-year-old man suddenly developed profound weakness of all his extremities. Physical examination demonstrated severe quadriplegia with preservation of respiration, facial and eyes movements, and absence of deep tendon reflexes. His laboratory workup was significant for a serum potassium level of 2 mEq/L. The most likely cause of these finding is

(A) acute peripheral nerve demyelination
(B) mutation in the calcium channel gene
(C) mutation in the chloride channel gene CLcN1
(D) mutation in the potassium channel gene KCNJ2
(E) expansion of unstable polymorphic cytosine–thymine–guanine (CTG) trinucleotide repeats

**35.** The association of facial weakness and ptosis without ophtalmoplegia is highly suggestive of

(A) myasthenia gravis
(B) acide maltase deficiency
(C) myotonic dystrophy type1
(D) Kearns–Sayre syndrome
(E) thyrotoxic paralysis

**36.** A 14-year-old boy was referred to the neurologist by his soccer coach because of difficulties in running at the beginning of the game, which improved 20 minutes later. Neurological examination was normal except that the boy had difficulty in relaxing his grip, which improved when he was asked to grip the examiner's hand several times. The most likely diagnosis associated with these clinical findings is

(A) myotonic dystrophy
(B) myotonia congenita
(C) paramyotonia congenita
(D) myasthenia gravis
(E) Lambert–Eaton myasthenic syndrome

**37.** The presence of anti-Jo-1 antibodies in a 48-year-old woman who was diagnosed with dermatomyositis precludes the use of

(A) cyclosporine
(B) mycophenolate mofetil
(C) intavenous immunoglobulin
(D) prednisone
(E) methotrexate

**38.** In myoadenylate deaminase deficiency, the forearm ischemic test would be expected to produce which of the following results?

(A) A fivefold increase in the levels of ammonia and lactate
(B) A fivefold increase in the level of lactate with no change in the level of ammonia
(C) No change in the levels of lactate and ammonia
(D) No change in lactate level and a fivefold increase in the level of ammonia
(E) A less than threefold increase in the level of ammonia and a fivefold increase in the level of lactate

**39.** The most frequent malignancy associated with subacute sensory neuronopathy is

(A) adenocarcioma of the lung
(B) small cell lung cancer
(C) breast cancer
(D) ovarian cancer
(E) lymphoma

**40.** Deletion of D4Z4 repeats is associated with

(A) fascioscapulohumeral dystrophy
(B) myotonic dystrophy
(C) myotonia congenital
(D) hereditary neuropathy with a tendency toward pressure palsies
(E) Charcot–Marie–Tooth neuropathy type IA

**41.** Which of the following descriptions best characterizes endplate noise?

(A) Regularly occurring spikes fire at 0.5 to 10 Hz with a sound similar to rain on a roof and an initial positive deflection. They are not specific for muscle fiber damage.
(B) The spike is formed by an initial brief positive wave followed by a slow negative phase. It may be seen in cases of denervation.

(C) Low-amplitude monophasic potentials fire at 20 to 40 Hz and have a characteristic hissing sound on EMG.
(D) Spikes wax and wane in both amplitude and frequency.
(E) Brief, irregular spikes have a negative initial deflection and a crackling sound on EMG.

**42.** Which of the following descriptions best characterizes endplate spike?

(A) Regularly occurring spikes fire at 0.5 to 10 Hz with a sound similar to rain on a tin roof and an initial positive deflection. They are not specific for muscle fiber damage.
(B) The spike is formed by an initial brief positive wave followed by a slow negative phase. It may be seen in cases of denervation.
(C) Low-amplitude monophasic potentials fire at 20 to 40 Hz and have a characteristic hissing sound on EMG.
(D) Spikes wax and wane in both amplitude and frequency.
(E) Brief, irregular spikes have a negative initial deflection and a crackling sound on EMG.

**43.** Which of the following descriptions best characterizes positive sharp waves?

(A) Regularly occurring spikes fire at 0.5 to 10 Hz with a sound similar to rain on a tin roof and an initial positive deflection. They are not specific for muscle fiber damage.
(B) The spike is formed by an initial brief positive wave followed by a slow negative phase. It may be seen in cases of denervation.
(C) Low-amplitude monophasic potentials fire at 20 to 40 Hz and have a characteristic hissing sound on EMG.
(D) Spikes wax and wane in both amplitude and frequency.
(E) Brief, irregular spikes have a negative initial deflection and a crackling sound on EMG.

**44.** Which of the following descriptions best characterizes fasciculation?

(A) There is a spontaneous involuntary discharge of an individual motor unit.
(B) They are 150-Hz decrementing discharges of a single motor unit that have a characteristic pinging sound on EMG.
(C) It occurs from depolarization of a single muscle fiber, followed by ephaptic spread to adjacent denervated fibers.
(D) They are rhythmically grouped repetitive discharges of the same motor unit, often noted in radiation plexitis.
(E) Brief, irregular spikes have a negative initial deflection and a crackling sound on EMG.

**45.** Which of the following descriptions best characterizes complex repetitive discharges?

(A) There is a spontaneous involuntary discharge of an individual motor unit.
(B) They are 150-Hz decrementing discharges of a single motor unit that have a characteristic pinging sound on EMG.
(C) It occurs from depolarization of a single muscle fiber, followed by ephaptic spread to adjacent denervated fibers.
(D) They are rhythmically grouped repetitive discharges of the same motor unit, often noted in radiation plexitis.
(E) Brief, irregular spikes have a negative initial deflection and a crackling sound on EMG.

**46.** Which of the following descriptions best characterizes myokymic discharges?

(A) There is a spontaneous involuntary discharge of an individual motor unit.
(B) They are 150-Hz decrementing discharges of a single motor unit that have a characteristic pinging sound on EMG.
(C) It occurs from depolarization of a single muscle fiber, followed by ephaptic spread to adjacent denervated fibers.
(D) They are rhythmically grouped repetitive discharges of the same motor unit, often noted in radiation plexitis.
(E) Brief, irregular spikes have a negative initial deflection and a crackling sound on EMG.

**47.** Which of the following descriptions best characterizes neuromyotonic discharges?

(A) There is a spontaneous involuntary discharge of an individual motor unit.
(B) They are 150-Hz decrementing discharges of a single motor unit that have a characteristic pinging sound on EMG.
(C) It occurs from depolarization of a single muscle fiber, followed by ephaptic spread to adjacent denervated fibers.
(D) They are rhythmically grouped repetitive discharges of the same motor unit, often noted in radiation plexitis.
(E) Brief, irregular spikes have a negative initial deflection and a crackling sound on EMG.

**48.** Which of the following needle EMG parameters is seen in acute neuropathic axonal damage?

(A) Increased duration of the motor unit action potential
(B) Increased amplitude of the motor unit action potential
(C) Increased phases of the motor unit action potential
(D) Decreased activation of the motor unit action potential
(E) Decreased interference pattern on maximum voluntary effort

**49.** On needle EMG, early recruitment of the motor unit action potential is seen in the case of

(A) stroke
(B) chronic inflammatory demyelinating polyneuropathy
(C) acute inflammatory demyelinating polyneuropathy
(D) acute myopathy
(E) early reinnervation following severe denervation

**50.** Which of the following conditions is commonly associated with type I muscle fiber atrophy?

(A) Corticosteroid-induced myopathy
(B) Myotonic muscular dystrophy
(C) Hyperthyroidism myopathy
(D) Disuse atrophy
(E) Upper motor neuron disease

**51.** Which of the following is characteristic of myotonic muscular dystrophy type 1?

(A) The mutation in the myotonic dystrophy gene is an extension of the trinucleotide CTG.
(B) The abnormal gene is located on chromosome 17.
(C) Cardiac conduction abnormalities are rarely seen.
(D) Testicular hypertrophy is seen in most cases of myotonic dystrophy.
(E) There is no clinical myotonia.

**52.** The third cranial (oculomotor) nerve is most frequently affected in cases of

(A) diphtheria
(B) sarcoidosis
(C) diabetes mellitus
(D) Lyme disease
(E) porphyria

**53.** Primary axonopathy, with secondary demyelination and abnormal marker of the connexin-32 gene is a characteristic of

(A) hereditary sensory and motor neuropathy type I
(B) hereditary sensory and motor neuropathy type II
(C) hereditary sensory and motor neuropathy type III
(D) hereditary sensory and motor neuropathy type IV
(E) X-linked Charcot–Marie–Tooth disease

**54.** Which of the following myopathies is most likely to be associated with arrhythmia?

(A) Centronuclear myopathy
(B) Nemaline myopathy
(C) Acid maltase deficiency
(D) Carnitine deficiency
(E) Kearns–Sayre syndrome

**55.** The asymmetric and bilateral slowly progressive weakness of wrists, ulnar finger flexors, and knee extensors with normal facial muscles in a 55-year-old male is highly suggestive of

(A) inclusion body myositis
(B) acid maltase deficiency
(C) myotonic dystrophy
(D) polymyositis
(E) nemaline myopathy

**56.** Point mutation in the muscle chloride channel gene causes

(A) hyperkalemic periodic paralysis
(B) myotonia congenita
(C) hypokalemic periodic paralysis
(D) paramyotonia congenita
(E) none of the above

**57.** Which of the following differentiate Charcot–Marie–Tooth neuropathy type IA from Charcot–Marie–Tooth neuropathy type IB?

(A) It is anutosomal dominant disorder.
(B) It is an autosomal recessive disorder.
(C) Hammertoes and pes cavus are seen in up to 75% of patients.
(D) In nerve conduction studies, definite conduction block is characteristically present.
(E) PMP-22 is defective.

**58.** Which of the following is true of the dominant form of X-linked Charcot–Marie–Tooth disease?

(A) It is primarily a demyelinating disorder with secondary axonal degeneration.
(B) Mental retardation is commonly seen.
(C) The autosomal recessive form is more frequent than the autosomal dominant form.
(D) Cranial nerves are frequently involved.
(E) The connexin-32 gene is defective.

**59.** Which of the following is true of multifocal motor neuropathy?

(A) Anti-GQ1b antibodies are elevated in about 50% of patients.
(B) Bulbar function and cranial nerves are affected early.
(C) Upper motor neuron dysfunction is observed in most cases.
(D) Nerve conduction studies show conduction block and temporal dispersion.
(E) It is treated effectively with corticosteroids.

**60.** Which of the following excludes a diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy?

(A) Hyporeflexia or areflexia in four limbs
(B) Sensory level
(C) Evidence of demyelination and remyelination on histological examination of the nerve
(D) Prolonged distal latencies in two or more nerves in nerve conduction studies
(E) Negative VDRL in the cerebrospinal fluid

**61.** Which of the following characteristics is common to multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)?

(A) Symmetric distribution of weakness
(B) Prolonged F wave on nerve conduction study
(C) Normal sensory nerve conduction studies
(D) High anti-$G_{M1}$ antibody titers
(E) Effectively treated with prednisone

**62.** Which of the following may cause a predominantly sensory neuropathy?

(A) Arsenic exposure
(B) N-hexane exposure
(C) Dapsone
(D) Pyridoxine intoxication
(E) Nitrofurantoin

**63.** Which of the following is true of polymyalgia rheumatica?

(A) It is the most common cause of pain in young adults.
(B) It is more common in males than females by a ratio of 3 to 1.
(C) High creatine kinase is commonly found.
(D) The sedimentation rate is high.
(E) The response to steroids is poor.

**64.** Which of the following muscles is spared in facioscapulohumeral dystrophy?

(A) Latissimus dorsi
(B) Trapezius
(C) Rhomboid
(D) Serratus anterior
(E) Deltoid

**65.** Which of the following myopathies is caused by a defective synthesis of dysferlin *and* is linked to an abnormal gene located on chromosome 2p13?

(A) Miyoshi myopathy
(B) Nonaka myopathy (distal myopathy with rimmed vacuoles)
(C) Bethlem myopathy
(D) Emery–Dreifuss muscular dystrophy
(E) Oculopharyngeal muscular dystrophy

**66.** In Duchenne muscular dystrophy, the biochemical defect is based on a deficit of which of the following proteins?

(A) Dystrophin
(B) Myotonia protein kinase
(C) Laminin alpha 2
(D) Myelin basic protein
(E) Ryanodine receptor channels

**67.** Which of the following myopathies is related to a chloride channel defect?

(A) Becker myotonia
(B) Myotonic dystrophy
(C) Paramyotonia congenita
(D) Hyperkalemic periodic paralysis
(E) Potassium-aggravated myopathy

**68.** Which of the following is true of congenital myotonic dystrophy?

(A) Myotonia is the cardinal clinical sign in the neonatal period.
(B) It is caused by an abnormal, unstable trinucleotide repeat on chromosome 17.
(C) Neonatal respiratory failure never occurs.
(D) Spasticity is one of the clinical signs.
(E) The defective gene expresses a serine/threonine kinase.

**69.** Which of the following statements is true of hyperkalemic periodic paralysis?

(A) It is an autosomal recessive disease.
(B) It is caused by a mutation on 1q32.
(C) The first symptoms usually occur at birth.
(D) Muscle exercise with subsequent rest may trigger symptoms.
(E) Spironolactone is an effective treatment.

**70.** A 7-month-old male died following a progressive neurological illness over 6 weeks, with somnolence, blindness, deafness, and generalized limb spasticity. Autopsy showed bilateral symmetric necrotic lesions of the thalamus, pons, inferior olive, and spinal cord. The most likely diagnosis is

(A) Leber hereditary optic neuropathy
(B) mitochondrial neurogastrointestinal encephalopathy
(C) Leigh syndrome
(D) Alpers disease
(E) myoclonic epilepsy with ragged-red fibers

**71.** A 25-year-old male developed recurrent episodes of nausea, vomiting, and diarrhea concomitant with decreased ocular motility, weakness, and numbness in the lower extremities. Neurological examination demonstrated symmetric extraocular ophthalmoplegia. EMG/NCS showed a generalized sensorimotor neuropathy. The most likely diagnosis is

(A) Leber hereditary optic neuropathy
(B) mitochondrial neurogastrointestinal encephalopathy
(C) Leigh syndrome
(D) Alpers disease
(E) myoclonic epilepsy with ragged-red fibers

**72.** A 25-year-old male developed a painful decrease of his visual acuity with decreased ocular motility over 6 weeks. Neurological examination demonstrated bilateral external ophthalmoplegia, bilateral centrocecal scotoma, abnormal color vision, bilateral optic atrophy, and a visual acuity of 20/400 bilaterally. The most likely diagnosis is

(A) Leber hereditary optic neuropathy
(B) mitochondrial neurogastrointestinal encephalopathy
(C) Leigh syndrome
(D) Alpers disease
(E) myoclonic epilepsy with ragged-red fibers

**73.** A 2-year-old infant was brought to the emergency room by her mother because of intractable seizures, developmental delay, failure to thrive, and episodes of vomiting. Neurological examination showed developmental delay and generalized hypotonia. CT scan of the head showed bilateral occipital and temporal hypodensities with cortical atrophy. EEG showed generalized slow-wave activity. Lab workup showed increased liver enzymes. Liver biopsy showed fatty degeneration. The most likely diagnosis is

(A) Leber hereditary optic neuropathy
(B) mitochondrial neurogastrointestinal encephalopathy
(C) Leigh syndrome
(D) Alpers disease
(E) myoclonic epilepsy with ragged-red fibers

**74.** A 15-year-old youth consulted the neurologist because of recurrent headache, vomiting, and transient right hemiparesis. He also reported two episodes of generalized tonic–clonic seizures. Neurological examination showed no focal deficits. MRI of the head revealed multiple subacute ischemic lesions in small vessels of the parietal lobes. Lab workup showed elevated lactic acid levels in serum and cerebrospinal fluid. The most likely diagnosis is

(A) Leigh syndrome
(B) Alpers disease
(C) myoclonic epilepsy with ragged-red fibers
(D) Kearns–Sayre syndrome
(E) mitochondrial encephalomyelopathy with lactic acidosis and stroke-like episodes

**75.** A 17-year-old youth came to the emergency room because of an episode of syncope. He reported a decrease in his visual acuity and ocular motility over the preceding weeks. Neurological examination demonstrated bilateral retinal degeneration, mild bilateral extraocular ophthalmoplegia, and mild cerebellar ataxia. The rest of the physical examination was unremarkable. ECG showed a Mobitz type II atrioventricular block. The most likely diagnosis is

(A) Leigh syndrome
(B) Alpers disease
(C) myoclonic epilepsy with ragged-red fibers
(D) Kearns–Sayre syndrome
(E) mitochondrial encephalomyelopathy with lactic acidosis and stroke-like episodes

**76.** A 30-year-old man developed progressive ataxia, myoclonic seizures, and severe myopathy. The most likely diagnosis is

(A) Leigh syndrome
(B) Alpers disease
(C) myoclonic epilepsy with ragged-red fibers
(D) Kearns–Sayre syndrome
(E) mitochondrial encephalomyelopathy with lactic acidosis and stroke-like episodes

**77.** Kearns–Sayre syndrome is characterized by

(A) hypotonia
(B) retinal degeneration
(C) age of onset after 20 years
(D) mytonia
(E) seizure

**78.** Cardiac conduction defects are frequent features of

(A) Kearns–Sayre syndrome
(B) Leigh syndrome
(C) myoclonic epilepsy with ragged-red fibers
(D) mitochondrial encephalomyelopathy with lactic acidosis and stroke-like episodes
(E) the dominant form of progressive external ophthalmoplegia

**79.** A 30-year-old man consulted the neurologist because of exercise intolerance, especially when lifting heavy weights and walking uphill. He also complained of myalgia, premature fatigue, and muscle swelling (relieved by rest). He reported increased shortness of breath and palpitations on exercise. Neurological examination was normal. Laboratory evaluation showed normal pyruvate and lactate levels in serum, myoglobinuria with exercise, CK 1200 UI/ML, normal CBC and liver function tests, and normal electrolytes. The administration of epinephrine induced a normal rise of the blood sugar. Which of the following is true of this condition?

(A) There is a decrease in the ADP level in the muscle cells during exercise.
(B) Glucose infusion may cause a substantial drop in the patient's exercise capacity.
(C) It is caused by a myophosphorylase deficiency.
(D) It is caused by a phosphofructokinase deficiency.
(E) Phosphorous magnetic spectroscopy may detect a high phosphomonoester peak.

**80.** Which of the following is true of acquired myasthenia gravis?

(A) The loss of acetylcholine receptors results in increased postsynaptic sensitivity to acetylcholine.
(B) Within 1 year of onset, the disease remains purely ocular in 80% of cases.
(C) Bulbar symptoms are present in about 16% of patients at the onset of the disease.
(D) Magnesium-containing drugs may improve the symptoms of myasthenia gravis.
(E) A repetitive stimulation study at 50 Hz will show a decremental response.

**81.** Which of the following is characteristic of Lambert–Eaton myasthenic syndrome?

(A) The N type of voltage-gated calcium channel is detected in less than 10% of patients with Lambert–Eaton myasthenic syndrome associated with malignancy.
(B) The first symptom is usually facial weakness.
(C) Autonomic symptoms are usually rare.
(D) An incremental response at a rate of 3 Hz is highly suggestive.
(E) Postactivation stimulation may be seen after voluntary exercise of 10 seconds or after a tetanic stimulation of 20 to 50 Hz.

**82.** A 25-year-old man developed an acute episode of nausea, vomiting, diarrhea, and abdominal pain, followed a few hours later by diplopia, dysarthria, and progressive lower extremity weakness. Neurological examination demonstrated bilateral external ophthalmoplegia, dilated pupils, paraparesis with absent deep tendon reflexes in the lower extremities, and a normal sensory examination. Nerve conduction study showed decreased compound muscle action potentials of lower extremity muscles. Needle EMG showed small amplitude and short duration of recruited motor unit action potentials under voluntary contraction. Repetitive nerve stimulation showed a decrement at 3 Hz and an incremental response at 50 Hz. The most likely diagnosis is

(A) botulism
(B) tetanus
(C) venom poisoning
(D) Lambert–Eaton myasthenic syndrome
(E) organophosphate poisoning

**83.** Which of the following drugs does *not* exacerbate the neuromuscular blockade in myasthenia gravis?

(A) Magnesium sulfate
(B) Tobramycin
(C) Quinidine
(D) Ciprofloxacin
(E) Acyclovir

**84.** Which of the following hereditary myasthenic disorders has autosomal dominant penetrance?

(A) Familial infantile myasthenia
(B) Limb-girdle myasthenia
(C) Benign congenital myasthenic syndrome with facial dysmorphism
(D) Slow-channel myasthenic syndrome
(E) Acetylcholine deficiency syndrome

**85.** Which of the following drugs may cause a necrotizing myopathy?

(A) Lovastatin
(B) Amiodarone
(C) Zidovudine
(D) D penicillamine
(E) Colchicine

**86.** The most frequent cranial nerve involved in sarcoidosis is the

(A) glossopharyngeal nerve
(B) vestibulocochlear nerve
(C) oculomotor nerve
(D) trigeminal nerve
(E) facial nerve

**87.** The most frequent cranial nerve involved in diphtheria is the

(A) glossopharyngeal nerve
(B) vestibulocochlear nerve
(C) oculomotor nerve
(D) trigeminal nerve
(E) facial nerve

**88.** The most frequent cranial nerve involved in diabetes is the

(A) glossopharyngeal nerve
(B) vestibulocochlear nerve
(C) oculomotor nerve
(D) trigeminal nerve
(E) facial nerve

**89.** The olfactory nerve as well as the vestibulocochlear nerve are most commonly affected cranial nerves in

(A) acute inflammatory demyelinating polyneuropathy
(B) Refsum disease
(C) Miller–Fisher syndrome
(D) Sjögren syndrome neuropathy
(E) Wegener granulomatosis

**90.** A predominantly motor neuropathy is seen in cases of

(A) pyridoxine neuropathy
(B) paraneoplastic neuropathy
(C) spinocerebellar degeneration
(D) dapsone-induced neuropathy
(E) a deficiency in vitamin E neuropathy

**91.** Which of the following is *not* true about the safety factor in neuromuscular transmission?

(A) It is defined by the difference between the membrane potential and the threshold potential for initiating an action potential.
(B) Postsynaptic folds form a high-resistance pathway and increase the action potential threshold.
(C) The loss of synaptic folds increases the safety factor.
(D) Myasthenia gravis, like all neuromuscular transmission disorders, is characterized by a compromise of the safety factor.
(E) The conduction properties and density of acetylcholine receptors contribute to the safety factor.

**92.** Which of the following suggests that CD4+ T helper cells have a major role in the pathogenesis of myasthenia gravis?

(A) Most antiacetylcholine receptor antibodies in myasthenia gravis patients are high-affinity IgG; their synthesis requires CD4+ and T helper factors.
(B) Acetylcholine receptors reactivate CD4+ cells from the blood, and the thymus of myasthenia gravis patients has a T-cell cytotoxic function.
(C) Thymectomy does not modify the reactivity of blood T cells against acetylcholine receptors.
(D) In vitro treatment of CD4+ T cells from the blood of myasthenia gravis patients with anti CD4+ antibodies increases the reactivity of T cells to acetylcholine receptors.
(E) In experimental autoimmune myasthenia gravis, suppression of the synthesis of pathogenic antiacetylcholine receptor antibodies requires CD4+ cells.

**93.** Which of the following is true of the role of the thymus in myasthenia gravis?

(A) Ten percent of patients with myasthenia gravis have follicular hyperplasia of the thymus.
(B) Acetylcholine receptors are expressed only in the thymus of these patients.
(C) Thymic myoid cells expressing acetylcholine receptors, or antigenically similar proteins may act as antigen-presenting cells.
(D) Only myasthenia gravis patients have CD4+ T cells that react against self-antimuscle acetylcholine receptors; normal patients' CD4+ T cells do not react to self-antigens.
(E) Myoid cells are the only thymic cells that express acetylcholine receptor sequences.

**94.** Which of the following is true of the mechanism of action of corticosteroids in the treatment of myasthenia gravis?

(A) Stimulation of lymphocyte proliferation
(B) Stimulation of antigen processing by macrophages
(C) Reduction of acetylcholine receptor synthesis in the muscle
(D) Redistribution of lymphocytes from circulation
(E) Increasing lymphocyte differentiation

**95.** In the pathogenesis of dermatomyositis, recent microarray studies have demonstrated upregulation of genes induced by

(A) interferon $\gamma$
(B) interferon $\alpha$
(C) antibodies to specific endothelial antigen
(D) macrophage
(E) major histocompatibility complex (MHC) class I

# Answers and Explanations

**1.** (A) Vasculitic neuropathy may complicate the course of hepatitis C. The disorder is often painful and asymmetric skeletal muscle weakness is prominent. Central nervous system disease may accompany the neuropathy. Palpable purpura, which is due to a leukocytoclastic vasculitis, is often seen in the legs in a distal greater than a proximal distribution. The tempo of the vasculitic neuropathy may be subacute, chronic, or acute on chronic. Progression to multiorgan failure may occur, especially when the baseline viral load is high (greater than 2 to 3 million ge/mL serum) or if the hepatitis C virus genotype is 1a and 1b. *(Souayah,* Neurol Neurophysiol Neurosci *5; Khella, 101–106)*

**2.** **(D)** Several types of peripheral neuropathy are associated with human immunodeficiency virus (HIV) infection. GBS occurs most often at the time of seroconversion or in the early course of infections where the CD4+ cell count is relatively preserved. Occasionally, GBS is reported in an advanced stage of acquired immunodeficiency syndrome (AIDS) with a CD4+ cell count less than 50/mm$^3$ or during immune reconstitution. (*Souayah,* J Neuroimmunol *188, 143–145*).

**3.** **(B)** With the effectiveness of antiretroviral treatment and the consequent decline in the incidence rates of central nervous system infections and HIV dementia, HIV-associated neuropathies have become the most common neurological disorders associated with AIDS. The most common HIV-associated neuropathy is distal sensory polyneuropathy (DSP), a disorder characterized mostly by sensory symptoms, often including spontaneous or evoked pain with a subacute and chronic course usually developing during the advanced stages of AIDS. Clinical and electrophysiological studies suggest that DSP is predominantly an axonal neuropathy. In some patients, DSP may coexist with a toxic neuropathy associated with the use of specific nucleoside antiretrovirals. Inflammatory demyelinating polyneuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP) and acute inflammatory demyelinating polyneuropathy (AIDP) are less common but can occur in the setting of HIV infection, often during seroconversion, before AIDS or immunosupression appears. Rarely, AIDP may occur after severe CD4+ depletion. Progressive polyradiculopathies are frequently associated with CMV infection, mostly in the very late stages of AIDS, when the CD4+ cell count is below 50/mm$^3$. Mononeuritis multiplex (MM) may also present in the early stages of AIDS as a manifestation of a vasculitic neuropathy (sometimes associated with hepatitis B or C) or during the late stages as the result of CMV infection. *(Cornblath, 446–450; Souayah, 143–145)*

**4.** **(C)** Because of fears of an influenza pandemic, the 1976 National Influenza Immunization Program A/New Jersey "swine flu" influenza (A/NJ/1976/H1N1) vaccination campaign was designed to immunize almost the entire adult population in the United States as well as children at risk for serious influenza virus infection. The program was stopped after reports of vaccine-associated GBS. The A/NJ/1976 vaccine was shown to be associated with the development of GBS, with attributable risk estimates for GBS in the 6 weeks after vaccination ranging from 4.9 to 11.7 cases per million adult vaccinees. Studies of subsequent influenza vaccines used after 1976 in

general detected no significant increase in the overall risk for GBS in adult vaccinees, although a borderline statistically significant elevated risk of less than one excess case per million adult vaccinees was reported during the 1992–1993 and 1993–1994 influenza seasons combined. The 1976 swine flu vaccine induced anti-$G_{M1}$ antibodies in mice, as did vaccines from 1991 to 1992 and 2004 to 2005. These preliminary studies suggests that influenza vaccines contain structures that can induce anti-$G_{M1}$ antibodies after inoculation into mice. *(Nachamkin, 226–233; Souayah,* Vaccine *25, 5253–5255)*

5. **(B)** Acute respiratory failure may complicate the course of myotonic dystrophy type 1 (DM1) and is the cause of death in 30% to 75% of patients. Acute respiratory failure may occur in DM1 patients undergoing anesthesia and it may rarely be the revealing symptom in DM1 patients undergoing surgery. It was also reported in a series of patients, in the first of whom ventilatory failure was the initial presentation of DM1 without the provocative challenge of anesthesia or surgery. Respiratory dysfunction may have a central origin with decreased respiratory drive or a peripheral origin as in the setting of aspiration pneumonia secondary to poor cough reflex and weakness of the diaphragmatic, pharyngeal, and masticatory muscles. Ventilatory failure generally parallels the development of limb weakness in DM1 patients, although the diaphragm may be more involved than limb muscles and cause supine dyspnea and nocturnal hypoventilation. No correlation was found between the occurrence of ventilatory failure and CTG repeat number. *(Souayah,* J Clin Neuromuscul Dis *9, 252–255)*

6. **(D)** MPZ is a transmembrane protein with extracellular and intracellular domains responsible for myelin compaction and adherence of adjacent wraps of myelin sheets. It is also involved in the signal transduction cascade responsible for interaction between the Schwann cell and axon as well as in the regulation of myelin-specific gene expression. MPZ mutations cause hereditary neuropathy with phenotypic clustering into two major clinical, electrodiagnostic, and pathological entities. The early-onset form causes severe neuropathy in infancy with delayed motor milestones, slow conduction velocities in the demyelinating range, and predominant demyelination on nerve biopsy. It seems that mutations that significantly disturb the tertiary structure of MPZ are responsible for this phenotype. The late-onset form presents in adulthood with a neuropathy that is slowly progressive; it includes axonal features to a greater extent than demyelinating features on electrodiagnostic and nerve biopsy studies. Mutations that subtly affect the MPZ structure may interfere with Schwann cell–axon interaction and cause this phenotype. *(Souayah,* J Neurol Sci *263, 177–179)*

7. **(B)** The action of BTX involves a four-step process. Step 1: after botulinum toxin is activated by proteolytic cleavage of the polypeptide chain into a 100-kDa heavy chain (H) and a 50-kDa light chain (L) linked by a disulfide bond (S-S), the heavy-chain (H) domain of the toxin binds to the presynaptic plasma membrane of the motor axon terminal. Step 2: the toxin complex is then internalized by energy-dependent endocytosis. Step 3: the light chain (L), a zinc endopeptidase, is released into the cytoplasm. Step 4: the light chain cleaves various components of SNARE, including SNAP 25 (BTX A), VAMP/synaptobrevin (BTX B), or syntaxin (BTX C), and thus prevents the fusion of acetylcholine synaptic vesicle with the plasma membrane. This blocks the release of the neurotransmitter into the synaptic cleft, causing local chemodenervation. *(Jankovic, 951–957)*

8. **(A)** BTX prevents acetylcholine release from the presynaptic neuromuscular junction. BTX binds to a receptor at the neuromuscular junction. It is then cleaved into two protein chains and moves into the cytoplasm, where it interferes with the neuroexocytosis apparatus within the cell. This results in a dose-dependent chemodenervation of the injected muscle. Mild and transitory generalized weakness has been reported after focal injection of BTX at a therapeutic dose. The classic neurophysiological finding in botulism is reduction of the compound muscle action potential (CMAP), which increases after repetitive high-frequency nerve stimulation. On needle

EMG, the common findings are spontaneous activity and small motor unit potentials of short duration and increased jitter and blocking on single-fiber EMG. However, in a case report of a high-dose injection of BTX A, no motor response was obtained either with single stimulation or high-frequency repetitive stimulation. On needle EMG, all sampled muscles were silent, and even the physiological endplate spikes and noise were absent. They reflect a severe chemodenervation and total depletion of acetylcholine release in the neuromuscular junction in response to nerve excitation. *(Souayah, Neurology 67, 1855–1856)*

**9.** **(D)** Myotonia on clinical examination is always associated with myotonic discharges on EMG. The converse is also nearly always true with one notable exception. Acid maltase disease consistently shows myotonic potentials on EMG with absent clinical myotonia. Adult-onset acid maltase deficiency (glycogenosis type II) is a glycogen storage disease presenting with truncal and proximal limb weakness; it is slowly progressive over the years. Death is usually caused by weakness of respiratory muscles. Occasionally, the presenting weakness is diaphragmatic. EMG shows evidence of multiple spontaneous discharges including myotonic discharges, fibrillation potentials, positive sharp waves, complex repetitive discharges (CRDs), and small motor unit action potentials. *(Miller, 293–299)*

**10.** **(B)** In 1943, Seddon proposed a classification of peripheral nerve injuries that is still useful today. Under this system, three types of injuries—neuropraxia, axonotmesis, and neurotmesis—are described. The mildest, neurapraxia, is the inability of nerve fibers to conduct an action potential despite axonal continuity. Loss of axonal continuity without associated disruption of the fascicular connective tissue elements is referred to as axonotmesis. Neurotmesis describes the most severe injury, with disruption of the entire nerve, including all glial and connective tissue supports.

Neurapraxia, or type 1 injuries, most often result from compression and subsequent focal demyelination. More severe closed trauma, such as crush or stretch injuries, may cause axonotmesis of varying degrees. Focal ischemia also may cause axonotmesis. Neurotmesis commonly results from lacerations or less commonly from severe crush or stretch injuries. *(Quan, 45–51)*

**11.** **(B)** Neurapraxia most often results from compression and subsequent focal demyelination. The time required for recovery in traumatic nerve injury depends on the type of injury and the relative contributions of three possible modes of recovery: remyelination, collateral sprouting from surviving axons, and axonal regeneration. Restoration of impulse conduction after neurapraxia depends on remyelination of the affected site. Of all nerve injuries, neurapraxia generally recovers most quickly, usually taking 6 to 8 weeks. Axonotmesis recovers by two processes. Lesions involving less than 20% to 30% of motor axons may recover fully by collateral sprouting of remaining axons over 2 to 6 months. With more extensive injury, surviving axons cannot fully supply the denervated muscle. Nerve regeneration from the proximal axon stump at the site of injury must compensate for the remainder. When more than 90% of axons are injured, regeneration becomes the predominant mechanism of recovery. The timing of recovery depends on the distance of the lesion from the denervated target muscle. Proximal regeneration occurs at a rate of 6 to 8 mm/day, whereas distal regeneration occurs at 1 to 2 mm/day. The prerequisite for regeneration is an intact Schwann cell basal lamina tube to guide and support axonal growth to the appropriate target muscle. Schwann cell tubes remain viable for 18 to 24 months after injury. If the axon does not reach its target muscle within this time, these supporting elements degenerate and effective regeneration cannot occur. *(Quan, 45–51)*

**12.** **(B)** Lambert–Eaton myasthenic syndrome (LEMS) is a rare condition in which weakness results from an abnormality of acetylcholine (ACh) release at the neuromuscular junction. LEMS results from an autoimmune attack against voltage-gated calcium channels (VGCCs) on the presynaptic motor nerve terminal. Cancer is present when the weakness begins or is later found in 40% of patients with LEMS. This is

usually a small cell lung cancer (SCLC), although LEMS has also been associated with non-SCLC, lymphosarcoma, malignant thymoma, or carcinoma of the breast, stomach, colon, prostate, bladder, kidney, or gallbladder.

Clinical manifestations frequently precede cancer identification. In most cases, the cancer is discovered within the first 2 years after onset of LEMS and within 4 years in virtually all cases.

Symptoms usually begin insidiously. Many patients have symptoms for months or years before the diagnosis is made. Weakness is the major symptom, with proximal muscles more affected than distal ones (especially in the lower limbs). Respiratory muscles are not usually affected, Most patients have a dry mouth, which frequently precedes other symptoms of LEMS. Some patients have other manifestations of autonomic dysfunction, including impotence in males and postural hypotension. Approximately 20% of patients note that weakness and fatigue are exacerbated by hot weather and during the course of taking hot bath.

Repetitive nerve stimulation at a low rate (2 to 3 Hz) often yields a decremental response that is maximal between the first and second responses and continues to decline until the fourth, fifth, or sixth response. Repetitive nerve stimulation at a low rate (20 Hz) is illustrated in Figure 5-1. It demonstrates a dramatic and serial increase of compound muscle action potential (CMAP) amplitude from the abnormally small to the normal CMAP range. *(Dumitru, 1177–1181)*

**13.** **(D)** Figure 5-2 shows an analysis of teased nerve fibers. By this method, individual myelinated fibers are separated from the nerve fascicles and lightly stained, allowing the integrity and thickness of the myelin sheath to be examined. Figure 5-2 illustrates focal thickening and folding of the myelin sheath in the perinodal or intermodal area, leading to the formation of tamacula. Tamacula (the Latin word for sausage) are commonly seen in hereditary neuropathy with a tendency for pressure palsies and occasionally in other forms of Charcot–Marie–Tooth disease to develop. *(Amato, 88–89)*

**14.** **(C)** Figure 5-3 illustrates teased nerve fibers with segmental demyelination (a short demylinating internode). This may be seen in chronic inflammatory demyelinating polyneuropathy. *(Amato, 89)*

**15.** **(B)** Figure 5-4A and B (respectively showing a semithin section and the same as seen under electron microscopy) illustrates onion-bulb formation. With sequential episodes of demyelination and remyelination, concentric tiers of Schwann cell processes accumulate around the axons, forming onion bulbs. They are typically seen in hereditary demyelinating neuropathies such as Charcot–Marie–Tooth disease types 1, 3, and 4. They can also be seen in chronic inflammatory demyelinating polyneuropathy. *(Amato, 89)*

**16.** **(B)** Primary lateral sclerosis (PLS) is characterized by exclusive or predominant upper motor neuron dysfunction, in which spasticity is the predominant source of impairment. Approximately 2% to 5% of amyotrophic lateral sclerosis (ALS) cases begin with a PLS phenotype. The average of onset is at about 50 years of age, 10 years earlier than typical ALS. The legs are involved first in 75% of PLS cases, making it impossible to run or hop effectively. In 10% of PLS cases, the upper extremities are the first region to become symptomatic. In approximately 15% of PLS cases, bulbar muscles are affected initially. In most cases, onset is asymmetric. Genitouronary symptoms such as urinary urgency and urgency incontinence do occur in PLS (as opposed to the absence of genitourinary involvement in ALS), presumably on the basis of detrusor–sphincter dyssynergia from upper motor neuron involvement. The life expectancy of individuals with PLS is considerably longer than that of those with ALS, since the average duration of PLS ranges from 7 to 14 years. Some 80% of PLS patients who evolve into ALS do so within the first 4 years of their disorder. *(Amato, 101)*

**17.** **(E)** Hereditary spastic paraplegias (HSPs) comprise a cluster of inherited neurological disorders characterized principally by lower extremity spasticity and weakness due to a length-dependent retrograde axonopathy of corticospinal motor neurons. The most common

form of autosomal dominant HSP is caused by mutations in the SPG4/SPAST gene, encoding spastin. Mutations in the gene encoding the large oligomeric GTPase atlastin-1 are responsible for SPG3A. SPG3A is the second most frequent gene mutated in autosomal dominant HSPs, accounting for approximately 10% of cases. SPG3A HSP is pure and almost indistinguishable from SPG4 HSP except that it usually begins earlier, in childhood or adolescence. *(Amato, 116; Depienne, 674–680)*

**18.** **(B)** Copper is an essential trace element required by all life forms. It is a component of key metalloenzymes that play a critical role in the structure and function of the nervous system. Cytochrome c oxidase is a component of the mitochondrial respiratory chain, superoxide dismutase is an important antioxidant, and dopamine [beta]-hydroxylase is important in the catecholamine biosynthetic pathway. Copper deficiency may cause signs of myelopathy and peripheral neuropathy. The clinical signs of myelopathy are similar to those seen in HSP and include ataxic gait, spasticity, and increased deep tendon reflexes. Signs of peripheral neuropathy are weakness, and reduced or lost vibration sensation and joint position. *(Amato, 307)*

**19.** **(C)** Spinal muscular atrophy type I (Werdnig–Hoffman disease) is the most severe form of spinal muscular atrophy. Its clinical manifestations are evident within the first 6 months of life. Affected patients are hypotonic with a symmetric, generalized, or proximally predominant pattern of weakness. Facial weakness is mild and extraocular muscles are spared. Fasciculations are seen in the tongue but rarely in limb muscles. Deep tendon reflexes are typically absent. Abdominal breathing, a weak cry, and a poor suck are commonplace. There is no intellectual impairment. Children with spinal muscular atrophy type I are distinguished from those with other types of spinal muscular atrophy by the fact that they never develop the ability to sit independently. *(Amato, 123–124)*

**20.** **(A)** The association of gynecomastia, fasciculations, fatigue, and mild CPK elevation in a young male is suggestive of X-linked bulbospinal muscular atrophy (Kennedy disease). It is an X-linked adult-onset of spinal muscular atrophy. Affected patients develop bulbar or proximal weakness at a median age of onset of 44 years. Initial symptoms are usually nonspecific and include muscle cramping, tremor, gynecomastia, fatigue, and mild CPK elevation. The clinical manifestations stem from lower cranial nerve motor nuclei and anterior horn cells of the spinal cord. The weakness is symmetric and progresses insidiously. In 10% of cases, the initial symptoms include difficulty in swallowing, chewing, or speaking. Facial weakness and dropped jaw may occur. The disorder results from a mutation of the androgen receptor gene on the X chromosome. *(Amato, 125–126)*

**21.** **(A)** Approximately 85% of people with Charcot–Marie–Tooth type 1A disease have a 1.5-megabase duplication within chromosome 17p11.2-12, wherein the gene for PMP-22 lies. *(Amato, 165)*

**22.** **(D)** Hereditary neuropathy with a tendency to develop pressure palsies is inherited in an autosomal dominant manner. It is characterized by the occurrence of a painless numbness and weakness in the distribution of a single nerve, although multiple neuropathies and cranial neuropathies can occur. The age of onset is usually within the second and third decade. The most commonly affected sites are the median nerve at the wrist, the ulnar nerve at the elbow, the radial nerve at the arm, and the peroneal nerve at the head of the fibula. Approximately 85% of cases of hereditary neuropathy with a tendency to develop pressure palsies are caused by a deletion of one copy of the PMP-22 gene . The neuropathy may be also caused by a mutation of the PMP-22 gene, resulting in loss of function of the PMP-22 protein. *(Amato, 167–168).*

**23.** **(A)** Approximately 20% of patients with Charcot–Marie–Tooth type 1 (CMT1) have CMT1B, which is caused by a mutation in the myelin protein zero (MPZ) gene located on chromosome 1q22-23. Mutation in the connexin-32 gene on chromosome Xq13 causes CMT1X. Mutations in the neurofilament light chain gene located on chromosome p13-21 causes CMT1F. Mutation in the

heat-shock 27-kDa protein-1 gene located on chromosome 7q11-q21 causes CMT2F, and mutation in the early growth response-2 protein (ERG2) gene causes CMT3. *(Amato, 162, 166–167)*

**24.** **(E)** The patient described in the vignette developed a combination of peripheral neuropathy, cerebellar ataxia, retinitis pigmentosa, and elevated proteins in the cerebrospinal fluid. These findings are suggestive of Refsum disease, a rare disorder inherited as an autosomal recessive trait that has its onset in late childhood, adolescence, or early adult life. Diagnosis is based on a combination of clinical manifestations—retinitis pigmentosa, ataxia, and chronic polyneuropathy—coupled with the metabolic marker of the disease: an increase in blood phytanic acid. Phytanic acid accumulates because of a deficiency of the peroxisomal enzyme phytanoyl-coenzyme A (CoA) hydroxylase. The deficiency is caused by mutations in one of two disparate genes. Cardiomyopathy and neurogenic deafness are present in most patients. The polyneuropathy is sensorimotor, distal, and symmetric in distribution, affecting the legs more than the arms. Although the nerves may not be palpably enlarged, "hypertrophic" changes with onion-bulb formation are invariable pathological features. The metabolic defect has been found to lie in the utilization of dietary phytol; a failure of oxidation of phytanic acid—a branched-chain tetramethylated 16-carbon fatty acid—that accumulates in the absence of activity of the enzyme phytanoyl-CoA-hydroxylase. Clinical diagnosis is confirmed by the finding of increased phytanic acid in the blood of a patient with a chronic, mainly sensory neuropathy; the normal level is less than 0.3 mg/dL, but in patients with this disease it constitutes 5% to 30% of the total fatty acids in serum lipids. *(Amato, 199; Ropper and Samuels, chapter 46)*

**25.** **(C)** Acute motor axonal neuropathy presents as an abrupt onset of generalized weakness. It may occur in children as well as adults. The distal limb muscles are often more severely affected than the proximal ones. Cranial nerve deficits and respiratory failure requiring mechanical ventilation can be seen in up to one third of patients. Sensory signs or symptoms are absent; however autonomic dysfunction may occur. The median time to recovery is similar to that seen with acute inflammatory demyelinating polyneuropathy; most affected patients have a good recovery within a year. The mortality rate is less than 5%. *(Amato, 222)*

**26.** **(B)** Multifocal motor neuropathy (MMN) is an immune-mediated demyelinating neuropathy characterized clinically by asymmetric weakness and atrophy, typically in the distribution of peripheral nerves. The prevalence of MMN remains unknown but is estimated to be about 1 per 100,000. The protracted and chronic nature of the disease means that the incidence is very much lower than this. MNN occurs more commonly in males (3:1) and presents mainly between 20 and 50 years of age, although up to 20% of cases may present later. Typically, a patient presents with progressive or sometimes stepwise asymmetric weakness affecting the upper limbs. If the presentation is late, there may be a history of static weakness or spontaneous remission. Weakness of a single nerve or nerve branch, such as a radial or posterior interosseous nerve, or a nerve territory, as seen in median or ulnar intrinsic hand weakness, is common early on, but weakness may spread to affect one or more other limbs, sometimes becoming confluent. Patients frequently complain of cramps, often outside clinically affected areas, fatigue, and twitching. Involvement of cranial or respiratory nerves is unusual but reported. Mild sensory symptoms and signs are not uncommon and should not exclude the diagnosis. At an early stage, weakness without wasting in identifiable nerve territories is typical. Occasionally, neurogenic muscle hypertrophy is evident, especially in areas affected by cramps. Fasciculation or, rarely, myokymia is seen, which may be exacerbated by exercise. Some 22% to 84% of patients with MMN have IgM serum antibodies directed against gangliosides, mainly $G_{M1}$ but also asialo-$G_{M1}$ and $G_{M2}$; however, the importance of these antibodies in the pathogenesis of MMN is unclear. *(Amato, 248–249; Lunn, 249–358)*

**27.** **(B)** Figure 5-5 illustrates winging of the right scapula which may be enhanced by having the

patient flex the arm forward at the shoulder. The figure shows that the whole scapula is winging with the inferior angle rotated medially. These findings are suggestive of neuropathy affecting the right long thoracic nerve. This nerve arises by three roots from the fusion of the fifth, sixth, and seventh spinal roots to innervate the serratus anterior. The roots from C5 and C6 pierce the scalenus medius, while the C7 root passes in front of the muscle. The nerve descends behind the brachial plexus and axillary vessels, resting on the outer surface of the serratus anterior. Owing to its long, relatively superficial course, it is susceptible to injury either by direct trauma or stretch. Injury has been reported in almost all sports, typically from a blow to the ribs underneath an outstretched arm. The long thoracic nerve can also be damaged during surgery for breast cancer, specifically radical mastectomies that involve removal of axillary lymph nodes. Injury to the nerve can result from carrying a heavy bag over the shoulder for a prolonged time. Damage to the dorsal scapular nerve may lead to winging of the scapula, with the inferior angle rotated laterally. An axillary nerve lesion may cause paralysis of the teres minor and deltoid muscles, resulting in impaired shoulder abduction and loss of sensation over a small part of the lateral upper arm. A thoracodorsal nerve lesion causes weakness of the latissimus dorsi muscle, which results in impaired ability to adduct, medially rotate, and extend the upper arm. A musculocutaneous nerve lesion causes weakness of elbow flexion and supination of the forearm. It also causes a discrete sensory disturbance on the radial side of the forearm. *(Amato, 398)*

**28.** **(C)** Figure 5-6 shows hematoxylin-and-eosin staining of a muscle biopsy. It demonstrates fiber size variability and increased endomysial and perimysial connective tissue, consistent with a dystrophic process. *(Amato, 548)*

**29.** **(A)** Figure 5-7 shows myotonic discharges. This is a spontaneous discharge of a muscle fiber in which the amplitude and frequency of the potential wax and wane. An individual myotonic potential may have either a positive wave or brief spike morphology. Myotonic discharges are easily differentiated from fibrillations and positive sharp waves by their characteristic waxing and waning of both frequency and amplitude. They can occur in some myopathies and occasionally in denervation from any cause. However, the myotonic discharges in denervation are usually single brief runs and are never the predominant waveform. *(Amato, 648)*

**30.** **(C)** Figure 5-8A shows a macular erythematous rash over the extensor surface of the knuckles suggestive of Gottron papules, as seen in dermatomyostis. Such papules are found over bony prominences, particularly the metacarpophalangeal joints, the proximal interphalangeal joints, and/or the distal interphalangeal joints. Papules may also be found overlying the elbows, knees, and/or feet. The lesions consist of slightly elevated violaceous papules and plaques. A slight scale and, occasionally, a thick psoriasiform scale may be present. These lesions may resemble those of lupus erythematosus or psoriasis. Other dermatological signs of dermatomyostis includes dilated capillary loops evident in the nail beds (Figure 5-8B); heliotrope rash, which is a violaceous eruption on the upper eyelids, often with swelling; the shawl (or "V") sign, which is a diffuse, flat, erythematous lesion over the chest and shoulders or in a "V" over the anterior neck and chest, worsened with UV light; and an erythematous lesion similar to the shawl sign but located in other areas, such as the malar region and the forehead. *(Amato, 688)*

**31.** **(B)** Figure 5-9 demonstrates atrophy of type 2B fibers. These findings are characteristic of steroid myopathy, the most common endocrine myopathy. *(Amato, 725–726)*

**32.** **(E)** Malignant hyperthermia is a syndrome rather than a specific disorder; it is characterized by severe muscle rigidity, myoglobinuria, fever, tachycardia, cyanosis, and cardiac arrhythmias precipitated by depolarizing muscle relaxants and inhalational anesthetic agents. In susceptible individuals, these drugs can induce a drastic and uncontrolled increase in skeletal muscle oxidative metabolism, which overwhelms the body's capacity to supply oxygen, remove

carbon dioxide, and regulate body temperature, eventually leading to circulatory collapse and death if not treated quickly. Susceptibility to malignant hyperthermia is often inherited as an autosomal dominant disorder, for which there are at least six genetic loci of interest, most prominently the ryanodine receptor gene (RYR1) (chromosome 19q13.1). Ryanodine receptor mutations are found in at least 25% of known malignant hyperthermia-susceptible individuals in North America. *(Amato, 675–676; Litman, 2918–2924)*

**33.** **(A)** Becker muscular dystrophy (BMD) is a milder form of dystrophinopathy. It can be distinguished from Duchenne muscular dystrophy (DMD) by its slower rate of progression and by dystrophin analysis. Most patients with BMD experience difficulties initially between 5 and 15 years of age; however, onset in the third or fourth decade or even later can occur. By definition, patients with Becker's dystrophy ambulate beyond the age of 15 years. Serum CK levels are elevated often 20 to 200 times the upper limit of normal. BMD may be distinguished histologically from DMD with immune staining, which—using carboxyl-terminal antibodies on muscle membranes—demonstrates the presence of dystrophin in most cases of BMD. In contrast, immunostaining with antibodies directed against the carboxyl terminal of dystrophin is usually negative in DMD. *(Amato, 537–538)*

**34.** **(B)** The patient in this vignette has signs and symptoms suggestive of hypokalemic periodic paralysis (hypoPP). This is an autosomal dominant disorder and is the most common form of primary periodic paralysis, with an estimated prevalence of 0.4 to 1 in 100,000. Attacks of generalized weakness may be triggered by rest after exercise and by a carbohydrate-rich meal the preceding day; they may last hours to days. Weakness may be mild and limited to certain muscle groups or may involve more severe full-body paralysis. Loss of deep tendon reflexes during an attack is characteristic of hypoPP Recovery is usually sudden when it occurs. Causal mutations were first identified in the [alpha]-subunit of the skeletal-muscle calcium channel gene CACNA1S (hypoPP1). It was later recognized that in about 10% of patients, hypoPP is due to mutations in SCN4A, a voltage-gated sodium channel $Na_v1.4$ found at the neuromuscular junction. Variants of HypoPP have been associated with mutations in KCNE3, a voltage-gated potassium channel. *(Amato, 671–672)*

**35.** **(C)** Ptosis and facial weakness are frequent manifestations of the classic form of myotonic dystrophy type 1. Although extaocular muscle weakness may occur, it is usually asymptomatic. External ophthalmoplegia is a rare sign in myotonic dystrophy type 1. *(Amato, 647–649)*

**36.** **(B)** The phenotype described in this vignette is highly suggestive of myotonia congenita in an autosomal recessive form.

Myotonia congenita may be inherited as an autosomal dominant (Thomsen) or recessive (Becker) trait. It has been reported that the same mutation may be inherited in a dominant fashion in one family and be recessive in another. Mutations in CLCN1, the gene encoding the human skeletal muscle chloride channel, were subsequently shown to cause recessive and dominant myotonia. In Thomsen disease, symptoms begin in early childhood. The myotonia is generalized and the lower limbs tend to be more severely affected. There may be marked muscle hypertrophy. Myotonia that diminishes with exercise (warmup phenomenon) is characteristic of both dominant and recessive disease. Becker disease, or recessive generalized myotonia, is the only skeletal muscle channelopathy inherited as an autosomal recessive trait. Although symptoms do not usually begin until the second decade, the myotonia tends to be more severe. The condition tends to progress slowly until the age of 30 to 40 years. Disability may result from severe myotonic stiffness of the lower limbs, which are often markedly hypertrophied. *(Amato, 655–658)*

**37.** **(E)** Anti Jo-1 antibodies are the most common antisynthetase antibodies and are directed against cytoplasmic translational proteins. These antibodies are associated with interstitial lung disease in as many as 20% of patients with inflammatory myopathy. Since methotrexate may cause pulmonary fibrosis, its administration in patients

with dermatomysitis and anti Jo-1 antibodies is not recommended. *(Amato, 681–688)*

**38. (B)** The forearm ischemic exercise test is an important step in the diagnosis of muscle energy disorders. In most normal patients, serum lactate concentrations are raised more than 20 mg/dL and serum ammonia concentrations are raised more than 100 μg/dL. If neither lactate nor ammonia concentration increases during the test, the subject did not exercise strenuously and the test should be repeated. Failure to increase ammonia concentrations more than 100 μg/dL above baseline coupled with normal elevation of lactate response suggests myoadenylate deaminase deficiency. This is a recessive genetic metabolic disorder that affects approximately 1% to 2% of populations of European descent. Myoadenylate deaminase is an enzyme that converts adenosine monophosphate (AMP) to inosine monophosphate (IMP), freeing an ammonia molecule in the process. It is a part of the metabolic process that converts sugar, fat, and protein into cellular energy. If myoadenylate deaminase is deficient, excess AMP builds up in the cell and is eventually transported by the blood to the liver to be metabolized or to the kidneys to be excreted. Clinically, the typical history is intermittent muscles pain and weakness. *(Amato, 609–611)*

**39. (B)** Small cell lung cancer is the most common malignancy that causes subacute sensory neuronopathy, but cases of carcinoma of the esophagus, breast, ovaries, and kidney as well as lymphoma have also been reported. *(Amato, 313)*

**40. (A)** Facioscapulohumeral muscular dystrophy **(**FSHD) is an autosomal dominant form of muscular dystrophy that initially affects the skeletal muscles of the face, scapula, and upper arms. Symptoms may develop in early childhood and are usually noticeable in the teenage years, with 95% of affected individuals manifesting disease by age 20. A progressive skeletal muscle weakness usually develops in other areas of the body as well; often the weakness is asymmetric. Life expectancy is normal, but up to 15% of affected individuals become severely disabled and must eventually use a wheelchair. Nonmuscular symptoms frequently associated with FSHD include subclinical sensorineural hearing loss and retinal telangectasias. More than 95% of cases of FSHD are associated with the deletion of integral copies of a tandemly repeated 3.2-kb unit (D4Z4 repeat) at the subtelomeric region 4q35 of the human genome, of which a normal chromosome will include between 11 and 150 repetitions of D4Z4. *(Amato, 552–554)*

**41. (C)** Endplate noise is generated at the endplate region. It represents normal spontaneous activity and is manifest as low-amplitude monophasic negative potentials that fire at 20 to 40 Hz. It has the characteristic of a seashell or hissing sound on EMG, representing miniature endplate potentials. Endplate noise is a normal finding in all individuals when the EMG needle is near the neuromuscular junction. *(Preston and Shapiro, 6–10)*

**42. (E)** Endplate spikes are another normal waveform that can occur when the needle is near the neuromuscular junction. They are brief, irregular spikes with an initial negative deflection for each spike. They have a crackling, buzzing, or sputtering sound on EMG and are caused by irritation of the terminal axon twig by the EMG needle, resulting in a depolarization of axon twigs. These propagate across the neuromuscular junction to produce motor fiber action potentials. *(Preston and Shapiro, 6–10)*

**43. (B)** Both fibrillation potentials and positive sharp waves represent the extracellular recording of a single muscle fiber's electrical activity occurring as a result of membrane instability. These are the electrophysiological markers of loss of functional activity between the motor axon and the muscle membrane. Fibrillation potentials are often described as producing a "rain on a roof" type of sound. They are primarily recognized by their regular firing pattern (usually at a rate of 1 to 10 Hz); their morphology is that of a single motor unit action potential, and they have an initial positive deflection (1 to 5 ms in duration and typically 10 to 100 μV in amplitude). Positive sharp waves have a brief initial positivity followed by a long negative phase. They create a dull popping sound. A myotonic discharge is the spontaneous discharge of a muscle fiber in which the potentials'

amplitude and frequency wax and wane. This is characteristically seen in myotonic dystrophy, myotonia congenita, and paramyotonia congenita. *(Preston and Shapiro, 6–10)*

**44.** **(A)** A fasciculation potential is a spontaneous involuntary discharge of an individual motor unit. The source generator of a fasciculation is the motor neuron or its axon. Fasciculations fire slowly, typically 0.5–1 Hz, and irregularly. Clinically, they are recognized as individual brief twitches that seldom result in significant movement of a joint. *(Preston and Shapiro, 11–19)*

**45.** **(C)** Complex repetitive discharges occur from depolarization of a single muscle fiber followed by ephaptic spread to adjacent denervated fibers. On EMG, they are recognized as high-frequency, multiserrated repetitive discharges with an abrupt onset and termination and a machine-like sound. They are present in chronic neuropathic and myopathic disorders. *(Preston and Shapiro, 11–19)*

**46.** **(D)** Myokymic discharges are rhythmic, grouped, and repetitive discharges of the same motor unit. Clinically, myokymia is usually recognized as the continuous, involuntary, quivering, rippling, or undulating movement of a muscle. Myokymia is seen in a variety of conditions, including radiculopathy, entrapment neuropathy, and demyelinating neuropathies. In a patient with a history of brachial plexopathy and of cancer and radiation therapy, the presence of myokymia is a specific although not necessarily sensitive, sign supporting the diagnosis of radiation plexitis rather than recurrent neoplastic invasion. *(Preston and Shapiro, 11–19)*

**47.** **(B)** Neuromyotonic discharges are high-frequency (150- to 250-Hz) decremental discharges of a single motor unit that have a characteristic pinging sound on EMG. *(Preston and Shapiro, 11–19)*

**48.** **(E)** Acute axonal damage in a nerve causes Wallerian degeneration after the first 4 to 7 days. This is followed by denervation of the distal muscle fibers of the involved motor units. Sprouting of the nearby axons reinnervates these denervated fibers. The number of newly reinnervated fibers may exceed the normal number of fibers in the motor unit. This may lead to an increase in the duration, amplitude, and number of phases. This process takes many weeks to months to occur. In the acute setting, the morphology of the motor unit action potential remains normal. The only abnormality is a decreased number of motor unit action potentials in weak muscles owing to the initial loss of motor units. *(Preston and Shapiro, 32–33)*

**49.** **(D)** In myopathies, the number of functioning muscle fibers in a motor unit decreases. Fewer muscle fibers per motor unit results in shorter-duration and smaller-amplitude motor unit action potentials. With dysfunction of the remaining muscle fibers, less synchronous firing results in increased polyphasia. However, the number of functioning motor unit action potentials remains normal. Thus, recruitment remains normal for the level of activation. Since each motor unit contains fewer muscle fibers, each unit generates less force. Consequently, more motor unit action potentials, as compared with normal, are needed to generate a level of force equivalent to the premorbid state, resulting in early full recruitment. *(Preston and Shapiro, 34–35)*

**50.** **(B)** In humans, two major types of muscle fibers, 1 and 2, have been defined on the basis of histochemistry and physiology. Type 1 fibers are high in myoglobin and oxidative enzymes and have many mitochondria, in keeping with their ability to perform tonic contraction; histologically, they are defined by their dark staining for adenosine triphosphatase (ATPase) at pH 4.2 but light staining at pH 9.4. Type 1 fibers are slow-twitch red fibers. Type 2 fibers are rich in glycolytic enzymes and are involved in rapid phasic contractions. They stain dark for ATPase at pH 9.4 but light at pH 4.2. Type 2 fibers are fast-twitch white fibers. Since the motor neuron determines fiber type, all fibers of a single unit are of the same type. These fibers are distributed randomly across the muscle, giving rise to the checkerboard pattern of alternating light and dark fibers, as demonstrated especially well with ATPase. Type-specific atrophy is characteristic of some disease states. Type 2 fiber

atrophy is a relatively common finding and is associated with inactivity or disuse. This type of "disuse atrophy" may occur after fracture of a limb and application of a plaster cast, in pyramidal tract degeneration, or in neurodegenerative diseases. It may also occur with hyperthyroid myopathy and corticosteroid-induced myopathy. Type 1 fiber atrophy occurs with myotonic muscular dystrophy, centronuclear myopathy, and congenital fiber-type disproportion myopathy. *(Karpali, 47–48)*

**51. (C)** Myotonic dystrophy type 1 (DM1) is an autosomal dominant multisystem degenerative disease characterized by myotonia, progressive muscular weakness, gonadal atrophy, cataracts, and cardiac dysrhythmias. The molecular basis of DM1 is an unstable trinucleotide repeat sequence—cytosine, thymine, and guanidine (CTG)—in the protein kinase–encoding gene (DMK) located at 19q13.3. The normal CTG repeat is between 5 and 30, whereas in DM1 the CTG repeat is 50 to several thousand. The size of the repeats correlates with the anticipation phenomenon as well as with the severity of symptoms. There is an estimated prevalence of 3 to 5 per 100,000 population and an incidence of 1 in 8,000 live births, making it the most common adult muscular dystrophy.

The clinical presentation is variable, ranging from a single relatively benign presentation (such as cataracts) of middle age to severe neonatal hypotonia, which can lead to death if respiratory support is not provided. The classic presentation of noncongenital DM1 includes marked weakness in the face, jaw, and neck muscles and milder weakness in the distal extremities, often perceived earlier than the myotonia. Myotonia can be elicited by a brisk percussion of the thenar muscles, causing flexion opposition of the thumb with slow relaxation. In the advanced stage of myotonic dystrophy, the patient may present a characteristic long, thin face with sunken cheeks, due to temporal and masseter wasting, and atrophy of the sternocleidomastoid, causing a swan neck and ptosis. Congenital myotonic dystrophy presents a distinctive picture that is different from that of other myotonic disorders. Facial diplegia, jaw weakness (without concomitant extremity weakness), hypotonia, and weakness of respiratory muscles (with absence of clinical myotonia) are hallmarks. Additionally, 75% of the noncongenital patients and 81% of the congenital patients have cardiac abnormalities, primarily conduction defects, demonstrated on ECG. The heart is prominently involved, and the severity of cardiac symptoms does not correlate with the severity of other symptoms in this disorder.

Central nervous system manifestations may include apathy, inertia, and hypersomnolence. Structural changes in the brain are not common; however, generalized atrophy and ventricular dilatation may be seen. Endocrinological abnormalities have been reported, including hyperinsulinism with reduced insulin receptors, elevated pituitary FSH and LH, testicular atrophy (seen in 60% to 80% of patients), Leydig cell hyperplasia, and reduced testosterone level. *(Goetz, 707–708)*

**52. (C)** Neurological complications of diphtheria parallel the extent of the primary infection and are multiphasic in onset. Some 2 to 3 weeks after the onset of oropharyngeal inflammation, weakness of the posterior pharynx, larynx, and facial nerves occurs, causing nasal speech. Death may occur from aspiration. Blurred vision, strabismus, and accommodation abnormalities are manifestations of oculomotor and ciliary paralysis and may occur in the fifth week. The peripheral nervous system manifestations of diphtheria include a symmetric polyneuropathy that appears between 10 days and 3 months after the onset of the disease, with distal weakness that progresses proximally as well as decreased deep tendon reflexes. Paralysis of the diaphragm can ensue. Complete recovery is likely. Rarely, 2 to 3 weeks after onset of the illness, dysfunction of the vasomotor centers can cause hypotension or cardiac failure.

Diabetic cranial mononeuropathies are caused by peripheral nerve microinfarction as well as fascicular ischemic lesions within the brain. Diabetic oculomotor cranial mononeuropathies primarily involve the oculomotor nerve, followed by the abducens nerve; the trochlear nerve is uncommonly affected alone. Clinically, the patient may report eye pain or headache followed by a diplopia. In the setting

of oculomotor involvement, pupillary sparing is noted in 80% to 90% of cases.

Sarcoidosis may affect virtually any part of the nervous system. Involvement of the facial nerve leading to unilateral facial nerve palsy is the most commonly recognized symptom, although any cranial nerve can be affected. Unusual combinations of neurological deficits affecting the central nervous system and/or peripheral nerves should raise the clinical suspicion of sarcoidosis.

The neuropathy in porphyria is primarily motor. Weakness begins in the proximal muscles, arms more commonly than legs. Paresis is often focal; cranial nerve involvement may occur, especially in the oculomotor, facial, and vagus nerves.

The possible neurological manifestations of Lyme disease include lymphocytic meningitis with episodic headache and mild neck stiffness, subtle encephalitis with difficulty with mentation, cranial neuropathy (particularly unilateral or bilateral facial palsy), motor or sensory radiculoneuritis, mononeuritis multiplex, cerebellar ataxia, and myelitis. In children, the optic nerve may also be affected because of inflammation or increased intracranial pressure, which may lead to blindness. *(Crimlisk, 319–328; Newman, Rose, and Maier, 1224–1234; Steere, 115–125)*

**53.** **(E)** The dominant form of X-linked Charcot–Marie–Tooth (CMT) neuropathy accounts for approximately 10% to 15% of the dominant forms of CMT neuropathy. It becomes symptomatic in the first decade of life. The disorder is related to an abnormal marker of the connexin-32 gene, which is a gap junction protein involving intercellular communication. Clinical manifestations include distal muscle weakness and atrophy, areflexia, distal sensory loss, pes cavus, hammertoes, and claw-hand deformity. Women are less severely affected than men. Enlarged nerves are infrequent. The recessive form is rare. Spasticity and pyramidal signs may also be present, but mental retardation is seen only when the onset is in infancy. Pathologically, there is primary axonopathy with secondary demyelination.

Charcot–Marie–Tooth neuropathy type 1 (CMT1) is the most common hereditary motor and sensory neuropathy (HMSN). It is an autosomal dominant disorder with onset before the second decade. Family history may be absent in about 20% of cases. There are two main genetic variants of CMT1: CMT1A (75%) and CMT1B (20%). Up to 90% of CMT1A patients have a tandem DNA duplication on the short arm of chromosome 17. Several laboratories have mapped the human PMP-22 gene to chromosome 17p11.2-p12. The duplication leads to an overexpression of the PMP-22. Histologically, CMT1A may show small-diameter axons and frequent onion bulbs.

CMT1B is linked to chromosome 1q22-q23, where the gene locus for myelin protein zero (P0) gene is mapped. Histologically, CMT1B biopsies show loss of myelinated fibers, small onion bulbs, and tomaculous formations.

Charcot–Marie–Tooth neuropathy type 2 (CMT2) is also an autosomal dominant condition. It is significantly less common than CMT1 and accounts for one third of all autosomal dominant CMT. There are three genetic variants: CMT2A, CMT2B, and CMT2C. Electrophysiologically, all CMT2 patients exhibit findings of primary axonal sensorimotor neuropathy. The motor nerve conduction velocities are normal or mildly slowed. Sensorimotor nerve action potential amplitudes are reduced. CMT2A is linked to the short arm of chromosome 1 (1p35-36), while CMT2B is mapped to the long arm of chromosome 3 (3q13-22).

Charcot–Marie–Tooth neuropathy type 3 (CMT3) is a severe neuropathy that begins in infancy or early childhood. Occasionally, infants have neonatal hypotonia and delayed motor milestones. There is proximal and distal limb weakness, significant sensory ataxia, and diffuse areflexia. The peripheral nerves are enlarged and palpable. Skeletal and foot abnormalities are present. Most CMT3 cases are sporadic, and the inheritance is traditionally described as autosomal recessive.

Charcot–Marie–Tooth neuropathy type 4 (CMT4) is rare. It also begins in infancy or childhood. There is a delay in acquiring motor milestones. The distal weakness and atrophy spread to proximal muscles in the second decade. Facial muscles may become weak; there is areflexia; adults become wheelchair-bound. Sensory loss is mild. Skeletal abnormalities are common.

Electrophysiologically, nerve conduction velocities are slowed to 15 to 30 m/s. This helps differentiate CMT4 from CMT3 and CMT2C, which also begin in childhood. CMT4 is inherited in an autosomal recessive mode. The Tunisian form was mapped to chromosome 8q13-21.1 and is termed CMT4A. *(Murakami, 233–235)*

**54. (E)** Involvement of organs or tissues other than muscle may provide helpful clues in making the appropriate diagnosis of myopathy. Cardiac arrhythmias are associated with Kearns–Sayre syndrome, Anderson syndrome, polymyositis, and Emery–Dreifuss muscular dystrophy. Congestive heart failure may be seen in Duchenne muscular dystrophy, Becker muscular dystrophy, Emery–Dreifuss myopathy, nemaline myopathy, acid maltase deficiency, carnitine deficiency, and polymyositis. Respiratory failure may be the presenting symptom of myotonic dystrophy, centronuclear myopathy, nemaline myopathy, or acid maltase deficiency. Hepatomegaly may be seen in myopathies associated with deficiencies in acid maltase, debranching enzyme, and carnitine. *(Schapira, 184)*

**55. (A)** The pattern of weakness described in this case shows distal arm and proximal leg weakness. The distal arm weakness involves the wrist and ulnar finger flexors. The proximal leg weakness involves the quadriceps, which is a knee extensor. The asymmetry of the weakness and sparing of the face make this pattern highly suggestive of inclusion body myositis. This pattern may also uncommonly occur in myotonic dystrophy; however, unlike inclusion body myositis, muscle weakness is symmetric. In acid maltase deficiency, the weakness involves the trunk and proximal limbs and the progression is slow, taking years. Nemaline myopathy is mainly seen in infancy and early childhood and is characterized by hypotonia and muscle weakness. Polymyositis has a pattern of symmetric proximal limb weakness involving the muscles of the hip, thigh, and shoulders. *(Schapira, 311–317)*

**56. (B)** Myotonia congenita is due to point mutations in the muscle chloride channel gene on chromosome 7q35. There are autosomal dominant and recessive forms that are allelic disorders. The autosomal dominant form is also known as Thomsen disease; the autosomal recessive form is known as Becker myotonia congenita. Both diseases are benign and associated with diffuse muscle hypertrophy and electrical myotonia. Cold increases the myotonia, and sustained exercise improves it (warmup phenomenon). There is no involvement of the heart or other organs. Patients with Thomsen disease are not weak, but those with Becker myotonia congenita develop limb-girdle weakness and the myotonia is more severe. Patients with myotonia congenita do not complain of pain, which is a feature that distinguishes them from those with proximal myotonic myopathy. The membrane defect consists of markedly reduced chloride conductance, resulting in hyperexcitability and afterdepolarization and producing involuntary myotonic potentials.

Paramyotonia congenita and hyperkalemic periodic paralysis are due to point mutations in the voltage-dependent sodium channel (SCN4A) gene on chromosome 17q23-25. These are autosomal dominant conditions. All have symptoms beginning in the first decade and continuing throughout life. Paramyotonia congenita is characterized by paradoxical myotonia in that the muscle symptoms increase with repetitive movements. This is often best observed on repeated forced eye closure: after several attempts, the patient cannot open the eyelids. Muscle stiffness is worsened by cold temperature. Hyperkalemic periodic paralysis is characterized by attacks of weakness lasting no more than 1 or 2 hours. Attacks are precipitated by fasting, by rest shortly after exercise (minutes or several hours), the ingestion of potassium-rich foods or compounds, and cold. During attacks, patients are areflexic with normal sensation and there is no ocular or respiratory muscle weakness. The serum potassium level may or may not be increased during the attack. Strength is generally normal between attacks, but some patients can have mild interictal limb-girdle weakness. Episodes of weakness are rarely serious enough to require acute therapy; oral carbohydrates or glucose may improve weakness.

Hypokalemic periodic paralysis is due to abnormal muscle membrane excitability arising

from mutations in the muscle calcium channel alpha-1 subunit on chromosome 1q31-32. The mutation produces a reduction of the calcium current in the T tubule. During attacks, there is an influx of potassium into muscle cells and the muscles become electrically unexcitable. Patients have an increased sensitivity to the effects of insulin on potassium. Hypokalemic periodic paralysis is an autosomal dominant condition. It is the most frequent form of periodic paralysis and is more common in males, with a reduced female penetrance. Attacks begin by adolescence and are provoked by exercise followed by sleep, stress, alcohol, or meals rich in carbohydrates and sodium. The episodes last from 3 to 24 hours. A vague prodrome of stiffness or heaviness in the legs can occur. Rarely, ocular, bulbar, and respiratory muscles can be involved in severe attacks. *(Schapira, 135–175)*

**57.** **(E)** Charcot–Marie–Tooth neuropathy type 1 (CMT1) is the most common hereditary motor and sensory neuropathy (HMSN). It is an autosomal dominant disorder with onset before the second decade. Although family history may not be reported in about 20% of cases, detailed investigations, including clinical and electrophysiological evaluations of asymptomatic family members, improve the yield significantly. In all CMT1 subtypes, 50% to 75% of patients have pes cavus and hammertoes. There is distal muscle weakness and atrophy in the legs. About 65% of cases have distal upper limb involvement. Distal sensory impairment is present but usually asymptomatic. The vibratory sensation is most often diminished. Muscle stretch reflexes are absent in about 50% of patients. Nerve enlargement is present in at least 25% of patients. Electrodiagnostic testing reveals slowing of nerve conduction velocities to less than 75% of the lower limit of normal in all nerves. The slowing is present in early childhood. Definite conduction block is characteristically absent. Compound sensory and motor action potential amplitudes are often low in the lower limbs. Needle EMG shows chronic neurogenic motor unit action potentials mainly in the distal muscles. The magnitude of axonal changes is a better prognostic indicator than slowing of nerve conduction velocities.

There are two main genetic variants of CMT1: CMT1A (75%) and CMT1B (20%). The remaining cases are genetically more heterogeneous. Up to 90% of CMT1A patients have tandem DNA duplication on the short arm of chromosome 17 (17p11.2-12), causing an overexpression of PMP-22, which is a 22-kDa membrane glycoprotein localized to the compact portion of the peripheral nerve myelin. Nerve biopsy in CMT1A may show small axonal diameter and onion bulbs. CMT1B is linked to chromosome 1q22-q23, where the gene locus for myelin protein zero (P0) gene is mapped. It is a member of the large family of adhesive molecules and plays a role in the compaction of peripheral nerve myelin. Histologically, CMT1B biopsies show loss of myelinated fibers, small onion bulbs, and tomaculous formations. *(Mendell, 431–436)*

**58.** **(E)** The dominant form of X-linked CMT disease (CMTX) becomes manifest in the first decade of life. There is distal muscle weakness and atrophy, distal sensory loss, and areflexia. Pes cavus and hammertoes are common, and claw-hand deformity may occur in the adult male. Women are mildly affected. Enlarged nerves are infrequent. The recessive form is rare. Spasticity and pyramidal signs are also present, but mental retardation is seen only when the onset is in infancy. Pathologically, there is primary axonopathy with secondary demyelination. The disorder is linked to the marker DXYS1, a marker for the connexin-32 gene. CX32 is a gap junction protein involved in intercellular communication. *(Mendell, 445–447)*

**59.** **(D)** Multifocal motor neuropathy (MMN) is a demyelinating neuropathy, presumably of autoimmune origin. The arguments in favor of an autoimmune origin are the presence of conduction blocks, as seen in chronic inflammatory demyelinating polyneuropathy (CIDP), the presence of anti-$G_{M1}$ antibodies, and the effectiveness of immunomodulating therapy. Age at onset is highly variable, with reports of patients in their 20s to as old as 70 years. It is more common in males than females. Patients have gradual, progressive, asymmetric weakness in the distribution of one or more motor nerves. The

duration of symptoms at presentation is usually greater than 1 year, and durations of 20 years or more have been reported. Upper extremity involvement is more common than lower extremity involvement, and there is usually a distal predominance.

Thus, the most common presentation is that of a young to middle-aged male with slowly progressive asymmetric hand weakness over months or years. Atrophy may or may not be present; one hallmark of MMN is weakness out of proportion to the degree of atrophy. Bulbar function and other cranial innervated muscles are usually spared. Sensory symptoms and signs are absent or minimal. Reflexes vary but are usually decreased focally in affected areas. MMN lacks the upper motor neuron findings of classic ALS. Features that can help differentiate the two include multifocal demyelination on electrodiagnostic studies in MMN, weakness in the distribution of major motor nerves in MMN, the presence of very high titers of anti-$G_{M1}$ antibodies in some but not all patients with MMN, and the response of MMN to intravenous immunoglobulin (IVIg) or cyclophosphamide. Corticosteroids generally have no effect on MMN or produce worsening. Plasma exchange has not been effective and may even worsen the condition. Cyclophosphamide leads to improvement in most patients. Although the effect may last for several months after completion of the course of cyclophosphamide, weakness often recurs after discontinuation of the medication, requiring resumption of treatment. IVIg is effective in most patients with MMN, including some who have been unresponsive to cyclophosphamide. *(Mendell, 192–201)*

**60.** **(B)** Chronic inflammatory demyelinating polyneuropathy (CIDP) is a clinical diagnosis based on symptoms and signs, electrodiagnostic studies, cerebrospinal fluid (CSF) examination, laboratory tests appropriate to the specific clinical situation, and, occasionally, nerve biopsy. Four features are used as the basis of diagnosis: clinical, electrodiagnostic, pathological, and CSF studies. These are further divided into (A) mandatory, (B) supportive, and (C) exclusionary. While these criteria have been established for research purposes, there is a highly variable spectrum of clinical presentation. Mandatory features are those required for diagnosis and should be present in all definite cases. Supportive features are helpful in clinical diagnosis but do not by themselves make a diagnosis. Exclusionary features strongly suggest alternative diagnoses.

The clinical mandatory features include progressive or relapsing motor and/or sensory dysfunction of more than one limb of a peripheral nerve (developing over at least 2 months), and hypo- or areflexia, usually of all four limbs. The supportive clinical features include large-fiber sensory loss predominating over small-fiber sensory loss. The exclusionary features include mutilation of hands or feet, retinitis pigmentosa, ichthyosis, appropriate history of drug or toxic exposure (known to cause a similar peripheral neuropathy), or family history of an inherited peripheral neuropathy, the presence of sensory level, and unequivocal sphincter disturbance. The mandatory electrodiagnostic study features include predominance of demyelination in the proximal nerve segments with reduced conduction velocity and prolonged distal latency. The mandatory CSF studies include a cell count below $10/mm^3$ if HIV-seronegative or below $50/mm^3$ if HIV-seropositive and there is a negative VDRL test. Elevated protein level in the CSF is a supportive feature. If nerve biopsy is performed, the mandatory pathological features include unequivocal evidence of demyelination and remyelination. The exclusionary pathological features for CIDP include vasculitis, neurofilamentous swollen axons, amyloid deposits, or intracytoplasmic inclusions in Schwann cells or macrophages, indicating adrenoleukodystrophy, metachromatic leukodystrophy, globoid cell leukodystrophy, or other evidence of specific pathology. However, nerve biopsies are not required to make a clinical diagnosis. *(Mendell, 173–191)*

**61.** **(B)** Inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic disorder of the peripheral nervous system. It may have a relapsing, monophasic, or progressive course and is generally steroid-responsive. Multifocal motor neuropathy (MMN) is characterized by a slowly progressive, asymmetric, multifocal weakness

with atrophy that may mimic motor neuron disease, but it demonstrates features of multifocal conduction block and slowing in motor nerves. This condition represents a demyelinating neuropathy, which is generally treatable.

Both CIDP and MMN may have their onset in adults of all ages; CIDP rarely affects children. Male predominance is found in both diseases. Weakness tends to be symmetric in CIDP and asymmetric in MMN, with upper extremities more involved than lower extremities and distal muscles more involved than proximal muscles. Large-fiber impairment is more common in CIDP, whereas it is minimal or absent in MMN. Reflexes are globally decreased in CIDP, whereas they are focally decreased or absent in MMN. Sensory nerve studies are usually abnormal in CIDP but normal in MMN. Motor nerve conduction studies in both MMN and CIDP demonstrate acquired demyelination with conduction block, abnormal temporal dispersion, slowed conduction velocities, prolonged distal latencies, and prolonged F-wave latencies. Low titers of anti-$G_{M1}$ antibodies may be present in CIDP patients, whereas they are present at high titers in about half of MMN patients. CSF protein is usually elevated in CIDP and normal or elevated to less than 100 mg/dL in MMN. Sensory nerve biopsy in CIDP may show demyelination, axonal degeneration, mononuclear inflammation, and endoneurial edema, whereas it is normal or shows minor abnormalities in MMN. Prednisone, IVIg, and plasma exchange are the usual treatment for CIDP, whereas IVIg and cyclophosphamide are usually used in MMN. *(Mendell, 173–201)*

**62.** **(D)** Peripheral neuropathy is a common and debilitating complication of arsenic intoxication. It may present as a distal symmetric axonal sensorimotor polyneuropathy with motor predominance. Neuropathic features begin 5 to 10 days after acute exposure, progressing over several weeks; they often resemble those of GBS. The neuropathy involves sensory and motor axons. Unlike the case in GBS, neuropathy is only one component of a systemic intoxication; other features provide important clues that something other than idiopathic GBS explains the neuropathy.

Early systemic symptoms of acute arsenic intoxication include nausea, vomiting, and diarrhea. Initial laboratory findings reflect abnormal liver function and depressed bone marrow, sometimes with pancytopenia and basophilic stippling of red blood cells. CSF protein is elevated in most patients with severe arsenic neuropathy. Increased urinary arsenic excretion is an important feature of recent exposure. The half-life of urinary arsenic excretion after acute exposure is about 3 weeks, making it a helpful test early after exposure. The magnitude of exposure also can be related to accumulation in hair or nails at a later time. Serial nerve conduction studies in patients with arsenic neuropathy demonstrate evidence of a distal dying-back neuropathy with progressive axonal degeneration (findings confirmed on nerve biopsy).

N-hexane, an organic solvent, is thought to be responsible for the neuropathy seen in glue sniffers. The sensory component is usually minimal as compared with the motor component. An unusual and characteristic of this neuropathy is that the clinical condition frequently continues to deteriorate for some months after exposure ceases. It is also characterized by a pure motor neuropathy or mixed neuropathy with motor predominance. Sufficient exposure to n-hexane produces a dying-back sensorimotor neuropathy characterized by distal weakness, stocking–glove sensory loss, and absent ankle reflexes. Involvement may be severe, as in the case example, with profound weakness and sensory loss. In the majority of reports, motor signs predominate, but pure motor neuropathy is unusual and inconsistent with the known sural nerve abnormalities. Nerve conduction studies in asymptomatic n-hexane–exposed individuals may be normal or demonstrate mildly slowed motor conduction velocities. In symptomatic patients, initial findings consist of reduced sensory amplitudes, followed by reduced motor amplitudes and conduction velocities, sometimes to 35% to 40% of the lower limit of normal. The reduced conduction velocity and partial conduction block are explained by secondary myelin changes caused in part by axonal swelling, demonstrated in humans and experimental animals in peripheral and central nerve fibers.

Dapsone produces a neuropathy characterized by weakness and muscle wasting that frequently involves the arms more than the legs. It is one of several toxins associated with motor involvement or motor greater than sensory involvement but no conduction block. Dapsone neuropathy is thought to reflect primary or exclusive axonal degeneration of motor fibers, although controversy exists regarding the presence or absence of sensory involvement.

Neuropathic toxicity of pyridoxine is dose-related, either to long-term cumulative exposure or short-term administration of large doses. Symptoms include unpleasant distal paresthesias and numbness. Associated signs include areflexia, profoundly reduced vibration and joint position sensations, with minimally decreased pinprick sensation. With particularly large doses of pyridoxine, sensory loss may be virtually complete, including facial and mucous membrane areas, with little resolution after removal from exposure. Such profound loss is consistent with a sensory neuronopathy. Sensory nerve conduction studies are the only tests able to localize sensory loss to the periphery, but sensory nerve action potentials persist for up to 10 days after clinical sensory loss is identified.

Neuropathy is the exclusive neurotoxicity associated with nitrofurantoin. Neuropathy develops in a small proportion (less than 0.5%) of patients receiving nitrofurantoin for extended periods (usually exceeding 1 to 2 months). Neuropathy is most common in elderly patients with abnormal renal function, presumably resulting in high blood levels. The neuropathy is a mixed sensorimotor polyneuropathy. Onset is with distal dysesthesias and sensory loss involving large-fiber modalities. With continued use, motor symptoms, sign development, and sensory loss may be severe. Weakness may be subacute and progress to respiratory failure, superficially resembling GBS. When the condition is recognized and nitrofurantoin discontinued, most patients improve or recover. *(Mendell, 316–330)*

**63. (D)** Polymyalgia rheumatica may be one of the more common causes of muscle pain in adults above 50 years of age. One study suggests that the prevalence of the disease is 600 per 100,000. The condition affects the older population, with a mean age at onset of 70 years and a female-to-male incidence of 3 to 1. The disorder is characterized by the indolent onset of myalgia, stiffness, aching, and fatigue predominantly affecting the neck, shoulder, and hip region. Symptoms are typically worse in the morning, when prominent stiffness occurs. Low-grade fever, depression, anemia, and weight loss can accompany the muscular manifestation. Laboratory evaluation reveals typically normal CK level and high sedimentation rate, often to a value greater than 100 mm/h. Muscle biopsies are invariably normal. Polymyalgia rheumatica occurs in approximately 50% of patients with giant cell arteritis. Approximately 15% of patients with the diagnosis of polymyalgia rheumatica will develop giant cell arteritis. Although occasional patients with polymyalgia rheumatica respond to nonsteroidal anti-inflammatory drugs, most require treatment with corticosteroids, which usually results in a dramatic improvement of the myalgia and stiffness. *(Schapira and Griggs, 40–41)*

**64. (E)** Facioscapulohumeral dystrophy is an autosomal dominant disorder. The prevalence is approximately 1 in 20,000. There are two distinctive patterns of progressive muscular weakness involving the face, scapular stabilizer, proximal arm, and peroneal muscles. The first is a gradually descending autosomal dominant form and the second is a jump form in which the progressive weakness jumps from the upper body to the peroneal muscles. The age of onset is from infancy to middle age. The initial weakness typically affects the facial muscles, especially the orbicularis oculi and oris. The masseter, temporalis, extraocular, and pharyngeal muscles are usually unaffected. Shoulder weakness is the presenting symptom in more than 82% of symptomatic patients. Involvement of the scapular fixator muscles—the latissimus dorsi, trapezius, rhomboids, and serratus anterior—causes a winging of the scapula, a highly characteristic sign. The scapula is placed more laterally than normal and moves upward in shoulder abduction. The deltoid muscle is typically not affected. *(Schapira and Griggs, 61–68)*

**65.** **(A)** Miyoshi myopathy is clinically characterized by autosomal recessive inheritance; the onset is in early adulthood with preferential gastrocnemius muscle involvement and dystrophic muscle pathology. The gene has been mapped to chromosome 2p13 and has been cloned. The predicted gene product has been named dysferlin. The location and function of dysferlin remain unknown. Mutations are variable and include insertions, deletions, altered splicing, and point mutations. Bethlem myopathy is a rare autosomal myopathy characterized by a slowly progressive limb-girdle weakness from childhood onward with periods of arrest for several decades and flexion contractures of fingers, elbows, and ankles. The disease has been demonstrated to be due to a type VI collagen gene defect. Emery–Dreifuss muscular dystrophy is an X-linked disorder characterized by a slowly progressive wasting and weakness of the scapulohumeral, anterior tibial, and peroneal muscle groups. Cardiomyopathy with conduction defects is common. The defective gene is mapped to Xq28. Oculopharyngeal muscle dystrophy is an autosomal dominant disease linked to the chromosome 14q11. Nonaka myopathy is linked to chromosome 9p1q1. *(Nonaka, 493–499)*

**66.** **(A)** Duchenne-type muscular dystrophy is the most common form of dystrophy. It is inherited as an X-linked recessive trait and therefore predominantly affects boys. It is a serious condition with progressive muscle wasting and weakness that causes most affected boys to start using wheelchairs by age 12 and to die in their 20s. The associated gene in Duchenne-type muscular dystrophy produces dystrophin. Histochemical studies on muscle sections without muscular dystrophy indicate that dystrophin is localized at the periphery of muscle fibers. It is a cytoskeletal protein located beneath the sarcolemma. In Duchenne-type dystrophy, there is dystrophin deficit and the majority of fibers fail to stain for dystrophin. *(Emery, 991–995)*

**67.** **(A)** Myotonic muscle disorders represent a heterogeneous group of clinically similar diseases sharing the feature of myotonia: delayed relaxation of muscle after voluntary contraction (action myotonia) or mechanical stimulation (percussion myotonia). In classic myotonia, the myotonia improves as muscles warm up, whereas in paradoxical myotonia (paramyotonia) it worsens with repeated muscle contractions. Genetic linkage studies have now pinpointed the lesions to chromosomal loci encoding specific ion channels and a protein kinase. In sodium channel diseases, the gene defect is located on chromosome 17; these include hyperkalemic periodic paralysis, paramyotonia congenita, and potassium-sensitive myotonia congenita. In protein kinase–related diseases, the gene defect is located on chromosome 19 and includes myotonic dystrophy. In chloride channel diseases, the gene defect is located on chromosome 7 and includes autosomal dominant myotonia congenita (Thomsen myotonia), and autosomal recessive myotonia congenita (Becker myotonia). *(Ptacek, Johnson, and Griggs, 482–489)*

**68.** **(E)** Congenital myotonic dystrophy is an autosomal dominant disorder caused by an abnormal unstable expansion of a trinucleotide repeat gene on chromosome 19. The tissues that are commonly involved, in addition to the skeletal muscle, include heart, smooth muscle, lens, brain, and endocrine tissues. The cardinal sign of adult myotonic dystrophy is myotonia. It is absent in cases of congenital myotonic dystrophy and gradually appears during childhood. At birth, there is a frequent history of hydramnios and reduced fetal movements. Neonatal respiratory distress may occur. Other signs of congenital myotonic dystrophy include hypotonia, bilateral facial weakness, feeding difficulty, and mental retardation. The gene defect results from an abnormal expansion of the trinucleotide repeat (CTG) of a gene on chromosome 19, which codes for serine/threonine kinase. *(Schapira and Griggs, 118–124)*

**69.** **(E)** Hyperkalemic periodic paralysis is an autosomal dominant disorder that can occur with or without myotonia or with paramyotonia. It usually begins in the first decade of life. The attack commonly starts in the morning before breakfast, lasts from 15 minutes to an hour, and then spontaneously resolves. Rest often provokes an attack, particularly if preceded by strenuous

exercise. Potassium loading usually precipitates an attack. Cold environment, emotional stress, glucocorticoids, and pregnancy provoke or worsen the attacks. The generalized weakness is usually accompanied by a significant increase of serum potassium, up to 5 to 6 mM/L. Sometimes, the serum potassium level remains within the upper normal range and rarely reaches a toxic level. The frequency of the attacks is variable, from a few times per year to daily. The gene defect is located on chromosome 17q23 (coding for the subunit of the adult human skeletal muscle sodium channel SCN4A). Preventive therapy consists of frequent meals rich in carbohydrates and low in potassium, avoidance of fasting, strenuous work, and exposure to cold, and continuous use of thiazide diuretics or acetazolamide. Some patients can abort or attenuate attacks by the prompt oral intake of a thiazide diuretic or by inhalation of an adrenergic agent that stimulates the sodium–potassium pump. *(Schapira and Griggs, 143–144)*

**70. (C)** The patient described in this vignette died of a progressive necrotizing encephalopathy involving the thalamus, pons, inferior olive, and spinal cord, with sparing of the cortex. These findings are suggestive of Leigh's syndrome, also known as subacute necrotizing encephalopathy. Although it is a multisystemic disorder with hepatic dysfunction and chronic acidosis, the clinical picture is dominated by nervous system involvement, including developmental delay and psychomotor regression, ataxia, optic atrophy, seizures, peripheral neuropathy, and brainstem dysfunction. Serum and CSF lactate and pyruvate are high; in most patients the diagnosis is further supported by a characteristic MRI showing midbrain, basal ganglia, and brainstem lucencies with or without cortical changes. Postmortem spongiform degeneration is seen in the brainstem, with marked loss of neuronal cells and vascular proliferation. The cerebral and cerebellar cortices are characteristically spared. *(Schapira and Cock, 886–898)*

**71. (B)** The association of extraocular ophthalmoplegia with neuromuscular and gastrointestinal symptoms is suggestive of myoneurogastrointestinal encephalopathy. It is defined by the combination of chronic intestinal pseudoobstruction with skeletal myopathy, ophthalmoplegia, and peripheral neuropathy. The gastrointestinal motility disturbance manifests as chronic nausea, vomiting, diarrhea, and malabsorption with progressive malnutrition, often leading to death in the third or fourth decade of life. Postmortem changes include a severe visceral neuropathy or scleroderma-like changes. The peripheral sensorimotor neuropathy and skeletal myopathy contribute to muscle weakness and atrophy accompanying the chronic progressive external ophthalmoplegia (CPEO). Deafness is also common, and there may be cognitive decline due to a leukoencephalopathy. CT or MRI has shown extensive white matter changes in around 50% of the cases described, and electrical studies confirm the presence of a sensorimotor neuropathy with both axonal and demyelinating components. Muscle biopsy shows numerous ragged-red fibers with a partial defect of cyclooxygenase (COX) as the most common biochemical finding. *(Schapira and Cock, 886–898)*

**72. (A)** A rapid loss of vision in a young healthy man with external ophthalmoplegia and bilateral optic atrophy, as described in this vignette, points to the diagnosis of Leber hereditary optic neuropathy (LHON). It is recognized as the most common cause of isolated blindness in young men, with an estimated incidence of 1 in 50,000. Maternal inheritance has long been recognized, and it is an obvious target in which to search for mtDNA mutations. Recovery is variable and to some extent may be linked to the underlying mtDNA genotype, but most individuals remain visually handicapped for life. *(Schapira and Cock, 886–898)*

**73. (D)** This question reports a 2-year-old female with intractable seizures, hypotonia, and liver dysfunction. These symptoms are consistent with the diagnosis of Alpers disease.

Alpers disease, or progressive neuronal degeneration of childhood with liver disease, is a rare familial disorder of unknown etiology. Typically, onset of symptoms follows normal delivery and early development. Infants most

often present with intractable generalized convulsions associated with developmental delay, marked hypotonia, episodes of vomiting, and failure to thrive. There may be signs of liver disease at presentation. Investigations reveal occipital and posterior temporal hypodensities and atrophy on CT scan, very slow activity of very high amplitude spikes interspersed with lower-amplitude polyspikes on EEG, absent visual evoked responses, and abnormal liver histology. *(Schapira and Cock, 886–898)*

**74.** **(E)** The patient described in this question has clinical and radiological evidence of recurrent episodes of stroke with headaches and biochemical evidence of lactic acidosis. The most likely diagnosis is mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes. The key features of the disease include stroke-like episodes with headache, vomiting, and focal neurological disturbance, lactic acidosis, and biochemical or morphological evidence of mitochondrial dysfunction on muscle biopsy. Other common features include a pigmentary retinopathy, psychomotor deterioration, convulsions, myopathy (87%), deafness, diabetes, and short stature (55%). *(Schapira and Cock, 886–898)*

**75.** **(D)** Mitochondria serve several important functions within the cell, the most important of which is the production of ATP by the oxidative phosphorylation system (OXPHOS). The ubiquity of mitochondria suggests that a defect of OXPHOS will affect the function of numerous tissues and implies that mitochondrial OXPHOS decrease will be multisystemic. However, different tissues have varying dependence on OXPHOS for normal function and survival: brain and muscle (heart and skeletal) are highly dependent, and bone and fibroblasts less so. Mitochondria also have their own DNA, inherited through the maternal line, since no sperm containing mitochondria enter the ovum, leaving the embryo to develop using only maternal mtDNA. Mutations of mtDNA have now been associated with a large variety of clinical presentations, most of which involve muscle and central nervous system features and are collectively referred to as the mitochondrial encephalomyopathies. Large-scale rearrangements of mtDNA, in particular deletions, are found in some 40% of adult patients with mitochondrial disease. Most commonly, the resultant clinical picture is one of CPEO, with or without the associated features that make up Kearns–Sayre syndrome (KSS), which are retinitis, ataxia, cardiac conduction block, or elevated CSF protein. The case described in this vignette shows a symptomatic high-degree atrioventricular heart block, ophthalmoplegia, retinal abnormalities, and cerebellar signs in a young patient. These symptoms are highly suggestive of KSS. The diagnostic criteria of KSS include onset before the age of 20 years, CPEO, and a pigmentary retinopathy in association with ataxia, heart block, or raised cerebrospinal fluid protein. A proximal myopathy commonly develops as the disease progresses, and there may also be deafness, stroke-like episodes, bulbar symptoms, areflexia, and lactic acidosis. Muscle biopsy may show up to 60% of all fibers lacking COX activity. *(Schapira and Cock, 886–898)*

**76.** **(C)** The association of cerebellar signs, seizures, and severe myopathy in a 30-year-old male, as described in this vignette, is suggestive of myoclonic epilepsy with ragged-red fibers. The major clinical features of the disease are myoclonic epilepsy, usually with tonic–clonic generalized seizures, a progressive cerebellar syndrome, and a myopathy. Deafness is common in both clinically overt cases and in otherwise asymptomatic maternal relatives. Other features may include pes cavus, peripheral neuropathy, optic atrophy, dorsal column loss, heart block, and, in severe cases, dementia. CPEO, pigmentary retinopathy, and stroke-like episodes are said to be typically absent. The onset is commonly in the second or third decade, but cases have been reported from ages 3 to 62 years. Early childhood development is often normal, but there may be a history of muscle fatigue, cramps, epilepsy, or developmental delay before the diagnosis becomes clear. In those with clear central nervous system involvement, the disease is usually progressive, although milder cases may remain minimally affected for many years. *(Schapira and Cock, 886–898)*

**77.** **(C)** KSS is a mitochondrial disease characterized by a clinical triad: progressive external ophthalmoplegia, retinal degeneration, and onset before the age of 20 years. It is variably associated with cerebellar ataxia, growth failure, sensorineuronal deafness, heart block, and raised CSF protein. Diabetes mellitus, hypoparathyroidism, and growth deficiency may occur. Both ragged-red fibers and COX-negativity are present in biopsied muscle. Ninety percent of patients have a large-scale rearrangement of their muscle mitochondrial DNA. *(Schapira and Griggs, 184)*

**78.** **(A)** Cardiac conduction defects are the frequent features of KSS, whereas hypertrophic cardiomyopathy has been reported in myoclonic epilepsy, with ragged-red fibers, mitochondrial encephalomyelopathy with lactic acidosis and stroke-like episodes, Leigh syndrome, and progressive external ophthalmoplegia. *(Schapira and Griggs, 190–191)*

**79.** **(C)** The patient described in this vignette has acute recurrent and reversible exercise intolerance (especially during a brief, intense isometric exercise or less intense but sustained exercise), normal neurological examination, increased CK level in the serum, myoglobinuria, and normal pyruvate and lactate levels in the serum. This is highly suggestive of a muscle energy deficit. The fuel used by muscle depends on several factors, most importantly, the type, intensity, and duration of exercise but also diet and physical conditioning. At rest, muscle uses predominantly fatty acids, whereas the energy for intense aerobic exercise derives from the oxidation of carbohydrate. The energy for maximal force generation in intense isometric exercise derives from anaerobic metabolism, particularly anaerobic glycogenolysis. During submaximal dynamic exercise, the type of fuel used by muscle depends on the relative intensity and duration of exercise. At low intensity, the initial oxidative fuel is glycogen, with increasing proportions of oxidative energy supplied by blood, glucose, and free fatty acids as exercise duration increases. The type of circulating substrate during mild exercise varies with time. There is a gradual increase in the use of free fatty acids (as exercise duration increases) over glucose until, a few hours into exercise, lipid oxidation becomes the major source of energy. At high intensities of aerobic exercise, the proportion of energy derived from carbohydrate oxidation increases and glycogen become an important fuel. Fatigue appears when the glycogen is exhausted. Hence, the symptoms of patients with glycogenoses are almost invariably related to a strenuous bout of exertion. In contrast, patients with a disorder of lipid metabolism usually have little difficulty with short-term intense exercise.

In this vignette, the observation that venous pyruvate and lactate did not increase after exercise pointed to a failure of the breakdown of glycogen to lactic acid. The administration of epinephrine elicited a normal rise of blood glucose, indicating intact hepatic glycogenolysis and abnormal muscle glycogen metabolism. The most likely diagnosis is myophosphorylase deficiency, or McArdle disease. In typical cases, the cardinal manifestation of the disease is exercise intolerance manifested by myalgia, premature fatigue, and weakness or stiffness of exercising muscles. Muscle necrosis and myoglobinuria after exercise occur in about half of the patients, and about half of these develop acute renal failure. Mild proximal limb weakness is seen in about one third of patients and is more common in older individuals. The EMG may be normal or may show nonspecific myopathic changes. No electrical activity is recorded by needle EMG from maximally shortened muscles during the cramps induced by ischemic exercise. Examination of a muscle biopsy specimen under light microscopy may show subsarcolemmal deposits of glycogen as bulges or blebs at the periphery of the fibers. Accumulation of glycogen, between myofibrils, generally is less marked but may be sufficient to give the fibers a vacuolar appearance.

In phosphofructokinase deficiency, typically, there is intolerance to intense exercise, often accompanied by cramps of exercising muscles, which are relieved by rest. Although a careful history reveals that exercise intolerance is present since childhood, patients usually do not come to medical attention until adolescence, and the diagnosis is established most commonly in young men. Symptoms are more likely to occur

with isometric exercise. The exercise intolerance seems to worsen with a high carbohydrate intake. The resting serum CK level is usually increased. The EMG may be normal or show myopathic abnormalities. Studies of 31 P-nuclear MR spectroscopy show the accumulation, even with mild exercise, of glycolytic intermediates in the form of phosphorylated monoesters. The accumulation of phosphorylated monoesters with exercise also occurs in other defects of glycolysis but not in myophosphorylase deficiency.

Another important clinical difference between McArdle disease and phosphofructokinase deficiency is related to the fact that because phosphofructokinase deficiency blocks the metabolism of glucose, these patients experience a substantial drop in exercise capacity in response to glucose infusion or high-carbohydrate meals. This response is termed the "out of wind" phenomenon and is related to the fact that in phosphofructokinase deficiency the muscle is highly dependent on the availability of fatty acids and ketones for oxidative metabolism. Glucose causes an insulin-mediated inhibition of triglyceride hydrolysis and a fall in blood levels of the fatty acids and ketones necessary for muscle oxidative fuel. Definitive diagnosis requires biochemical documentation of the enzyme defect in muscle or careful measurement of the enzyme activity in erythrocytes to show partial deficiency. *(Schapira and Griggs, 230–233)*

**80. (C)** The cardinal clinical features of myasthenia gravis (MG) are fluctuating weakness and abnormal fatigability affecting all voluntary muscles, with a predilection for extraocular, bulbar, and proximal limb muscles. Initial symptoms involve the external ocular muscles in approximately 50% of cases, but bulbar symptoms are present in 16% of cases, and more rarely limb muscles may also be affected initially. Muscle weakness tends to be worse with repeated or prolonged exercise and typically exhibits diurnal fluctuation, worsening toward the evening hours. Within 1 year of onset, the disease remains purely ocular in about 40% of cases, generalized in about 35% of cases, confined to the extremities in about 10% of cases, and bulbar or oculobulbar in about 15% of cases. Within 2 years after onset, myasthenic syndrome remains restricted to the extraocular muscles in only about 14% of the patients whose initial manifestations are only ocular, whereas about 86% of patients develop generalized manifestations. The primary pathogenic event in MG is identified as an antibody-triggered acceleration, internalization, and progressive loss of acetylcholine receptors associated with a complement-mediated degeneration of synaptic folds. The loss of acetylcholine receptors results in decreased postsynaptic sensitivity to acetylcholine. Repetitive stimulation studies are the most commonly used electrophysiologic test of neuromuscular transmission. In MG, the major physiological defect is the decremental response of the compound muscle action potential to a train of supramaximal stimuli, at a frequency varying from 2 to 3 Hz, of a nerve innervating the affected muscle. The administration of magnesium may depress the neuromuscular conduction and worsen the symptoms of MG. *(Schapira and Griggs, 254–266)*

**81. (E)** Lambert–Eaton myasthenic syndrome is due to an impairment of presynaptic release of acetylcholine at the neuromuscular junction. Presynaptic loss of voltage-gated calcium channels is the suggested primary pathological event in this disease. It is postulated that the calcium channels are the targets of autoantibodies. As a consequence, the influx of calcium into the nerve terminal is impaired, resulting in decreased quantal release of acetylcholine. Repetitive stimulation, which increases the external calcium concentration, promotes calcium entry into the nerve terminal, thus enhancing the acetylcholine release and neuromuscular transmission. In about 92% of patients with Lambert–Eaton myasthenic syndrome, antibodies directed against the P/Q type of voltage-gated calcium channels have been found with or without association to neoplasms. The N type of voltage-gated calcium channel antibodies are detected in 40% to 49% of all early Lambert–Eaton myasthenic syndromes and in approximately 70% of those associated with malignancies.

In its classic presentation, the syndrome is characterized by weakness and fatigability,

mostly affecting the proximal limb muscles, with minimum or moderate extraocular involvement or bulbar symptoms. Onset of symptoms usually occurs in the proximal lower limb muscles, which remain more predominantly involved. Autonomic symptoms and signs are usually prominent, and may include dry mouth and eyes, impotence, orthostatic hypotension, and hyperhidrosis. The reflexes are reduced or absent. Repetitive stimulation studies represent the most specific diagnostic tool. They may show the neurophysiologic characteristic of this presynaptic disorder: initial reduced compound muscle action potential amplitude with postactivation facilitation after voluntary exercise of 10 seconds or tetanic stimulation. There is an incremental response of the amplitude of the first compound muscle action potential of at least 100%. Tetanic stimulation at a rate of 20 to 50 Hz is more painful than the voluntary exercise and is indicated in cases of absent postactivation facilitation after voluntary activation. *(Schapira and Griggs, 272–274)*

**82. (A)** The case described in this vignette is highly suggestive of botulism intoxication. Botulinum toxin is one of the most potent poisons known. It is produced by the spores of *Clostridium botulinum*. The basic pathophysiology of botulism neurotoxicity relates to its inhibitory effect on acetylcholine release. Individual toxin types differ in their affinity for neuronal tissue, with type A being the most potent, followed by type B. Toxin-induced paralysis of cholinergic nerves involves three basic steps: (1) the binding of exotoxin to external receptors at ganglionic synapses, postganglionic parasympathetic synapses, and neuromuscular junction; (2) the translocated step, during which the toxin molecule or some portion of it passes through the nerve or muscle; and (3) the paralytic step, during which the release of acetylcholine is usually blocked.

Clinical features may include prodromal symptoms with nausea, vomiting, abdominal pain, and diarrhea. Cranial nerve signs appear early, with eye symptoms being the most common. There may be both an internal and external ophthalmoplegia. Rapid involvement of other cranial nerves produces vertigo, deafness, and dysphagia. Swallowing ultimately becomes impossible, and liquids are regurgitated through the nose. The voice often has a nasal quality and may be hoarse. Muscular weakness may appear between the second and fourth day of the illness. At first, the limbs may feel tired and the patient is unable to climb stairs. This weakness may become so severe that moving about or even turning in bed is impossible. Often this muscular involvement is limited to the neck muscles, so that the patient is unable to raise his or her head. Restlessness and agitation may occur; however, consciousness is preserved.

The neurophysiological findings of botulism are similar to the ones observed in Lambert–Eaton myasthenic syndrome. Sensory conduction studies are usually normal. In motor nerve conduction studies, the compound muscle action potential amplitudes are decreased in affected muscles with normal latencies and conduction velocities. Needle EMG may show abnormalities at rest with fibrillations and positive sharp waves. Repetitive stimulation studies may show decrement at slow rates of stimulation and characteristic increment, after a brief exercise or tetanic stimulation, between 20 and 50 Hz. The diagnosis is confirmed by detection of the neurotoxin in the patient serum or feces.

*Clostridium tetani* produces a powerful exotoxin under the anaerobic conditions of wounds or soil-contaminated injuries. Clinical features involve both the central and the peripheral nervous systems as well as the muscular system. The incubation period is usually from 5 to 25 days but may be as short as a few hours. In most cases, the clinical onset is characterized by a seemingly preferential affinity of the toxin for the facial and bulbar muscles. Premonitory signs may consist of a chill, headache, and restlessness, with pain and erythema at the site of injury. A sensation of tightness in the jaw and a mild stiffness and soreness in the neck are usually noticed within a few hours. Pain between the shoulder blades may also be present. Later, the jaw becomes stiff and tight and trismus results. This muscular involvement soon spreads to the throat muscles, producing dysphagia, and when the facial muscles are involved, facial asymmetry and a fixed smile result. As the disease progresses, muscular

hypertonicity may spread and become generalized, involving the muscles of the trunk and extremities. The rigidity of the back muscles produces an arching of the spine that, together with the retraction of the head, results in opisthotonos. Spasms or tonic contractions occur in any muscle group and may be spontaneous or precipitated by the slightest stimulus, such as noises, touching the patient, or even touching the bed.

Organophosphorus compounds are powerful inhibitors of acetylcholinesterase and pseudocholinesterase. In the human, the former enzyme is found in nervous tissue, specifically in brain and spinal cord myoneural junctions (at pre- and postganglionic parasympathetic synapses and at preganglionic synapses) and in some postganglionic sympathetic nerve endings. Excess acetylcholine causes overstimulation and then depolarization blockade of cholinergic transmission. Two major neurophysiological features of acetylcholinesterase inhibition are repetitive discharges following the compound muscle action potential (CMAP) and the decrement in the CMAP with repetitive stimulation.

Clinically, intoxication may range from latent, asymptomatic poisoning to a life-threatening illness, depending on the level of serum cholinesterase activity. A decrease of 10% to 50% of serum cholinesterase activity may not even be clinically detectable. When levels are moderately depressed (20% normal), sweating, cramps, tingling of the extremities, and mild bulbar weakness with fasciculation may occur. At 10% of serum cholinesterase activity, consciousness becomes depressed, and myosis with no pupillary response to light occurs. The patient may become cyanotic from respiratory weakness, and pooled secretions may obstruct the airway. Central nervous system manifestations include confusion, convulsions, depression of respiratory and circulatory centers, nightmares, headaches, progressive generalized weakness, slurred speech, ataxia, and tremor. Muscarinic manifestations include bradycardia with hypotension, excessive sweating and salivation, miosis and blurring of vision, nausea and vomiting with cramps, and wheezing with bronchial constriction. Nicotinic manifestations include muscular twitching, fasciculation, and cramps. Venom poisoning may rarely cause a disorder of the neuromuscular junction with a curare-like effect.

Lambert–Eaton myasthenic syndrome is diagnosed based on the triad of fatigable weakness predominantly in the proximal limb muscles, reduced or absent reflexes, and autonomic features. Repetitive stimulation studies show an incremental response on titanic stimulation. Antibodies against the P/Q voltage-gated calcium channel may be detected. *(Schapira and Griggs, 272–280)*

**83.** **(E)** The deleterious effects of aminoglycosides on neuromuscular transmission have been well established for practically all agents of this family of antibiotics, which are contraindicated in patients with MG. Most aminoglycosides, including neomycin and tobramycin, exert their effect through reduction of the number of acetylcholine quanta released at the nerve terminal, after the arrival of the propagated nerve action potential. Other antibiotics have been incriminated in myasthenic exacerbation, including ampicillin, ciprofloxacin, perfloxacin, and norfloxacin. Clindamycin and lincomycin may produce a neuromuscular blockage, not reversible with anticholinesterases but reversible with 3,4 aminopyridine. Quinidine can produce a worsening of weakness in patients with MG, acting at the nerve terminal by inhibiting acetylcholine synthesis or release. Magnesium derivate may worsen myasthenia symptoms by blocking calcium entry into the nerve terminal. *(Schapira and Griggs, 277–278)*

**84.** **(D)** Congenital myasthenic syndromes (CMS) are heterogeneous disorders arising from presynaptic, synaptic, or postsynaptic defects. In each CMS, the specific defect compromises the safety margin of neuromuscular transmission by one or more mechanisms. The European Neuromuscular Center's classification of congenital myasthenic syndrome classifies congenital myasthenia into three groups: Type I, with autosomal recessive transmission, includes familial infantile myasthenia, limb-girdle myasthenia, acetylcholinesterase deficiency, acetylcholine receptor deficiency, and benign congenital myasthenic syndrome with facial dysmorphism. Type II, with autosomal dominant transmission,

includes slow-channel syndrome. Type III includes sporadic cases. The clues for the diagnosis of a slow-channel myasthenic syndrome consist of selectively severe weakness of the forearm extensor muscles, repetitive compound muscle action potential response to single nerve stimuli that is accentuated by edrophonium, prolonged and biexponentially decaying miniature endplate current, and endplate myopathy. The endplate myopathy, which results from calcium overloading of the postsynaptic region, is evidenced by degeneration of junctional folds with loss of acetylcholine receptors and widening of the synaptic space. *(Engel et al., 140–156; Schapira and Griggs, 279–286)*

**85.** **(A)** Cholesterol- and lipid-lowering agents are associated with myopathy, occurring in less than 0.5% of patients on monotherapy and increasing in frequency up to 5% with combined lipid-lowering therapy. Patients complain of myalgia and weakness. CK concentration is elevated. Biopsy reveals type II atrophy and myofiber necrosis. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (such as lovastatin) and niacin have all been implicated in producing myopathy. The HMG-CoA reductase inhibitors produce rhabdomyolysis as a direct toxic effect on myocytes. Amiodarone may cause a lysosomal-related myopathy. Zidovidine may cause mitochondrial myopathy. D penicillamine may cause inflammatory myopathy. Colchicine may cause antimicrotubular myopathy. *(Schapira and Griggs, 364–366)*

**86.** **(E)** The facial nerve is the most commonly affected cranial nerve in sarcoidosis, but olfactory, oculomotor, and trochlear nerves can also be affected. *(Rolak, 81)*

**87.** **(A)** Diphtheritic neuropathy most commonly causes glossopharyngeal nerve palsy or, less commonly, oculomotor cranial nerve palsies. *(Rolak, 81)*

**88.** **(C)** Diabetic neuropathy may be associated with oculomotor nerve palsy with conservation of the pupillary reflexes. The trochlear, abducens, and facial nerves can be affected. *(Rolak, 81)*

**89.** **(B)** Cranial nerves may be affected in certain diseases that cause peripheral neuropathies. Guillain–Barré syndrome (GBS) may be associated with abducens and facial nerve paralysis, whereas Miller–Fisher syndrome (a variant of GBS) may be associated with oculomotor and trochlear nerve paralysis. Sjögren syndrome neuropathy may be associated with trigeminal neuropathy. Polyarteritis nodosa may commonly involve the oculomotor and facial nerves, less likely the vestibulocochlear nerve. Wegener granulomatosis may commonly affect the facial nerve. The trigeminal and facial nerves are the most commonly affected in Lyme disease. The trigeminal and vagus nerves are the most commonly affected cranial nerves in porphyria. The oculomotor nerve is the most commonly affected in syphilis. Primary amyloidosis commonly affects the facial, the trigeminal, and the oculomotor nerves, whereas in Refsum disease the olfactory nerve as well as the vestibulocochlear nerve are most commonly affected. *(Rolak, 81)*

**90.** **(D)** A predominantly sensory type of neuropathy may be seen in cases of pyridoxine or doxorubicin toxicity, sensory variants of acute and chronic demyelinating polyneuropathy, IgM paraproteinemia, paraneoplastic neuropathy, Sjögren syndrome neuropathy, vitamin E deficiency, abetalipoproteinemia, and spinocerebellar degeneration. A predominantly motor neuropathy is commonly seen in cases of GBS, diphtheric neuropathy, dapsone-induced neuropathy, porphyria, and multifocal motor neuropathy. *(Rolak, 82)*

**91.** **(C)** A useful concept in understanding neuromuscular transmission is the safety factor. It is defined as the difference between the membrane potential and the threshold potential of initiating an action potential. As long as the threshold potential is reached, the action potential initiates muscle contraction. Several factors contribute to the safety factor: quantal release, acetylcholine receptor conduction properties and density, and cholinesterase activity. Postsynaptic folds form a high-resistance pathway that focuses endplate current flow on voltage-gated sodium channels concentrated in the depth of the folds. Both these factors reduce the action

potential threshold at the endplate and serve to increase the safety factor. All disorders of neuromuscular transmission are characterized by the compromise of the safety factor for neuromuscular transmission. The functional effect of reduced acetylcholine receptors is decreased endplate potential. If quantal release is lowered (such as in cases of repetitive stimulation or activity), the endplate potential may fall below the threshold and the muscle action potential will not be generated. *(Schapira, 254)*

**92.** **(A)** Several lines of evidence suggest that CD4+ T helper cells have a major role in the pathogenesis of MG: (1) Most antiacetylcholine receptor antibodies in MG patients are high-affinity IgG and their synthesis requires CD4+ and T-helper factors. (2) Acetylcholine receptors reactive CD4+ cells from the blood, and the thymus of MG patients have a T-helper function. (3) Thymectomy decreases the reactivity of blood T cells against acetylcholine receptors. (4) In vitro treatment of CD4+ T cells from the blood of MG patients with anti CD4+ antibodies decreases the reactivity of T cells to acetylcholine receptors. (5) In experimental autoimmune MG, the synthesis of pathogenic antiacetylcholine receptor antibodies requires CD4+ cells. *(Drachman, 1797–1810)*

**93.** **(C)** MG is characterized clinically by muscle weakness, enhanced by physical effort. Although the acetylcholine receptor (AChR) expressed on muscle is the main target of the disease, the thymus has long been known to be involved in the pathogenesis of MG. Most myasthenic patients have thymic abnormalities: 70% of patients have lymphoid follicular hyperplasia, and 10% have a thymoma. Numerous arguments indicate a relationship between MG, the anti-acetylcholine receptor antibodies, and the thymus: (1) Thymic abnormalities are seen in seropositive patients. (2) Thymectomy has a beneficial effect. (3) Anti-AChR antibody titers are decreased after thymectomy. (4) There is a decreased in vitro production of anti-AChR antibodies from stimulated peripheral blood lymphocytes. (5) There is spontaneous in vitro production of anti-AChR antibodies by thymocytes from a hyperplasic thymus. (6) There is transfer by MG thymic explants of pathogenic parameters in some animal studies. The human thymus may express acetylcholine receptors. Thymic myoid cells may have a role in anti-AChR sensitization. This is supported by their characteristic and unusual microenvironment in MG thymuses with lymphoid follicular hyperplasia. In MG thymuses but never in normal thymuses, myoid cells, which do not express class II molecules, are in intimate contact with HLA-DR–positive reticulum cells close to, and occasionally inside, germinal centers. These histopathological findings suggest that the reticulum cells may function as antigen-presenting cells and acetylcholine receptor epitopes. *(Moulian et al., 397–406)*

**94.** **(D)** Corticosteroids are the mainstay of immunosuppressive treatment of MG. They have numerous effects on the immune system as a whole, leading to generalized immunosuppression. The beneficial effect therapy for MG appears to be related to (1) reduction of lymphocyte differentiation and proliferation; (2) redistribution of lymphocytes from the circulation into tissues that remove them from the site of immunoreactivity; (3) alteration of lymphokine function, primarily tumor necrosis factors IL-1 and IL-2; (4) inhibition of macrophage function, in particular antigen presentation and processing; and (5) increased acetylcholine receptor synthesis in muscle.

**95.** **(B)** Dermatomyositis has been modeled as a disease in which autoantibodies directed against endothelium cause vascular injury, leading to ischemic myofiber damage. Myofiber injury consists of perifascicular atrophy, with small, abnormal-appearing myofibers at the periphery of muscle fascicles. It has been proposed that the initial injury to capillaries in dermatomyositis results from the immune system's production of autoantibodies against an endothelial antigen, causing damage to the perifascicular area. This area was considered vulnerable to ischemia because it is a watershed region at the periphery of fascicles. However, a pathogenic autoantibody to a specific endothelial antigen has not been identified in dermatomyositis.

Perifascicular muscle fibers have not been shown to be preferentially vulnerable to ischemia. In fact, experimental models suggest that perifascicular myofibers are less vulnerable than central muscle fibers to ischemia. In addition, no evidence has been found that such fibers are indeed damaged by ischemia.

Recent microarray studies assessing the pattern of muscle gene expression in patients with dermatomyositis have shown upregulation of genes induced by type 1 interferons (interferon α and β) but not type 2 interferon (interferon-γ) as compared with normal patients. The plasmacytoid dendritic cells, natural interferon-producing cells, have been identified in dermatomyositis muscles, suggesting a possible intramuscular source of type 1 interferons.

Based on these findings, a revised model for dermatomyositis has been proposed: endothelial cells and myofibers may be injured by the chronic intracellular overproduction of one or more interferon 1–inducible proteins such as myxovirus resistance A protein. *(Greenberg, 2008–2019)*

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CHAPTER 6

# Behavioral Neurology
## Questions

**1.** Which of the following biomarkers is elevated in the cerebrospinal fluid (CSF) of patients with Alzheimer disease (AD)?

(A) Secretase enzymes
(B) Aβ-40 peptide
(C) Aβ-42 peptide
(D) Oligoclonal bands
(E) Phosphorylated tau

**2.** Frontotemporal dementia may be associated with

(A) multiple sclerosis
(B) motor neuron disease
(C) Parkinson disease (PD)
(D) Huntington disease
(E) Wilson disease

**3.** Degeneration of the left frontoinsular cortex is prominent in

(A) AD
(B) frontal variant of frontotemporal dementia
(C) nonfluent aphasia
(D) semantic dementia (SD)
(E) mild cognitive impairment

**4.** Alien limb is seen in

(A) progressive supranuclear palsy
(B) motor neuron disease
(C) AD
(D) corticobasal degeneration
(E) PD

**5.** The association of apathy, disinhibition, and eating disorder is suggestive of

(A) progressive supranuclear palsy
(B) Huntington disease
(C) frontal variant of frontotemporal dementia
(D) SD
(E) AD

**6.** In SD, the patient may develop

(A) agnosia for faces and objects
(B) early parkinsonism
(C) early short-term memory deficit
(D) apathy
(E) disinhibition

**7.** A deficit in articulatory planning resulting in an inability to command the speech musculature to produce sounds in a proper sequence defines

(A) motor aphasia
(B) sensory aphasia
(C) dysarthria
(D) speech apraxia
(E) perseveration

**8.** Which of the following is true of pick bodies?

(A) They are seen in most cases of frontotemporal lobe dementia.
(B) They are composed of randomly arranged filaments of tau proteins.
(C) They contain exclusively of amyloid precursor protein.
(D) They are rarely found in the hippocampus.
(E) Most often, they are located in the pyramidal cells of layer V.

**9.** The most important genetic mutation in frontotemporal dementia is located on

(A) chromosome 17q21-22
(B) chromosome 4
(C) chromosome X
(D) chromosome 19p13
(E) chromosome 9q21-q22

**10.** HMPAO-SPECT studies in SD demonstrated severe hypoperfusion of the

(A) bilateral frontal lobes
(B) bilateral anterior temporal lobes
(C) bilateral parietal lobes
(D) bilateral orbitofrontal cortex
(E) insula

**11.** Serotonin dysfunction has been reported in

(A) HIV dementia
(B) mild cognitive impairment
(C) mild AD
(D) severe AD
(E) SD

**12.** The major risk factor for AD is

(A) age
(B) family history of AD
(C) female gender
(D) low education level
(E) head trauma

**13.** Mutations causing early onset of AD have been localized in the

(A) ApoE ε2 gene
(B) presenilin-1 gene
(C) Parkin gene
(D) tau protein gene
(E) Notch3 gene

**14.** Which of the following changes in cognitive function is consistent with normal aging rather than AD?

(A) Loss of insight
(B) Apathy
(C) Anomia
(D) Retrieval deficit–type memory impairment that responds to clues
(E) Impaired visuospatial function

**15.** Which of the following drugs for AD is an N-methyl-D-aspartic acid (NMDA) receptor antagonist?

(A) Donepezil
(B) Rivastigmine
(C) Galantamine
(D) Memantine
(E) Vitamin E

**16.** Which of the following is true of mild cognitive impairment (MCI)?

(A) The prevalence of MCI is between 12% and 15%.
(B) It impairs activities of daily living.
(C) There is moderate impairment of cognitive function.
(D) The preservation of memory function excludes the diagnosis of MCI.
(E) Within a year after the diagnosis of MCI is established, 50% of patients progress to AD.

**17.** Which of the following predicts that mild cognitive impairment will progress to dementia?

(A) ApoE2 carrier
(B) Atrophic hippcampi on MRI
(C) Elevated Aβ level in the CSF
(D) Reduction in the level of tau in the CSF
(E) Hypometabolism of the frontal lobe on fluorodeoxyglucose positron emission tomography (FDG-PET) studies

**18.** Six months after being diagnosed with PD, a 63-year-old man noticed a progressive and fluctuating decline in his memory and cognitive function as well as visual hallucinations that interfered with his social and occupational function. This patient most likely has

(A) AD
(B) PD dementia
(C) dementia with Lewy bodies (DLB)
(D) frontotemporal dementia
(E) mild cognitive impairment

**19.** Alpha-synuclein pathology occurs with PD, multisystem atrophy, and

(A) Huntington disease
(B) AD
(C) vascular dementia
(D) HIV dementia
(E) DLB

**20.** Orthostatic hypotension is a prominent feature of

(A) corticobasal degeneration
(B) DLB
(C) motor neuron disease
(D) AD
(E) mild cognitive impairment

**21.** Which of the following clinical manifestation favors the diagnosis of vascular dementia versus other forms of dementia?

(A) Visual hallucination
(B) Memory loss sufficient to interfere with activities of daily living
(C) Stepwise deterioration
(D) Severe autonomic dysfunction
(E) Parkinsonism

**22.** The association of gait apraxia, early urinary incontinence, and progressive cognitive decline to confluent deep white matter changes on magnetic resonance imaging (MRI) is suggestive of

(A) normal-pressure hydrocephalus
(B) HIV dementia
(C) Notch3 gene mutation
(D) Binswanger syndrome
(E) Parkinson dementia

**23.** Which of the following is a factor favoring lack of cognitive improvement after shunting of normal-pressure hydrocephalus?

(A) Anomia
(B) Mild impairment in cognition
(C) Secondary normal-pressure hydrocephalus
(D) Gait disturbance preceding cognitive impairment
(E) Long duration of gait abnormality

**24.** It has been well established that on MRI spectroscopy, patients with AD show

(A) an elevated level of lactate
(B) a reduced level of choline
(C) a reduced level of N-acetyl aspartate
(D) a reduced level of phosphocreatine
(E) a reduced level of myoinositol

**25.** Donepezil demonstrates more benefit in the progression from mild cognitive impairment to definite dementia in

(A) APOE4-negative carriers
(B) APOE4-positive carriers
(C) APOE2-negative carriers
(D) APOE2-positive carriers
(E) Carriers of the Notch3 gene mutation

**26.** The most common psychiatric manifestation in mild cognitive impairment is

(A) delusions
(B) visual hallucinations
(C) depression
(D) euphoria
(E) disinhibition

**27.** The most pervasive neuropsychiatric symptom of AD is

(A) depression
(B) apathy
(C) anxiety
(D) delusions
(E) hallucinations

**28.** The most common neuropsychiatric symptom of DLB is

(A) auditory hallucinations
(B) visual hallucinations
(C) delusions
(D) anxiety
(E) agitation

**29.** Impulsivity and tactless conduct are seen at an early stage of

(A) mild cognitive impairment
(B) AD
(C) vascular dementia
(D) DLB
(E) frontotemporal dementia

**30.** The gene defect of familial frontotemporal dementia with amyotrophic lateral sclerosis is located on chromosome

(A) 17q21-22
(B) 3
(C) 9q21-22
(D) 1
(E) 14

**31.** Progranulin mutations have been associated with

(A) frontotemporal dementia
(B) HIV dementia
(C) vascular dementia
(D) AD
(E) DLB

**32.** Filament-containing neuronal processes in the distal axons are

(A) neurofibrillary tangles
(B) neuropil threads
(C) dystrophic neurites
(D) senile plaques
(E) Lewy bodies

**33.** AD was associated with mutations of gene coding for presenilin 2, which is located on

(A) chromosome 21
(B) chromosome 19
(C) chromosome 14
(D) chromosome 1
(E) chromosome 17

**34.** Injury to which of the following locations is most critical in causing memory impairment in AD?

(A) Hippocampus
(B) Amygdala
(C) Basal forebrain cholinergic system
(D) Brainstem monoaminergic system
(E) Neocortex

**35.** In AD, the enzyme responsible for the endoproteolytic cleavage of amyloid precursor protein to generate N-terminal of Aβ peptide is

(A) α-secretase
(B) BACE1
(C) BACE2
(D) γ-secretase
(E) none of the above

**36.** Which of the following is true of the β-amyloid peptide?

(A) The soluble β-amyloid peptide is the major constituent of the senile plaque.
(B) β-secretase cleaves the N terminal of amyloid precursor protein.
(C) P3 deposits are found in patients with AD.
(D) AD patients have a reduced glial reaction as compared with normal patients.
(E) Cox1 expression is increased in AD.

**37.** In early-stage AD, neuropsychological tests show a defect in

(A) remote memory
(B) immediate memory
(C) recent memory
(D) concrete reasoning
(E) calculation

**38.** Positron emission tomography shows that the most severe reduction in cerebral metabolism in cases of AD is located in the

(A) temporal association cortex
(B) frontal association cortex
(C) motor cortex
(D) parietal association cortex
(E) basal ganglia

**39.** In AD, the most common psychiatric symptom is

(A) depression
(B) visual hallucination
(C) auditory hallucination
(D) delusion
(E) verbal aggressiveness

**40.** Posterior cortical atrophy, a dementia syndrome with early prominent visual and visuospatial disturbances, is most frequently seen in

(A) corticobasal degeneration
(B) AD
(C) Creutzfeldt–Jakob disease
(D) subcortical gliosis
(E) Huntington disease

**41.** Which of the following characteristics is a feature of frontotemporal dementia that distinguishes it from AD?

(A) Hyperorality
(B) Impairment in executive function
(C) Decreased verbal memory
(D) Visuospatial short-term memory
(E) Association with chromosome 4

**42.** Which of the following neurodegenerative diseases is associated with the aggregation of tau isoforms without exon 10?

(A) Supranuclear palsy
(B) Corticobasal degeneration
(C) AD
(D) Pick disease
(E) Familial frontotemporal dementia

**43.** Which of the following is a feature of progressive supranuclear palsy?

(A) Aphasia
(B) Unilateral dystonia
(C) Marked slowing of vertical saccades followed by the development of vertical supranuclear gaze palsy
(D) Hallucinations not related to medications
(E) Onset of symptoms at the age of 30 years

**44.** In progressive supranuclear palsy, high-density neurofibrillary tangles are *least* likely to be seen in the

(A) striatum
(B) thalamus
(C) pallidum
(D) dentate nucleus
(E) prefrontal cortex

**45.** Which of the following is true of neurofibrillary tangles?

(A) Neurofibrillary tangles are more specific to AD than neuritic plaques.
(B) They contain reactive astrocytes and microglia.
(C) Their main location is the leptomeningeal and superficial cortical vessels.
(D) Neurofibrillary tangles begin in the transentorhinal cortex and progress to the limbic cortex to reach the neocortical areas.
(E) They are made up of dense granules that react with antineurofilament antibodies.

**46.** Which of the following is true of neurotransmitter disturbance in AD?

(A) There is a dramatic increase in the level of choline acetyltransferase activity in the nucleus basalis of Meynert.
(B) Acetylcholinesterase activity is reduced.
(C) The number of M1 muscarinic receptors is decreased.
(D) M2 muscarinic and nicotinic receptors are preserved.
(E) The level of GABA activity is increased and correlates with the severity of the disease.

**47.** Early onset of familial AD has been associated with

(A) chromosome 21
(B) chromosome 4
(C) chromosome 6
(D) chromosome 12
(E) chromosome 17

**48.** Early HIV dementia is associated with

(A) impaired retrieval
(B) impaired calculation
(C) impaired attention
(D) impaired language
(E) impaired recognition memory

**49.** The most characteristic neuropathological feature of HIV dementia is

(A) neurofibrillary tangles
(B) periventricular demyelination
(C) caudate atrophy
(D) multinucleated giant cells
(E) neuritic plaques

**50.** Which of the following is a feature of progressive nonfluent aphasia that differentiates it from dementia of frontal type?

(A) Phonological paraphasic errors are an early feature.
(B) Apathy, lack of motivation, and mental flexibility are extremely common.
(C) There is a isproportion between poor executive function and preservation of memory and language functions.
(D) Atrophy of the left polar temporal lobe is commonly seen.
(E) Atrophy of the orbitomedial cortex is universal.

**51.** Which of the following cognitive functions is the *least* affected in case of DLB?

(A) Memory
(B) Visuospatial function
(C) Executive function
(D) Attention
(E) Construction ability

**52.** The *least* supportive of the diagnosis of DLB is

(A) progressive cognitive decline
(B) spontaneous parkinsonism
(C) neuroleptic hypersensitivity
(D) auditory hallucinations
(E) multiple falls

**53.** Alpha-synuclein aggregates are found in

(A) Pick disease
(B) multiple-infarct dementia
(C) Huntington disease
(D) spinocerebellar atrophy
(E) multiple system atrophy

**54.** In brain injury, irritability and disinhibition are seen in which of the following areas of the frontal lobe?

(A) Dorsolateral frontal lobe
(B) Frontal eye field
(C) Orbitofrontal area
(D) Medial frontal area
(E) Supplementary motor area

**55.** Which of the following is an implicit form of memory?

(A) Episodic memory
(B) Semantic memory
(C) Memory that needs a deliberate conscious effort
(D) Priming
(E) Short-term memory

**56.** Associative visual agnosia is caused by a lesion in the

(A) posterior parietal cortex
(B) occipital cortex
(C) inferotemporal cortex
(D) association area of the frontal cortex
(E) thalamus

**57.** A perceptive visual agnosia is caused by a lesion in the

(A) posterior parietal cortex
(B) occipital cortex
(C) inferotemporal cortex
(D) association area of the frontal cortex
(E) thalamus

**58.** Prosopagnosia is caused by a lesion in the

(A) posterior parietal cortex
(B) occipital cortex
(C) inferotemporal cortex
(D) association area of the frontal cortex
(E) thalamus

**59.** Source amnesia is caused by a lesion in the

(A) posterior parietal cortex
(B) occipital cortex
(C) inferotemporal cortex
(D) association area of the frontal cortex
(E) thalamus

**60.** The process that makes information more stable for long-term storage is called

(A) encoding
(B) consolidation
(C) storage
(D) retrieval
(E) priming

**61.** Which of the following is true of the hippocampal pathways involved in the storage of explicit memory?

(A) There are projections from the entorhinal cortex to the pyramidal cells of CA3.
(B) Mossy fibers project to pyramidal cells of CA3.
(C) Pyramidal cells of CA1 project to CA3.
(D) Entorhinal cortex cells project to CA1 cells.
(E) Mossy fibers project to the entorhinal cortex cells.

**62.** Which of the following is true of long-term potentiation in the mossy fiber pathway?

(A) GABA is the neurotransmitter used by synaptic terminals of mossy fibers.
(B) The blockade of NMDA receptors affects long-term potentiation in mossy fibers.
(C) Long-term potentiation in mossy fibers is dependent on presynaptic calcium.
(D) Cooperativity is a typical feature of long-term potentiation in mossy fibers.
(E) Long-term potentiation in mossy fibers requires the concomitant activation of pre- and postsynaptic cells.

**63.** Conduction aphasia may result from a lesion located in the

(A) supramarginal gyrus
(B) internal capsule
(C) corpus callosum
(D) angular gyrus
(E) orbitofrontal areas

**64.** A patient demonstrating the use of a toothbrush at the level of the chest has

(A) sensory neglect
(B) ideomotor apraxia
(C) motor neglect
(D) hemispatial neglect
(E) limb kinetic apraxia

# Answers and Explanations

1. **(E)** Elevations of CSF total tau and phosphorylated tau (P-tau) and a reduction of CSF A[beta]-42 levels are characteristic of AD. Recent studies provide evidence that a reduction in the ratio of A[beta]-42 to P-tau may help distinguish patients with early AD from those with frontotemporal dementia and identify those with mild cognitive impairment who later develop AD. *(Hansson, 165–173, 228–234; Schoonenboom, 1580–1584; Schott, 552–558)*

2. **(B)** Frontotemporal dementia (FTD) or frontotemporal lobar degeneration (FTLD) is a group of related neurodegenerative conditions that present as a disturbance of behavior or language. A division of FTLD into three subgroups is now widely accepted, particularly since the publication in 1998 of diagnostic consensus criteria. The first subgroup is the frontal or behavioral variant FTD (fvFTD or bvFTD, or confusingly sometimes just FTD), which accounts for about half of FTLD cases. The others are progressive nonfluent aphasia (PNFA) and SD, which often present as a fluent progressive aphasia but are due to a deficit of conceptual knowledge rather than of language. The motor syndromes of corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and motor neuron disease (MND) may also be associated with FTLD features and pathology; some authorities see these as part of the same spectrum. FTLD has a strong genetic component but only a small proportion of cases show simple Mendelian inheritance. Goldman and colleagues have examined this issue in detail by selecting FTLD pedigrees from their genetic counseling service and stratifying them according to the strength of association of the FTLD syndromes within each pedigree. They found that FTD-MND was the most heritable of the syndromes, although even here only 37% of cases occurred in pedigrees with an autosomal dominant pattern of inheritance while 41% had no family history. Most of the responsible genes in the pedigrees with an apparent single-gene defect could not be identified on screening for recognized mutations, implying that many loci remain to be described. *(Goldman, 1817–1819; Knibb, 565–571; Neary, 1546–1554)*

3. **(C)** Frontotemporal lobar degeneration (FTLD) has been divided into three clinical syndromes: frontal variant of frontotemporal dementia (FTD), semantic dementia (SD), and nonfluent aphasia (NFA), based primarily on the relative degeneration seen in the frontal and temporal lobes and the right and left hemispheres. Individuals with FTD show primarily right frontal involvement and present with behavioral abnormalities such as disinhibition, apathy, emotional blunting, and lack of insight. Patients with NFA have selective left frontoinsular degeneration and present with agrammatism, hesitant, nonfluent speech output, and speech apraxia. With SD, which is a temporally predominant disorder, two syndromes emerge: SD patients with predominantly left temporal degeneration have profound anomia associated with progressive loss of conceptual knowledge of words, while predominantly right temporal cases are associated with deficits in empathy and knowledge about people's emotions. *(Viskontas 87–108, 528–545)*

4. **(D)** Corticobasal degeneration (CBD) is defined by the presence of asymmetric parkinsonism

with dystonia, rigidity, limb apraxia, and an alien limb; it is a motor disorder defined by involuntary hand or arm movements that occur either in addition to or instead of a planned or willed movement. Pathological examination demonstrates neuronal inclusions with tau present in astrocytes and neurons. CBD brains have ballooned neurons that may be found throughout the neocortex but mostly in the superior frontal and parietal lobes, including primary motor or sensory cortex. Neuronal loss and gliosis is also visible in affected regions, often in the basal ganglia. *(Boeve, 795–800; Dickson, 935–946)*

5. **(C)** Frontotemporal dementia (FTD) is characterized by a multitude of behavioral changes that often herald its onset. These include alterations in social decorum and personal regulation, including disinhibition, apathy, overeating, emotional blunting, personality changes toward coldness and submissiveness, repetitive motor behaviors, and impairment in judgment and insight. With these behavioral changes, deficits in executive control emerge and patients have problems with planning, organizing, shifting patterns, and generating ideas. Approximately 15% of patients develop amyotrophic lateral sclerosis, and extrapyramidal deficits are common. *(Viskontas, 87–108)*

6. **(A)** SD is a temporally predominant syndrome that attacks either the left or the right temporal lobe asymmetrically. In classic SD, patients show problems with word finding, sometimes with nouns more than verbs. Speech remains fluent, but anomia worsens and patients show trouble not only in naming words but even in recognizing them. Compulsive interest in visually appealing objects is common, sometimes leading to compulsive playing of card games such as solitaire. As the disease spreads to the right side patients, begin to have problems recognizing emotions in others. Eventually, prosopagnosia and multimodality agnosia for objects develop. *(Viskontas, 87–108)*

7. **(D)** Nonfluent aphasia has an insidious onset. It emerges with a decreased output of words while, soon thereafter, shortened phrase lengths and deficits in articulation develop. The use of nouns remains intact, but deficits in the understanding of grammar are common. Many patients exhibit speech apraxia, which is characterized by a deficit in articulatory planning, resulting in an inability to command the speech musculature to produce sounds in a proper sequence. *(Viskontas 87–108)*

8. **(B)** The pathological feature of Pick disease is severe cortical atrophy caused by severe and often complete loss of large pyramidal cells in cortical layer III and the small pyramidal and nonpyramidal cells of layer II. The remaining neurons also show two distinctive histological features: swelling (called a ballooned or Pick cell) and an inclusion within the perikaryon, most often in layer II (Pick body). Pick bodies are usually found in the limbic (greatest concentration is in the amygdala and hippocampus, including the dentate gyrus), paralimbic, and ventral temporal lobe cortex but may also be seen in anterior frontal and dorsal temporal lobes. Pick bodies are composed of randomly arranged filaments of the tau protein, which is an axonal protein involved in microtubule assembly. Only a minority of patients diagnosed with Pick disease will show the classic Pick pattern at autopsy. Furthermore, even among patients with tau inclusions, the majority will not show the classic Pick body, which stains positive with silver (argyrophilic) stains. *(Mann, 605–614; Viskontas, 87–108)*

9. **(A)** The first important genetic mutations in FTLD were seen in tau. This syndrome is called FTD with parkinsonism linked to chromosome 17 (FTLD-17). FTLD-17 turned out to be associated with mutations in the exon or intron regions of the tau gene localized to 17q21-22. Three of the mutations account for more than half of the genetically characterized cases currently reported in the literature. These three mutations are the P301L, associated with the classic FTD phenotype; exon 10 5′ splice-site +16, associated with a syndrome that includes memory or language impairment and parkinsonism; and N279K, with features of parkinsonism and PSP, also called pallidopontonigral degeneration. The tau protein binds to microtubules, thereby facilitating microtubule

assembly. Via this mechanism, the protein maintains the stability of cytoskeletal structural elements. In a healthy brain, tau is soluble and expressed as six major protein isoforms generated by alternative splicing of the gene on chromosome 17q21. Abnormal tau protein may alter its binding affinity. *(Hong, 1914–1917; van Slegtenhorst, 461–471; Viskontas, 87–108; Wilhelmsen, 159–1165)*

**10.** **(B)** On HMPAO-SPECT, patients with SD show severe bilateral but asymmetric hypoperfusion in the anterior temporal lobes. Bilateral atrophy of the anterior temporal lobes is well illustrated on structural MRI scans, which may differentiate SD from AD. In fact, detailed volumetric measurements may show that hippocampal atrophy is more severe in SD than in AD; it is usually asymmetric, accompanied by more severe atrophy of the amygdala as well as the temporal pole and the fusiform and inferolateral temporal gyri. *(Edwards–Lee, 1027–1040; Galton, 216–225; Mummery, 61–73; Viskontas, 87–108)*

**11.** **(D)** The pathogenesis of AD involves a cascade of mechanisms that include β-amyloid deposition and its toxic effect, neuroinflammation, abnormal phosphorylation of tau, free radical toxicity, disturbed calcium homeostasis, synaptic loss, cholinergic dysfunction, neuronal loss, and norepinephrine and serotonin dysfunction. Interestingly, although considerable evidence suggests that β-amyloid and its toxic effects on the brain may play the key role in initiating the pathophysiological cascade of processes that lead to AD, the progression of clinical dementia seems to correlate more closely with the number of neurofibrillary tangles and/or loss of synapses. As the disease progresses, a cascade of pathological processes involving different mechanisms occurs, including free radical formation and inflammation. Neuronal systems as defined by neurotransmitters are differentially affected. The cholinergic system is particularly susceptible to deterioration, and cholinergic deficiency has been correlated with the clinical progression of AD. Similarly, as AD progresses, glutaminergic, noradrenergic, and serotonergic system deficiencies develop; these have been associated with further cognitive deterioration and/or behavioral abnormalities. *(Farlow, 39–68)*

**12.** **(A)** The major risk factor for AD is aging. Although the illness has very rarely been reported to occur in patients in their 20s and 30s, onset of clinical symptoms is uncommon until the 50s, with prevalence rapidly increasing to age 65, when 1% to 2% of the population is affected. By age 75, the prevalence is estimated at 15%; by age 85, it has been estimated to be present in 35% to 50% of the general population, with some studies suggesting that the prevalence continuing to climb, such that the majority of individuals in their 90s show clinical signs of at least mild dementia. The second major risk factor for AD is family history, with approximately 20% of patients with AD having one or more siblings or parents affected and a pattern of autosomal inheritance. In families with AD, several genetic mutations have been identified that seem to be causative for the disease, such as mutations in the amyloid precursor protein gene, mutations in the presenilin-1 (PS-1) gene on chromosome 14 and the presenilin-2 (PS-2) gene on chromosome 1, and the APOE polymorphism [varepsilon]4 gene. Other factors associated with differential risk for AD are gender and education. Women are at modestly greater risk for AD, even with adjustment for their greater survival to older ages. In several studies, a higher educational level has been associated with reduced risk for AD or later onset of dementia. Head trauma has been suggested as a risk factor for AD, but studies have been muddled by wide differences in reported series in the criteria applied to define significant previous history of head trauma. *(Farlow, 39–68)*

**13.** **(B)** Early onset of AD is caused by a mutation in the amyloid precursor protein (APP) gene that codes for the β-amyloid proteins. It is thought that these mutations cause abnormal β-amyloid metabolism, resulting in chronically higher levels of this protein—a process leading to AD. Onset of clinical symptoms typically occurs in the late 30s to 60 years of age. The other mutations causing early-onset disease have been localized to the presenilin-1 (PS-1) gene on chromosome 14 and the presenilin-2 (PS-2) gene on chromosome 1. The presenilins have been found to operate in a complex that acts functionally as γ-secretase, which is critically

involved in slicing APP to produce β-amyloid. *(Farlow, 39–68)*

**14. (D)** Changes in cognition, behavior, and global functioning may occur with normal aging and should be differentiated from changes related to AD. In normal aging, there is a retrieval-deficit type of memory impairment (which responds well to clues and multiple-choice questions), retained insight, preservation of activities of daily living, minor delays in word finding, and preservation of visuospatial function and social engagement.

In AD, there is an amnestic-type of memory impairment that does not respond to clues, loss of insight, impaired activities of daily living, apathy, anomia, and impaired visuospatial function and social engagement. *(Farlow, 39–68)*

**15. (D)** Current therapies for AD are primarily symptomatic; they are focused on treating either cognitive or behavioral symptoms. No therapy has been proven to delay biological progression of the disease. Cholinesterase inhibitors were developed as a treatment after it was recognized that cholinergic deficiency worsens in parallel with deterioration of memory and other cognitive functioning. Donepezil is an inhibitor that is more selective for acetylcholinesterase; rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase; and galantamine, in addition to inhibiting cholinesterase, apparently modulates stimulation at nicotinic receptors. Memantine belongs to a second class of drugs that work by antagonizing glutamate at the NMDA receptor, potentially improving signal transmission and preventing excess calcium from rushing into neurons with glutamate stimulation, thus providing neuroprotection. In patients with moderate to severe disease, memantine mildly improves cognitive deficits and also activities of daily living and behavior. In a large double-blind, placebo-controlled trial, vitamin E was originally found to delay functional deterioration, nursing home placement, and death in patients with moderate to severe AD by approximately 25%. However, no cognitive benefits were seen in the group taking vitamin E. Also, the vitamin E group in the Alzheimer's Disease Cooperative Study Group–MCI study showed no benefit versus placebo. *(Farlow, 39–68)*

**16. (A)** Mild cognitive impairment (MCI) involves an abnormal process that probably represents the prodromal stages of a dementing condition; as such it is fundamentally different from the extremes of normal aging. It is characterized by memory impairment for age and education with preserved general cognitive function and intact activities of daily living. The prevalence of MCI is probably in the range of 12% to 15% among individuals 65 years of age and older; the incidence rates are in the range of 1% per year, similar to the figures for AD.

The original criteria developed for MCI were centered on memory impairment and designed to characterize the early stages of an AD-like process. However, as the field has expanded, it has become apparent that not all patients with MCI evolve to AD. Therefore, the criteria have been expanded to include many types of intermediate cognitive impairments that may be precursors to a variety of dementing disorders. Once the determination of MCI has been made, the patient may be classified in the amnestic MCI subtype if memory impairment is part of the clinical picture or in the non-amnestic MCI group if the patient does not have significant memory dysfunction but has deficits in other cognitive domains such as language, executive function, or visuospatial skills.

If patients meet the criteria for amnestic MCI, the progression rate is likely to be in the range of 10% to 15% per year. However, in community studies, where a more heterogeneous patient population exists, the rates may be lower, perhaps in the range of 8% to 10% per year. *(Petersen, 15–38)*

**17. (B)** An individual with mild cognitive impairment is more likely to progress to dementia or AD if he

–is an APOE4 carrier.
–has atrophic hippocampi on MRI.
–has an elevated tau level in the CSF.
–has a reduced Aβ level in the CSF.
–has hypometabolism of the temporoparietal lobe on FDG-PET studies.

–has a positive amyloid imaging on PET scan.
–has clinical manifestation of severe MCI.

*(Petersen, 15–38)*

**18.** **(C)** The patient described in this vignette developed a fluctuating decline in cognitive function with visual hallucinations shortly after being diagnosed with PD. These findings are suggestive of DLB. Cognitive symptoms in DLB usually have a gradual onset and progression. A prominent feature is fluctuation of cognitive function, which may be difficult to identify.

Cognitive symptoms in DLB include forgetfulness; impaired judgment, organization, and planning; getting lost; and trouble with spatial perception. Parkinsonism varies in DLB and may be more subtle than that found in idiopathic PD. Many studies have noted a preponderance of axial signs, including gait difficulty and postural instability, with less common rest tremor, which resembles the postural instability gait disorder subtype of PD that is more likely to point to the development of cognitive impairment. Patients with DLB are predisposed to falling for a number of reasons, including parkinsonism, impaired postural (righting) reflexes, and autonomic impairment as well as general problems such as those associated with aging, deconditioning due to lack of activity, and dementia. Recurrent complex visual hallucinations are among the most helpful features in DLB. Patients typically report seeing people, animals, or insects and can sometimes describe them in great detail. DLB patients with visual hallucinations have more severe visuospatial dysfunction than those without. Other clinical manifestation of DLB include delusions, depression, apathy, rapid eye movement (REM) behavior disorder, autonomic dysfunction, agitation, and anxiety. *(Galasko, 69–86)*

**19.** **(E)** Alpha-synuclein is a protein of unknown function primarily found in neural tissue, where it is seen mainly in presynaptic terminals. Expressed mainly in the neocortex, hippocampus, substantia nigra, thalamus, and cerebellum, it is predominantly a neuronal protein but can also be found in glial cells. Normally, an unstructured soluble protein, α-synuclein can aggregate to form insoluble fibrils in pathological conditions characterized by Lewy bodies, such as PD, DLB, and multiple system atrophy. Alpha-synuclein is the primary structural component of Lewy body fibrils. *(Jellinger, 1219–1235; Saito, 742–749)*

**20.** **(B)** Autonomic impairment is well documented in DLB and also in other synucleinopathies such as PD and multiple system atrophy. The most serious symptoms include orthostatic hypotension and syncope, but excess salivation, altered sweating, and seborrhea may also occur. Pathology in several pathways—such as carotid sinus sensitivity, cardiac autonomic denervation, and central autonomic pathway dysfunction—may predispose patients with DLB to syncope. *(Galasko, 69–86)*

**21.** **(C)** Memory loss sufficient to interfere with activities of daily living may have a stepwise course of deterioration associated with a patchy distribution of deficits, preservation of consciousness, and focal neurological signs and symptoms suggestive of vascular dementia. *(Chui, 109–143)*

**22.** **(D)** Binswanger syndrome comprises the combination of severe, confluent deep white matter changes together with a slowly progressive decline in cognition and gait. The white matter changes are postulated to result from chronic hypoperfusion, incomplete infarction, and demyelination in periventricular and deep white border zones. Clinically, Binswanger syndrome is characterized by a slowly progressive decline in cognition, gait apraxia, and early urinary incontinence. Although this symptom triad may be confused with normal-pressure hydrocephalus, Binswanger syndrome can usually be distinguished by the accompanying diffuse cerebral atrophy and confluent deep white matter changes. *(Chui, 109–143)*

**23.** **(A)** Factors favoring clinical improvement after the shunting of normal-pressure hydrocephalus include secondary normal-pressure hydrocephalus, gait disturbance preceding cognitive impairment, mild impairment in cognition,

short duration of cognitive impairment, and clinical improvement following lumbar puncture. Factors associated with lack of clinical improvement after shunting include diffuse cerebral atrophy and extensive white matter disease on MRI, moderate or severe cognitive impairment, history of ethanol abuse, presence of aphasia, and history of cognitive impairment preceding gait disturbance. Long duration of gait abnormalities is of unproved significance. *(Chui, 109–143)*

**24.** **(C)** Proton magnetic resonance spectroscopy ($^1$H-MRS) is a noninvasive technique that allows the assessment of specific brain metabolites. The protein-containing metabolites most commonly measured include N-acetylaspartate (NAA), which provides a marker of neuronal density; myoinositol (MI), which provides a marker of glial cell activity; and choline (Cho), which is thought to reflect the level of membrane turnover. Although absolute levels of metabolite signal can be quantified, results vary greatly across subjects and study centers; therefore a reference signal is usually measured. This can be either the signal of water or, more commonly, the level of the metabolite creatine plus phosphocreatine (Cr), which is thought to be unaffected in patients with dementia. It has been well established that patients with AD show a decrease in the level of NAA in a number of brain regions, including the posterior cingulate and temporal, parietal, and frontal lobes, compared with normal controls. In contrast, the levels of MI/Cr increase in patients with AD. *(Whitwell, 180–203)*

**25.** **(B)** In the Alzheimer's Disease Cooperative Study, patients with mild cognitive impairment (MCI) were randomized to one of three treatment groups: donepezil (10 mg per day), vitamin E (2000 IU per day), or placebo. The study had projected that the progression rate for the subjects with amnestic mild cognitive impairment (aMCI) would be 10% to 15% per year and the study was powered to reduce the rate of progression by 33%. The results indicated that neither of the two active treatment arms was able to reduce the risk of progressing to AD over the entire 36 months. However, donepezil reduced the risk of progression to AD for the first 12 months of the study in all subjects and up to 24 months in the APOE4 carrier subgroup. *(Petersen, 15–38; Petersen et al., 2379–2388)*

**26.** **(C)** Neuropsychiatric symptoms are common in mild cognitive impairment (MCI). The symptoms with highest prevalence were found to be depression, apathy, irritability, anxiety, and agitation. Psychotic symptoms (delusions and hallucinations), euphoria, and disinhibition were relatively rare. The presence and severity of neuropsychiatric symptoms in MCI correlate with the degree of cognitive and functional impairment. *(Apostolova, 165–179)*

**27.** **(B)** Apathy is the most pervasive neuropsychiatric symptom in AD, affecting 42% of patients with mild, 80% of those with moderate, and 92% of those with advanced AD. It is thought to reflect frontosubcortical dysfunction and disconnection of the anterior cingulate cortex from other cortical and subcortical areas. It presents with loss of interest in previously enjoyed activities, including hobbies, social outings, or spending time with family; aloofness, diminished spontaneity and emotional behavior; and reduced motivation. Anxiety, another early feature of AD, is frequently felt as apprehension and inner feeling of nervousness with or without associated autonomic manifestations such as tachycardia, perspiration, xerostomia, and angina-like chest tightness. The prevalence of anxiety among cognitively normal elderly persons is around 6%. Agitation and irritability frequently co-occur. Depression is very common in AD, occurring in 10% of mild, 40% to 60% of moderate, and 60% or more of patients with severe AD. The symptoms are rarely severe enough to merit diagnosis of major depressive disorder; rather, they represent the less severe dysphoria or minor depression.

Psychosis in AD presents with hallucinations, delusions, or delusional misidentifications. Psychotic symptoms may be medication- or delirium-induced or, in the case of visual hallucinations, triggered by poor visual acuity. Psychotic symptoms occur more frequently in the moderate and advanced stages of AD. As many as 10% to 20% of patients with AD experience hallucinations, which are most frequently visual. *(Mega, 130–135; Apostolova, 165–179)*

**28.** **(B)** DLB is the second most common neurodegenerative dementia of older adults. It is a disorder in which a detailed neuropsychiatric evaluation is of utmost importance, as visual hallucinations are a core diagnostic criterion and delusions and prominent early depression are supportive features. Up to 98% of patients with DLB experience some neuropsychiatric symptoms in the course of their illness. These symptoms, along with cognitive fluctuations and extrapyramidal symptoms, differentiate DLB from other common types of dementia, such as AD and vascular dementia (VaD). Visual hallucinations in DLB are brightly colored three-dimensional representations of people and animals. Other common themes are insects, fire, children, objects, and birds. These images are frequently animated and may also speak or make noise (i.e., they co-occur with auditory hallucinations). Visual hallucinations are sometimes more pronounced in the evening, when the lack of strong sensory stimulation and solitude promote their appearance. *(Apostolova, 165–179)*

**29.** **(E)** Frontotemporal dementia is an insidious, relentless disorder manifesting with early prominent behavioral disturbances and personality changes. Impulsivity, tactless conduct, antisocial trends, disinhibition, lack of concern with social norms, loss of interpersonal boundaries, apathy, self-centeredness, and lack of empathy are hallmark features of this disorder. Obsessive–compulsive and stereotyped behaviors also are common. *(Apostolova, 165–179)*

**30.** **(C)** Several studies of families with amyotrophic lateral sclerosis associated with frontotemporal dementia (in one study, SOD1 mutations had been excluded) identified a subset of cases linked to chromosome 9q21-22. *(Sikkink, 693–698)*

**31.** **(A)** Progranulin is a 68.5-kDa (90-kDa when it is heavily glycosylated on sodium dodecyl sulfate Western blot), 589–amino acid pluripotent secreted glycoprotein composed of 12 exons covering 3.7 kb. It is made up of seven tandem repeats of the 12-cysteine granulin domain. Elastase digests progranulin within intergranulin linkers to form eight individual granulin peptides—a process regulated by the secretory leukocyte protease inhibitor, which complexes progranulin, preventing elastase-mediated digestion into fragments. Progranulin is involved in a range of cellular processes, including epithelial cell growth regulation, tumor growth and invasion in vivo, host defense and wound repair, development, inflammation, and signal transduction involving the extracellular regulated kinase signaling pathways. In human brain, progranulin mRNA is expressed at low levels, although in situ hybridization has demonstrated expression in specific neuronal cells, including Purkinje cells, pyramidal cells of the hippocampus, and some cerebral cortical neurons. Baker and colleagues analyzed more than 80 candidate genes in 43 kindreds with frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) within a 6.19-Mb region on 17q21 and identified seven mutations in the gene encoding progranulin. Subsequently, several mutations in the progranulin gene have been identified and associated with FTDL-U. *(Baker, 442:916–919; Bhandari, 1715–1719; Cruts, 920–924; Gass, 2988–3001; Le Ber, 846–855)*

**32.** **(C)** In AD, many neurons exhibit fibrillary accumulations in the cytoplasm, including neurofibrillary tangles (NFTs—neurofibrillary pathology in cell bodies and proximal dendrites), neuropil threads (filamentous accumulations in dendrites), dystrophic neurites (filament-containing neuronal processes, particularly distal axons/terminals), and senile plaques of which the β-amyloid peptide is the major constituent. Ultrastructurally, fibrillary inclusions represent intracellular accumulations of straight filaments and paired helical filaments; both are composed principally of hyperphosphorylated isoforms of tau, a low-molecular-weight, microtubule-associated protein. Because hyperphosphorylated tau species bind poorly to microtubules and alter microtubule stability, this biochemical modification could affect other cytoskeletal constituents, intracellular transport, cellular geometry, and/or neuronal viability. *(Price, 461–493)*

**33. (D)** The inheritance of one of the following genes may predispose the carrier to an increased risk of AD:

- Polymorphic variant of the apoE gene on chromosome 19
- Presenilin 1 gene located on the long arm of chromosome 14
- Presenilin 2 gene isolated and mapped to chromosome 1
- Amyloid precursor protein gene linked to chromosome 21.

*(Price, 461–493)*

**34. (A)** The disease process in AD selectively damages brain regions and neural circuits critical for cognition and memory, including neurons in the neocortex, hippocampus, amygdala, basal forebrain cholinergic system, and brainstem monoaminergic nuclei. The severity of memory impairments and density of senile plaques correlates with levels of synaptophysin (a presynaptic vesicle protein) in the hippocampus of individuals with AD. Alterations in the basal forebrain cholinergic system are also believed to contribute to memory difficulties and to deficits in arousal/attention. *(Price, 461–493)*

**35. (B)** AD is characterized by a progressive deposition of neurofibrillary and Aβ-amyloid tangles in many areas of the brain, particularly the hippocampus and cerebral cortex. Endoproteolytic cleavage of amyloid precursor protein by β and γ secretase generates toxic Aβ peptides. BACE1 and BACE2 are two secretases involved in the generation of amyloid precursor protein. The secretion of Aβ peptide is abolished in cultures of BACE1-deficient embryonic cortical neurons. BACE1 is the principal neuronal protease required to cleave amyloid precursor protein at +1 and +11 sites that generate the N-terminal of Aβ peptides. *(Cai, 233–234)*

**36. (B)** The β-amyloid peptide is the major constituent of senile plaques. It is present in a soluble nontoxic form in all human brains. It undergoes conformational changes and becomes relatively insoluble in AD. Soluble β-amyloid peptide is mainly formed by 40–amino acid sequences and may originate from cells of the central nervous system as well as from the peripheral nervous system. The amyloid precursor protein is cleaved in its N and C terminials by β and γ secretases, respectively. P3 fragment, a major component of diffuse plaques, originates from the cleavage of the amyloid precursor protein by an α secretase. P3 deposits are seen in normal aging as well as in AD patients. P3 deposits in normal aging patients lack abnormal neurites and display a reduced glial reaction compared with P3 deposits in AD. Cyclooxygenase enzymes 1 and 2, biosynthesis inflammatory mediators, are constitutively expressed and mitogen-induced, respectively. Cyclooxygenase-2 level is sensitive to IL-1, IL-2, and TNF proinflammatory interleukins. The expression of cyclooxygenase 2, but not cyclooxygenase 1, increases in cases of AD, especially in neurons that are destined for apoptosis. *(Halliday, 1–8)*

**37. (C)** Deficits in recent memory are typically the first symptom of AD and may be clinically reported when the patient misplaces objects, repeats questions and statements, and forgets names. Both verbal and visuospatial memory changes occur. Impairments in visuospatial memory are often experienced as getting lost. Early in the disease, these deficits in memory are primarily for recent information. On examination, AD patients have marked difficulty remembering word lists, stories, and designs. As the disease progresses, the cognitive impairment becomes more diffuse, with reduced ability to do multiple tasks or carry out complex mental tracking, decreased concentration, difficulty with mental arithmetic, and a decline in abstract reasoning. Remote memory impairments also emerge, with the oldest memories tending to be the most stable. Semantic memory as well as implicit memory become impaired as the disease progresses. *(Kramer, 447–454)*

**38. (D)** Positron emission tomography (PET) examines regional cerebral metabolic rates for oxygen and glucose and has proved to be an effective means of studying brain functioning in dementia patients. PET studies have consistently found that association cortex, primarily

in posterior regions, is most severely affected in AD. Primary sensory and motor cortices, basal ganglia, thalamus, and cerebellum are relatively spared. The parietal lobe has the largest reductions in metabolism. Patients with mild to moderate AD have reductions in rate of metabolism that range from 23% to 39% for parietal association cortex, 15% to 30% for temporal association cortex, and 15% to 21% for frontal association cortex. Metabolic rate shows further reductions as the severity of the dementia worsens. *(Kramer, 447–454)*

**39.** **(A)** Depression is the most common psychiatric symptom associated with AD. It occurs in 15% to 20% of AD patients. As the dementia advances, delusions become more common. More severely demented AD patients may have visual and auditory hallucinations as well as restlessness, irritability, repetitive behavior, disturbed sleep patterns, and verbal aggression. *(Kramer, 447–454)*

**40.** **(B)** Pathological studies have shown that the most frequent cause of posterior cortical atrophy is AD. This syndrome can also be seen in subcortical gliosis and Creutzfeldt–Jakob disease. Careful postmortem study has shown that relative to typical AD cases, patients who initially present with prominent visual symptoms have higher densities of plaques and tangles in primary and visual association areas and relatively fewer lesions in the prefrontal cortex. *(Kramer, 447–454)*

**41.** **(A)** Frontotemporal dementia (FTD) is characterized by the prominence of behavioral abnormalities such as loss of personal awareness, hyperorality, stereotyped and perseverative behavior, and progressive reduction of speech with conservation of spatial orientation. Loss of spatial orientation is more prominent in AD than in frontotemporal dementia, where inappropriate behavior is more prominent. Informed-based questionnaire as well as other behavioral and neuropsychological tests serve to differentiate frontotemporal dementia from AD. Free recall does not differ between AD and frontotemporal dementia patients, but the benefit from semantic cueing and recognition is significantly better in FTD patients, suggesting that FTD patients mainly experience retrieval difficulties provided that encoding is controlled. Verbal and visuospatial short-term memories are both decreased in AD, whereas only verbal memory is decreased in FTD. Language comprehension profiles in FTD are mainly characterized by sentence comprehension difficulties caused by impaired processing of grammatical phrase structure as well as a relatively selective impairment in action naming. FTD patients perform better than AD patients on construction and calculation and have greater impairment in executive than in memory tasks. FTD has been linked to chromosome 17q21-22 in a population-based study. Huntington disease has been linked to chromosome 4. *(Pasquier, 417–427)*

**42.** **(D)** Tau proteins are the basic components of neurofibrillary neuronal inclusions that affect numerous causes of dementia. They stabilize microtubules, which play an important role in intraneuronal transport. They are formed by six isoforms resulting from the translation of exons 2, 3, and 10. Tau proteins may be abnormally phosphorylated and aggregate into neuronal inclusions. These inclusions may be biochemically different from one type of dementia to another. In AD, all six tau isoforms (with and without exon 10) are aggregated. This is not specific to AD; the same pattern of tau aggregation is seen in postencephalitic parkinsonism, Niemann–Pick type C disease, and Down's syndrome. In progressive supranuclear palsy and corticobasal degeneration, there is an aggregation of tau isoforms with exon 10, mainly in the frontal subcortical and cortical areas. They are mainly located in small pyramidal cells and astrocytes of layers II and III of the cerebral cortex. In familial frontotemporal dementia, tau isoforms with exon 10 are aggregated. In Pick disease, there is aggregation of two main tau variants lacking exon 10: tau 55 and tau 64. They are found in the frontotemporal areas and involve the small pyramidal cells of neocortical layers II and III as well as granule cells of the dentate gyrus. *(Pasquier, 417–427)*

**43.** **(C)** Progressive supranuclear palsy is characterized by early postural instability, supranuclear

vertical gaze palsy, parkinsonism insensitive to levodopa therapy, pseudobulbar palsy, and subcortical dementia. Histological features include degeneration in different areas of the basal ganglia and brainstem. The presence of early instability and multiple falls during the first year of symptom onset in a patient with parkinsonism should point to the diagnosis of progressive supranuclear palsy, although early instability may be seen in cases of multiple system atrophy and corticobasal degeneration. Marked slowing of vertical saccades is followed by the development of vertical supranuclear gaze palsy. This distinguishes progressive supranuclear palsy from corticobasal degeneration and multisystem atrophy. In corticobasal degeneration, the saccades may have increased latency but normal speed and are equally affected in the vertical and horizontal planes. In multiple system atrophy, the saccades have normal speed and latency. Frontal lobe signs including apathy, impaired abstract thought, decreased verbal fluency, and imitation behavior are seen early in the course of progressive supranuclear palsy, as well as prominent swallowing and speech difficulties. Red flags against the diagnosis of supranuclear palsy include the presence of aphasia, onset earlier than age 40, duration of the disease of more than 20 years, presence of cortical dementia or cortical sensory or visual deficit, hallucinations not due to medications, and maintained response to levodopa replacement. *(Litvan, 41–48)*

**44. (B)** Progressive supranuclear palsy is characterized on neuropathological examination by neuronal loss, gliosis, and the presence of neurofibrillary tangles and/or neuropil threads in specific areas of the basal ganglia and brainstem. The National Institute of Neurological Disorders and Stroke (NINDS) neuropathological criteria for typical progressive supranuclear palsy are:

- High density of neurofibrillary tangles and neuropil threads in at least three of the following areas: pallidum, subthalamic nucleus, substantia nigra, or pons.
- Low to high density of neurofibrillary tangles or neuropil threads in at least three of the following areas: striatum, oculomotor complex, medulla, or dentate nucleus.
- Clinical history compatible with progressive supranuclear palsy.

*(Litvan, 41–48)*

**45. (D)** The pathological characteristics of AD include neurofibrillary tangles, neuritic plaques, loss of synapses and neurons, granulovacuolar degeneration, amyloid angiopathy, and nonβ-amyloid (Aβ), plaque-like deposits (AMY) plaques. Neurofibrillary tangles are formed by paired helical filaments that occupy the cell body and may extend to the dendrites but not to the axon. These filaments are arranged to form a tubule that contains abnormally phosphorylated tau protein. They are preferentially located in large pyramidal neurons, particularly those with long ipsilateral cortical–cortical connections. Neurofibrillary tangles are produced in the transentorhinal cortex in the beginning of the disease and progress to limbic cortical regions to reach the neocortical areas. The pattern of progression of neurofibrillary tangles correlates with the early memory deficit seen in AD. Neurofibrillary tangles are not specific to AD; they are seen in progressive supranuclear palsy, postencephalitic PD, and subacute sclerosing panencephalitis. Neuritic plaques are more specific to AD than neurofibrillary tangles and are formed by a central immunoreactive amyloid core surrounded by dystrophic neurons, which contain paired helical filaments, normal glial processes, abnormal organelles, reactive astrocytes, and microglia. Amyloid angiopathy involves leptomeningeal and superficial cortical vessels in Alzheimer patients. Granulovacuolar degeneration involves the pyramidal cell layer of the hippocampus with the presence in the cytoplasm of the pyramidal cell of vacuoles. *(Cummings, S2–S17)*

**46. (B)** The nucleus basalis of Meynert is affected early in the course of AD. It is a major source of choline acetyltransferase, which is responsible for the synthesis of acetylcholine. There is a marked and consistent decrease of choline acetyltransferase and acetylcholine synthesis as well as a reduction of the activity of acetylcholinesterase, the enzyme responsible of the degradation of acetylcholine. M1 muscarinic receptors located in the hippocampus and in the upper and

lower levels of the cerebral cortex are relatively preserved in AD as compared with M2 muscarinic receptors located in the brainstem and nucleus basalis, which are markedly reduced. Nicotinic receptors, serotonin, norepinephrine, GABA, and somatostatin are also reduced. *(Cummings, S2–S17)*

**47.** **(A)** Early onset of familial AD has been linked to mutations in chromosomes 21, 14, and 1. It is inherited as an autosomal dominant disease. Mutations in chromosome 21 involve the amyloid precursor gene affecting the processing of the amyloid precursor protein. Mutations in chromosome 14 involve the presenilin gene and cause an increase of the production of the amyloid-β peptide. Mutations in chromosome 1 involve presenilin 2 gene and also cause an increase of the production of the amyloid-β peptide. Mutations on chromosomes 17, 12, and 6 are considered genetic risk factors in AD. *(Cummings, S2–S17)*

**48.** **(A)** Early symptoms of HIV dementia are subtle and may be confused with psychiatric complaints, the effect of substance abuse, or delirium. They are characterized by the prominence of subcortical involvement. These symptoms may include:

- Memory impairment, both verbal and nonverbal.
- Impaired manipulation of acquired knowledge.
- Impaired retrieval, and general slowing of psychomotor speed and thought processes.

Attention, language, and recognition memory are relatively preserved. *(McArthur, 129–150)*

**49.** **(D)** Multinucleated giant cells are characteristically seen in HIV dementia. Their presence correlates with the degree of dementia and the detection of HIV DNA. *(McArthur, 129–150)*

**50.** **(A)** Progressive nonfluent aphasia, in contrast to the fluent language disorder of SD, is characterized by a nonfluent, Broca-like aphasia, ultimately leading to a state of mutism. Pathological studies show diffuse left perisylvian atrophy involving both the frontal and temporal lobes. The nonfluent output relates to breakdown in the phonological and grammatical aspects of language. These deficits affect production and comprehension. An early feature is phonological, as opposed to semantic, paraphasic errors. Buccofacial apraxia is also a common feature: patients are unable to perform tasks such as licking their lips or blowing out matches on command. In spite of profound language dysfunction, these patients often continue to maintain an independent lifestyle without significant behavioral or social disturbance.

Dementia of the frontal type presents with neuropsychiatric symptoms rather than neuropsychological deficits. Patients become distractible and impulsive yet lack mental flexibility. Apathy and lack of motivation are extremely common; social skills degenerate, with tactlessness, lack of emotional warmth, and disinhibited behavior. The key feature of dementia of the frontal type on neuropsychological examination is a disproportionately poor performance on tests sensitive for frontal lobe function (executive function) in the absence of a significant memory, language, or visuospatial disorder. The orbitomedial frontal lobes are affected earlier than dorsolateral lobes in dementia of the frontal type. Since classic frontal lobe tasks reflect dorsolateral function rather than orbitomedial pathology, patients with gross behavioral changes may perform normally on these frontal lobe tests for a number of years.

Neuroimaging studies may show left perisylvian atrophy in progressive nonfluent aphasia and orbitomedial frontal lobe atrophy in dementia of the frontal type. *(Nestor, 439–446)*

**51.** **(A)** DLB is characterized by a progressive cognitive decline sufficient to interfere with social or occupational function. Fluctuation of cognitive function as well as well-formed and complex visual hallucinations are common features of the disease. Spontaneous parkinsonism is the final core feature of DLB that leads to the diagnosis being considered. In early stages of the disease, there is a distinctive profile that distinguishes DLB from other types of dementia, as the trend over time is for the development of global impairment. The typical early

profile is one of disproportionate involvement of attention, executive, and visuospatial domains. Visual deficits affect perceptual, spatial, and constructive abilities; when matched for degree of dementia, memory function is superior to that seen in AD. *(Nestor, 439–446)*

**52. (D)** The consensus criteria for antemortem diagnosis of DLB are divided into mandatory criteria, core features, supportive criteria, and criteria against the diagnosis. The only mandatory criterion for the diagnosis of DLB is progressive cognitive decline that interferes with social and occupational function. The core features for the diagnosis of DLB include fluctuating state with significant variations in attention and alertness, spontaneous motor features of parkinsonism, and recurrence of hallucinations, particularly of the visual type. Supportive criteria for the diagnosis include repeated falls, syncope, transient loss of consciousness, neuroleptic hypersensitivity, systematized delusions, and nonvisual hallucinations. Criteria against the diagnosis of DLB include the presence of evidence of other physical or neurological illness sufficient to explain the clinical features. *(Nestor, 439–446)*

**53. (E)** Alpha-synuclein is a 140 amino acid protein of unknown function that is abundantly expressed in the brain, where it is located in presynaptic nerve terminals with little staining of nerve cell bodies and dendrites.

An α-synuclein 35-residue has been found in the nonamyloid component of AD plaques. This 35-residue segment is referred to as a nonamyloid component (NAC) and α-synuclein as a NAC precursor protein. NAC was the second component, after the Alzheimer-β protein, to be found in extracellular AD plaques. Alpha-synuclein aggregates are found not only in the Lewy bodies of PD but also in the cortical Lewy bodies of LBD and in glial cytoplasmic inclusions throughout the brain in multiple system atrophy. Although α-synuclein deposits occur in several neurodegenerative diseases, this is not a ubiquitous phenomenon after neuronal damage; brains of patients with multi-infarct dementia have no synuclein inclusions and the tau-positive neuronal inclusion bodies in Pick disease do not have synuclein associated with them. *(Schulz, 433–439)*

**54. (C)** Frontal lobe function is characterized by the presence of five parallel but independent circuits defined by their distinct major reciprocal subcortical connections. Each circuit involves a frontal lobe area, specific projections to striatal regions, continuation to globus pallidus, return to the thalamus, and then back to the frontal region of origin. There are two motor circuits, one involving the supplementary motor area and the second the frontal eye fields. Three circuits determine cognitive and affective behaviors initiating in three separate regions of the prefrontal cortex: dorsolateral, lateral orbital, and medial frontal/anterior cingulate. Distinct cognitive and behavioral profiles are associated with lesions in the last three separate circuits. Dorsolateral prefrontal lesions produce deficits in verbal and nonverbal fluency, decreased problem solving and set shifting, and reduced learning and retrieval. Orbitofrontal lesions cause disinhibition and irritability. Medial frontal/anterior cingulate lesions result in apathy and decreased initiative. Damage at any point in each circuit will produce similar deficits. Lesions in the subcortical segments of these anatomical systems often cause mixed syndromes because of the proximity of the subcortical structures involved in the different circuits. The rationale for splitting the frontal lobes into these separate operating systems is supported by parallel anatomical observations. The cortical portions of these systems have different connections with posterior cortical areas. *(Alexander, 427–437)*

**55. (D)** Long-term memory is divided into two types: implicit or nondeclarative memory and explicit or declarative memory. Implicit memory is unconscious memory of how to do something, as in training reflexive motor or perceptual skills, whereas explicit memory involves factual knowledge of people, places, things, and what these facts mean. Explicit memory involves a deliberate, conscious effort to associate

multiple pieces of information in a highly flexible way. In contrast, implicit memory is more rigid, tightly connected to the original stimulus conditions under which learning occurred. Explicit memory is further divided into episodic memory, a memory of events and personal experience, and semantic memory, a memory for facts.

Priming is a form of nondeclarative memory in which the recall of words or objects is improved by prior exposure to words or objects. Memory of procedural skills and habits as well as habituation and sensitization are part of the implicit memory and are linked, respectively, to the striatum and reflex pathways. Classical and operant conditioning are parts of associative learning, which is a part of implicit memory. The emotional response of the classical and operant conditioning involves the amygdala, whereas skeletal musculature response involves the cerebellum. The amygdala is involved in affective aspects of memory which is related to implicit as much as explicit memory. Explicit memory is acquired through a processing in one or more of the three polymodal association cortices (the prefrontal, limbic, and parietooccipitotemporal cortices) that synthesizes visual, auditory, and somatic information. The association cortices then convey the information in series to the parahippocampal and perirhinal cortices, the entorhinal cortex, the dentate gyrus, the hippocampus, the subiculum, and finally back to the entorhinal cortex. The information is then sent back from the entorhinal cortex to the parahippocampal and perirhinal cortex and finally back to the polymodal association areas of the neocortex. *(Kandell, 1128–1132)*

**56.** **(A)** Associative visual agnosia results from damage to the posterior parietal cortex. The patient cannot name objects but can identify them by selecting the correct drawing and can faithfully reproduce detailed drawings of the object. *(Kandell, 1236–1237)*

**57.** **(B)** A perceptive visual agnosia is caused by a lesion in the occipital lobe and surrounding region. The patient is unable to draw objects but can identify them if appropriate perceptual cues are made available. *(Kandell, 1236–1237)*

**58.** **(C)** Prosopagnosia is defined by the inability to recognize familiar faces or learn new faces and is caused by a lesion in the inferotemporal cortex. *(Kandell, 1236–1237)*

**59.** **(D)** Source amnesia is caused by damage to the association areas of the frontal lobes. These areas of the cortex are responsible for the long-term storage of episodic knowledge. A patient with source amnesia has a tendency to forget how the information was acquired. *(Kandell, 1236–1237)*

**60.** **(B)** Explicit memory is processed by at least four distinct types of processing: encoding, consolidation, storage, and retrieval. *Encoding* refers to the processes by which newly learned information is processed when first encountered. The quality of the encoding is critical for the integration and storage of newly acquired information. *Consolidation* refers to the processes that alter the newly stored and still labile information to make it more stable for long-term storage. It involves the expression of genes and the synthesis of proteins that give structural changes necessary for stable storage of the information. *Storage* refers to mechanisms and sites by which memory is retained over time. *Retrieval* refers to processes that permit the recall and use of stored information. *(Kandell, 1237)*

**61.** **(B)** Three major hippocampal pathways are involved in the processing of explicit memory: the perforant pathway, which projects from the entorhinal cortex to the granule cells of the dentate gyrus; the mossy fiber pathway, which contains the axons of the granule cells and runs to the pyramidal cells in the CA3 region of the hippocampus; and the Schaffer collateral pathway, which consists of the excitatory collaterals of the pyramidal cells in the CA3 region and ends on the pyramidal cells of the CA1 region. *(Kandell, 1259)*

**62.** **(C)** The mossy fiber pathway consists of the axons of the granule cells of the dentate gyrus. The mossy fiber terminals release glutamate as a neurotransmitter, which binds to both NMDA and non-NMDA receptors. NMDA

receptors have a minor role in synaptic plasticity. The blockage of NMDA receptors as well as the postsynaptic influx of calcium has no effect on long-term potentiation in mossy fiber pathways. However, the presynaptic calcium influx has been found to play a major role in mossy fiber long-term potentiation. Cooperativity (the process of activating several afferent axons together) as well as associativity (the concomitant activation of pre- and postsynaptic cells to adequately depolarize the postsynaptic cell) are distinctive features of long-term potentiation in the Schaffer collateral pathway. *(Kandell, 1260)*

**63.** **(A)** Conduction aphasia is characterized by fluent speech with paraphasic errors, with conserved comprehension and impaired repetition. It can be caused by lesions in a variety of locations including the supramarginal gyrus as well as by interruption of fiber tracts lying deep to the sensory cortex in the parietal lobe. *(Saffran, 409–418)*

**64.** **(B)** Patients with ideomotor apraxia make several types of errors when performing skilled, purposive limb movements. The most common errors in ideomotor apraxia are spatial errors. One type of spatial error involves the failure to position the hand in an appropriate posture (e.g., closed-fist posture for drinking from a cup). A second type of spatial error involves the failure to orient the movement toward an imagined object (e.g., demonstrating the use of a toothbrush at the level of the chest). A third type of spatial error involves the failure to coordinate joint movement (e.g., demonstrating a screwdriver by rotating at the shoulder instead of at the elbow). Another common apraxic error involves using a body part as if it were the imagined tool (e.g., extending the finger to represent the blade of the screwdriver instead of positioning the hand around the handle of the screwdriver). Apraxic patients may also make sequencing errors (e.g., demonstrating the use of a key by rotating the wrist, then extending the arm) and timing errors such as failure to coordinate speed with the spatial aspects of the gesture. *(Alexander, 427–437; Ochipa, 417–478)*

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CHAPTER 7

# Cerebrovascular Diseases
## Questions

**1.** After administering intravenous recombinant tissue-type plasminogen activator (t-PA) without complication, prophylaxis for deep venous thrombosis with subcutaneous unfractionated heparin may be started

(A) immediately
(B) in 24 hours
(C) in 4 days
(D) in 7 days
(E) in 10 days

**2.** Ischemic penumbra tissue has a cerebral blood flow higher than

(A) 3 mL/100 mg per minute
(B) 5 mL/100 mg per minute
(C) 7 mL/100 mg per minute
(D) 10 mL/100 mg per minute
(E) 15 mL/100 mg per minute

**3.** On magnetic resonance imaging (MRI), the area of diffusion/perfusion mismatch in acute stroke corresponds to the

(A) area of the brain with irreversible ischemic damage
(B) area of the brain with reversible ischemic damage
(C) healthy brain tissue
(D) hemorrhagic brain lesion
(E) area of the brain with cerebral blood flow less than 5 mL/100 mg per minute

**4.** The main cause of neural death in the core of an ischemic stroke is

(A) mitochondrial dysfunction
(B) free radical production
(C) apoptosis
(D) metabolic acidosis
(E) necrosis

**5.** A 46-year-old woman with a history of atrial fibrillation developed a sudden onset of right-sided weakness and slurred speech. The patient was seen in the emergency room within 90 minutes of symptom onset and found to be eligible for treatment with t-PA. Prior to the initiation of this treatment, which of the following tests should be ordered?

(A) Urine toxicology screen
(B) Blood alcohol level
(C) Chest x-ray
(D) Arterial blood gas
(E) Blood glucose

**6.** Which of the followings is true of poststroke infection?

(A) It is an uncommon complication in the first 5 days after stroke onset.
(B) Chest infection occurs exclusively in patients with dysphagia.
(C) Age greater than 65 years is an independent predictor of pneumonia.
(D) Cellulitis is the most frequent infectious complication in the first week after stroke.
(E) Prophylactic administration of antibiotics is strongly recommended in brainstem stroke.

**7.** Which of the following presentations exposes a stroke patient to a high risk of dysphagia?

(A) Cortical blindness
(B) Brainstem stroke
(C) Asonognosia
(D) Age greater than 65 years
(E) Preservation of consciousness

**8.** A 55-year-old man developed acute right-sided weakness with aphasia. He was assessed in the emergency room within 2 hours of symptoms onset and found to be eligible for recombinant tissue-type plasminogen activator (rt-PA). However, his blood pressure was 220/110. The most recommended drug to lower his blood pressure before being treated with rt-PA is

(A) Lasix
(B) Enalapril
(C) Losartan
(D) Labetalol
(E) Prazosin

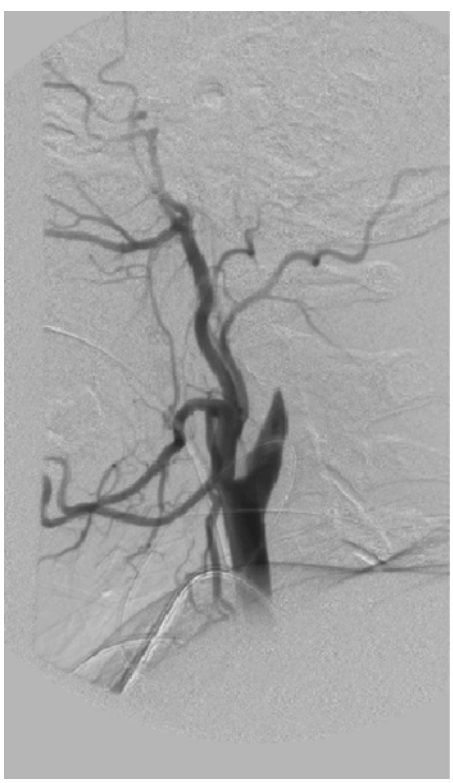

FIG. 7-1

**9.** A few days after developing a left-sided headache, a 42-year-old man suddenly developed ptosis of the left eye, slurred speech, and right-sided weakness. His angiogram (Figure 7-1) is suggestive of

(A) basilar artery stenosis
(B) left vertebral artery dissection
(C) left carotid artery dissection
(D) left middle cerebral artery occlusion
(E) complicated migraine

**10.** A 67-year-old woman with a history of hypertension suddenly developed left-sided weakness. Her angiogram (Figure 7-2) is suggestive of

(A) anterior cerebral artery occlusion
(B) middle cerebral artery occlusion
(C) posterior cerebral artery occlusion
(D) vertebral artery occlusion
(E) basilar artery occlusion

**11.** The angiogram in Figure 7-3 demonstrates

(A) carotid artery stenosis
(B) vertebral artery stenosis

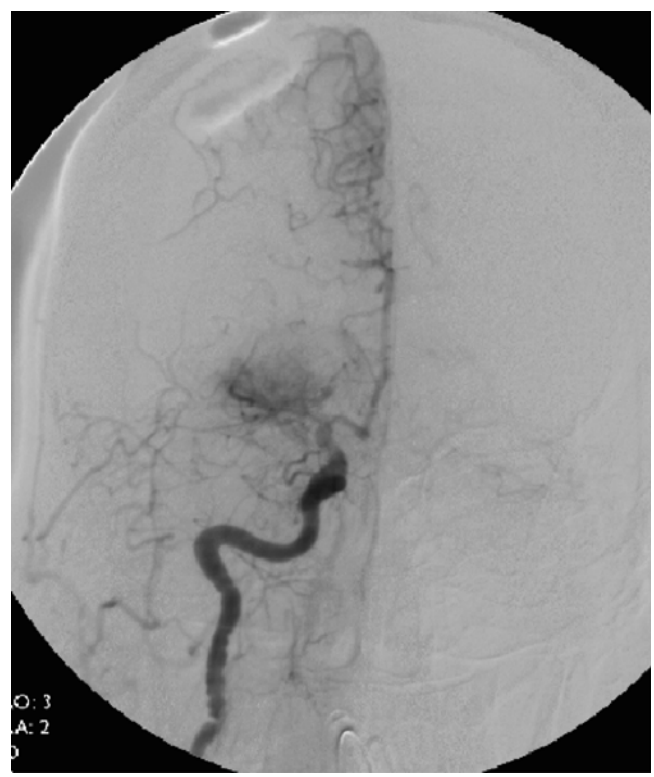

FIG. 7-2

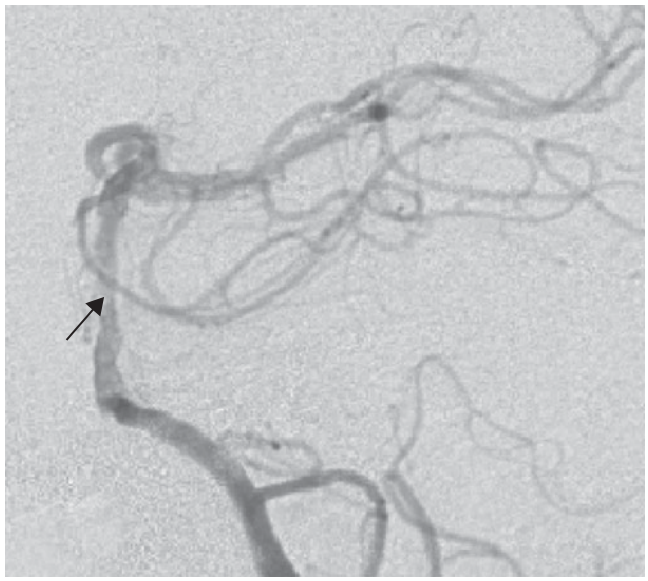

FIG. 7-3

(C) middle cerebral artery stenosis
(D) basilar artery stenosis
(E) anterior cerebral artery stenosis

**12.** The angiogram in Figure 7-4 demonstrates

(A) anterior cerebral artery occlusion
(B) middle cerebral artery occlusion
(C) posterior cerebral artery occlusion
(D) vertebral artery occlusion
(E) basilar artery occlusion

**13.** After 9 hours of sleep, a 56-year-old man awoke with right-sided weakness and dysarthrias. A computed tomography (CT) scan showed early ischemic changes in the left internal capsule. The most appropriate treatment for this patient would be

(A) heparin
(B) aspirin
(C) intravenous rt-PA
(D) intra-arterial rt-PA
(E) no anticoagulation because of the risk of hemorrhagic transformation

**14.** Subhyaloid hemorrhage is seen in association with

(A) subarachnoid hemorrhage
(B) seizure
(C) metabolic encephalopathy
(D) basilar artery occlusion
(E) ischemic encephalopathy

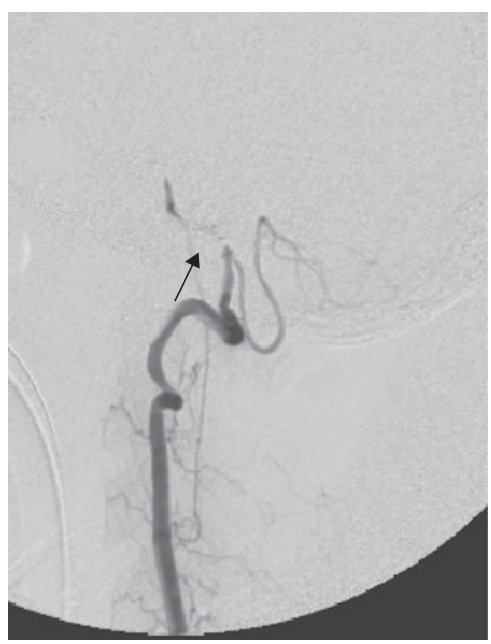

FIG. 7-4

**15.** A 44-year-old woman developed a transitory loss of vision in her right eye. Her fundoscopic examination demonstrated a fibrin platelet embolus in a branch of the retinal artery. The most likely diagnosis is

(A) multiple sclerosis
(B) optic neuritis
(C) complicated migraine
(D) central nervous system vasculitis
(E) amaurosis fugax

**16.** Radiological and postmortem studies indicate that preoperative strokes are predominantly

(A) thrombotic
(B) hemorrhagic
(C) lacunar
(D) due to hypoperfusion
(E) embolic

**17.** Which of the following is true of subarachnoid hemorrhage?

(A) The mean age at presentation of patients with subarachnoid hemorrhage is 35 years.
(B) The risk for a male is 1.5 times that for a female.
(C) Most deaths from subarachnoid hemorrhage occur within the first 24 hours.
(D) Altered level of consciousness on admission points to a poor prognosis.
(E) Diabetes is a major modifiable risk factor for subarachnoid hemorrhage.

**18.** The most frequent location of an intracranial aneurysm is the

(A) posteroinferior cerebellar artery
(B) basilar tip
(C) posterior communicating artery
(D) internal carotid bifurcation
(E) pericallosal artery

**19.** An ischemic central nervous system lesion causing ipsilateral ataxia and weakness of the muscles of mastication with contralateral hemiplegia of face and body as well as loss of all sensory modalities is located in the

(A) medial medulla
(B) lateral medulla
(C) ventral pontine
(D) lower dorsal pontine
(E) upper dorsal pontine

**20.** An ischemic central nervous system lesion causing ipsilateral Horner syndrome and severe tremor with contralateral loss of all sensory modalities is located in the

(A) lower dorsal pontine
(B) upper dorsal pontine
(C) ventral midbrain
(D) dorsal midbrain
(E) dorsolateral midbrain

**21.** An ischemic central nervous system lesion causing ipsilateral oculomotor paresis with ptosis and dilated pupils and contralateral hemiplegia including the lower face is located in the

(A) lower dorsal pontine
(B) upper dorsal pontine
(C) ventral midbrain
(D) dorsal midbrain
(E) dorsolateral midbrain

**22.** Spontaneous dissection of the carotid or vertebral artery in young patients accounts for

(A) 1% of all ischemic strokes
(B) 1.5% of all ischemic strokes
(C) 2% of all ischemic strokes
(D) 3% of all ischemic strokes
(E) 10% of all ischemic strokes

**23.** In cases of carotid dissection, the most frequently affected cranial nerve is the

(A) facial cranial nerve
(B) glossopharyngeal cranial nerve
(C) trigeminal cranial nerve
(D) spinal accessory cranial nerve
(E) hypoglossal cranial nerve

**24.** A 27-year-old man with a history of migraine developed a right-sided headache and right anterolateral cervical pain 4 days after chiropractic manipulation of the neck. One day after becoming symptomatic, he consulted a neurologist because of transient right-eye blindness that resolved within a few hours. Neurological examination demonstrated right miosis, ptosis, and mild right tongue deviation. The most likely diagnosis is

(A) vertebral artery dissection
(B) basilar artery occlusion
(C) complicated migraine
(D) carotid artery dissection
(E) cluster headache

**25.** The chain of events that produces the abnormalities seen on diffusion-weighted MRI in acute stroke includes

(A) an increased apparent diffusion coefficient
(B) glial and neuronal swelling
(C) activation of the sodium potassium pumps
(D) intracellular accumulation of potassium
(E) an increase in extracellular space

**26.** A lacunar stroke located in the subthalamic nucleus causes

(A) hemichorea–hemiballismus
(B) pure motor hemiparesis
(C) dysarthria and clumsy hand syndrome
(D) ataxic hemiparesis
(E) agnosia

**27.** Which of the following is true of the diagnosis of subarachnoid hemorrhage?

(A) Subarachnoid hemorrhage may appear isodense to brain parenchyma if the serum hemoglobin level is below 12 g/dL.
(B) Modern CT scanning has 93% sensitivity for the diagnosis of subarachnoid hemorrhage when done in the first 12 hours.
(C) Standard MRI is more sensitive than CT in detecting subarachnoid hemorrhage.
(D) The presence of xanthochromia in the cerebrospinal fluid of patients with a negative head CT scan is the primary criterion for the diagnosis of subarachnoid hemorrhage.
(E) Less than 10% of patients with subarachnoid hemorrhage have a cardiac arrhythmia.

**28.** Which of the following is true of the study Warfarin-Aspirin Recurrent Stroke Study (WARSS) comparing aspirin to warfarin in preventing the recurrence of ischemic strokes?

(A) It was a randomized double-blind multicenter study comparing aspirin to warfarin in preventing the recurrence of cardioembolic strokes.
(B) The only endpoint of this study was death from an ischemic stroke.
(C) Aspirin showed a higher risk of major bleed than warfarin when used for preventing the recurrence of nonembolic ischemic strokes.
(D) Warfarin was superior to aspirin in preventing the recurrence of nonembolic ischemic strokes.
(E) Warfarin was equivalent to aspirin in preventing the recurrence of nonembolic ischemic strokes.

**29.** Currently, the most consistent and important predictor of stroke is

(A) hypertension
(B) diabetes
(C) high serum cholesterol
(D) smoking
(E) obesity

**30.** Which of the following is true of the use of thrombolytics in the treatment of acute ischemic stroke?

(A) The use of rt-PA showed a significant benefit in the first 24 hours.
(B) For every 100 patients treated with rt-PA, an additional 11 patients have a favorable outcome as compared with 100 patients not treated with rt-PA.
(C) The administration of rt-PA did not show any benefit on stroke due to small vessel disease.
(D) Within the first 36 hours of rt-PA, significant intracerebral bleed was present in 0.6% of cases and was comparable to that in the placebo group.
(E) Administration of rt-PA is contraindicated if the patient is over 75 years of age.

**31.** Which of the following is *not* true of serum homocysteine level and the risk of ischemic stroke?

(A) The relative risk of stroke in patients with an abnormal homocysteine level is 1.8 and depends on the level of homocysteine in the serum.
(B) Homocysteine has a mitogenic effect on vascular smooth muscle.
(C) Elevated homocysteine increases the activity of coagulation factor XII.
(D) Statins reduces the plasma homocysteine level by 25%.
(E) The progression of atherosclerotic carotid plaque may be decreased by lowering the homocysteine level.

**32.** Positron emission tomography (PET) studies in ischemic stroke show that the blood flow in necrotic tissue is less than

(A) 30 mL/100 gr per minute
(B) 24 mL/100 gr per minute
(C) 18 mL/100 gr per minute
(D) 12 mL/100 gr per minute
(E) 6 mL/100 gr per minute

**33.** Which of the following is the most important risk factor for spontaneous intracerebral hemorrhage?

(A) Hypertension
(B) Ethanol abuse
(C) Cerebral amyloid angiopathy
(D) Cholesterol greater than 200 mg/dL
(E) Mutation of the gene coding for coagulation factor XIII

**34.** Which of the following is true about the management of spontaneous intracerebral bleed?

(A) Since a marked increase of intracerebral pressure is seen in all patients with intracerebral hemorrhage, the early use of hyperventilation or osmotic agents is recommended.
(B) Corticosteroids may be used in intracerebral bleed if an osmotic agent or hyperventilation fails to reduce the intracranial pressure.
(C) Early surgical evacuation of hematoma from the basal ganglia or pons has a better prognosis than medical treatment.
(D) Early craniotomy is recommended in cases of cerebellar hematoma.
(E) Long-term use of antiseizure medications is recommended because most seizures occur after the first 24 hours following formation of the hematoma.

**35.** The *least* common presentation of an arteriovenous malformation of the brain is

(A) intracerebral hemorrhage
(B) seizure
(C) headache
(D) focal neurological deficit without signs of underlying hemorrhage
(E) progressive neurological deficit without signs of underlying hemorrhage

**36.** Which of the following MR spectroscopy peaks typically increases in acute ischemic stroke?

(A) Lactate peak
(B) Creatine peak
(C) N-acetyl aspartate peak
(D) Choline peak
(E) None of the above

# Answers and Explanations

1. **(B)** Without the use of heparin prophylaxis, deep venous thrombosis (DVT) of a lower extremity may occur in up to half of patients with hemiplegic stroke. The highest incidence occurs between the second and seventh day poststroke. Elderly patients and those immobilized after stroke appear to be at highest risk. The greatest clinical concern related to proximal DVT is fatal pulmonary embolism (PE). Estimates of early deaths attributable to PE range from 13% to 25% and occur most frequently between the second and fourth week. Measures to prevent DVT should be routine for all patients with ischemic stroke admitted to the hospital. The use of low-intensity anticoagulation for DVT prophylaxis is recommended for all immobilized patients with stroke. Anticoagulants should not be used for 24 hours after administration of thrombolytic therapy. In patients with primary intracerebral hemorrhage, initiation of anticoagulation for DVT prophylaxis is often delayed for 3 to 4 days. However, definitive evidence to guide management after intracerebral hemorrhage is not available. *(Barrett, 61–79)*

2. **(C)** The ischemic penumbra presents tissue that is functionally impaired but structurally intact and, as such, potentially salvageable. It corresponds to a high cerebral blood flow (CBF) limit of 17 mL/100 mg per minute to 22 mL/100 mg per minute and a low CBF limit of 7 mL/100 mg per minute to 12 mL/100 mg per minute. Salvaging this tissue by restoring its flow to nonischemic levels is the aim of acute stroke therapy. *(Jovin, 28–45)*

3. **(B)** In acute ischemic stroke, the loss of blood flow from the occluded vessel leads to a time-dependent compartmentalization of the ischemic brain into tissue that is irreversibly damaged (ischemic core), tissue that is functionally impaired but structurally intact and thus potentially salvageable (penumbra), and tissue that is hypoperfused but not threatened under normal circumstances (oligemic brain). The timing for recanalization of occluded vessels in acute stroke was based on the concept that the ischemic penumbra has a short lifespan, being rapidly incorporated into the core within hours of the onset of the acute stroke. Several investigators have estimated the penumbra based on diffusion/perfusion MRI (diffusion-weighted imaging [DWI]/perfusion-weighted imaging [PWI]) mismatch in acute stroke. This was based on the concept that the diffusion abnormalities are presumed to represent an approximation of the irreversible ischemic lesion and the perfusion abnormalities are presumed to represent the brain territory at risk, the area of mismatch between DWI and PWI is considered a territory still viable but at risk of undergoing infarction and corresponds theoretically to the concept of ischemic penumbra. *(Jovin, 28–45)*

4. **(E)** In acute ischemic stroke, neuronal cell death occurs as a result of two main mechanisms: necrosis and apoptosis. Necrosis occurs mainly as a consequence of disruption of cellular homeostasis due to energy failure and is accompanied by cellular swelling, membrane lysis, inflammation, vascular damage, and edema formation. Apoptosis, or programmed cell death, is characterized by cell shrinkage,

chromatin clumping, and cytoplasmic blebbing and is not associated with inflammation or secondary injury to surrounding brain. These two distinct types of neuronal death appear to represent opposite poles of a spectrum that coexist within the ischemic brain, with necrosis being the main mechanism of neuronal injury in the ischemic core and apoptosis being the main mechanism of neuronal injury in the penumbra where, because of the milder degree of ischemia, sufficient energy is produced to allow for expression of new proteins that mediate apoptosis. *(Jovin, 28–45; Bhardwaj, 160–167)*

5. **(E)** Before the administration of thrombolytic therapy, ancillary tests are performed to supplement the clinical impression based on the bedside assessment. These tests may help to distinguishing condition that may mimic a stroke (e.g., hypoglycemia) or identifying conditions that contraindicate thrombolytic therapy. Recently published guidelines by Adams and coworkers recommend routine laboratory testing of blood glucose, electrolytes, complete blood count, prothrombin time, activated partial thromboplastin time, international normalized ratio, and renal function. Testing for stool guaiac is not routinely recommended unless an indication exists (e.g., melena or hematochezia). Cardiac enzymes and a 12-lead ECG are recommended for all stroke patients. The utility of routine chest radiography as part of the acute stroke evaluation is limited and currently not routinely recommended. Cerebral spinal fluid examination is not routinely indicated unless the patient complains of severe headache, which raises the possibility of subarachnoid hemorrhage or central nervous system infection. Urine toxicology screen, blood alcohol level, arterial blood gas, or pregnancy tests may be indicated when the clinical history is limited or uncertain. *(Adams, 1655–1711; Barrett et al., 13–27)*

6. **(C)** Strokes may be complicated by infections, which are common complications during the first 5 days after hospital admission and are associated with worse short-term outcomes. Age greater than 65 years, dysarthria or expressive aphasia, modified Rankin Scale score of 4 or greater, and failure of the bedside water swallow test are considered to be independent predictors of pneumonia. Pneumonia may occur even without frank aspiration events or dysphagia. Pneumonia may occur in 5.6% of patients after stroke and has been associated with a significantly increased cost of hospitalization and likelihood of extended care requirements upon discharge. A study performed by Chamorro and associates assessing prophylactic antibiotics to prevent infection after stroke does not support their routine use. Urinary tract infection is common among hospitalized patients with stroke, especially in patients with indwelling bladder catheters, which are often placed in immobilized patients for urinary retention or incontinence after stroke. Less common infections in patients with stroke include cellulitis (in association with catheter placement or pressure ulcers) and cholecystitis. *(Adams, 1655–1711; Azzimondi, 2040–2043; Chamorro, 1495–1500; Katzan, 1938–1943; Kwan, 331–338; Sellars, 2284–2291)*

7. **(B)** Dysphagia may occur after a stroke in 51% to 55% of patients. Hemispheric lesions may cause motor impairment of the face, lips, or tongue and/or attentional deficits that can compromise normal swallowing function. Brainstem lesions can impair the normal coordination of pharyngeal swallow, laryngeal elevation, glottic closure, and cricopharyngeal relaxation. Other risk factors of dysphagia after a stroke include impaired consciousness, difficulty or inability to sit upright, shortness of breath, slurred speech, facial weakness or droop, expressive aphasia, weak or wet cough, and hoarse voice. *(Barrett et al., 61–79; Martino, 2756–2763)*

8. **(D)** Attempts to lower blood pressure before rt-PA administration may be undertaken to obtain the required parameter of less than 185/110 mmHg. The American Heart Association recommends the use of intravenous labetalol, nicardipine, or nitropaste patch to manage hypertension before rt-PA administration. *(Khatri, 46–60)*

9. **(C)** The patient described in this vignette has an angiogram significant for a flame-shaped carotid occlusion. This finding, associated the clinical manifestation described in the vignette, is suggestive of left carotid dissection. Some patients with carotid dissection may develop

warning attacks of unilateral cranial or facial pain followed within minutes to days by signs of ischemia in the territory of the internal carotid artery. The pain is nonthrobbing and centered most often in and around the eye; less often, it is in the frontal or temporal regions, angle of the mandible, or high anterior neck over the carotid artery. A unilateral Horner syndrome is often present. Cervical bruit—sometimes audible to the patient—amaurosis fugax, faintness and syncope, and facial numbness are less common symptoms. Most of the patients described by Mokri and coworkers presented with one of two distinct syndromes: (1) unilateral headache associated with an ipsilateral Horner syndrome or (2) unilateral headache and symptoms of delayed focal cerebral ischemia. Some patients have evidence of involvement of the vagus, spinal accessory, or hypoglossal nerve; these nerves lie in close proximity to the carotid artery and are nourished by small branches from it. *(Ropper, chapter 34; Mokri, 59–60, 677–680)*

**10.** **(B)** The angiogram in Figure 7-2 demonstrated occlusion of the proximal part of the middle cerebral artery (MCA). The MCA is by far the largest cerebral artery and is the vessel most commonly affected by cerebrovascular accident (CVA). The MCA has superficial and deep hemispheral branches. Through its cortical branches, it supplies the lateral convexity, part of the cerebral hemisphere. Its cortical territory encompasses (1) the cortex and white matter of the lateral and inferior parts of the frontal lobe—including motor areas 4 and 6, contraversive centers for lateral gaze—and motor speech area of Broca (dominant hemisphere); (2) the cortex and white matter of the parietal lobe, including the sensory cortex and the angular and supramarginal convolutions; and (3) superior parts of the temporal lobe and insula, including the sensory language areas of Wernicke. The deep penetrating or lenticulostriate branches of the middle cerebral artery supply the putamen, part of the head and body of the caudate nucleus, outer globus pallidus, posterior limb of the internal capsule, and corona radiata. The middle cerebral artery may be occluded in its stem (the term M1 is used by radiologists to denote this portion of the vessel)—the portion that is distal to its origin at the distal internal carotid and proximal to its bifurcation. An occlusion here blocks the flow in the small deep penetrating vessels as well as superficial cortical branches; alternatively, an occlusion at the distal end of the stem blocks the orifices of the divisions of the artery in the sylvian sulcus but leaves unaffected the more proximal deep penetrating vessels. The picture of total occlusion of the stem is one of contralateral hemiplegia (face, arm, and leg), hemianesthesia, and homonymous hemianopia (due to infarction of the lateral geniculate body), with deviation of the head and eyes toward the side of the lesion; in addition, there is a variable but usually global aphasia with left hemispheric lesions and anosognosia and amorphosynthesis with a right-sided ones. Once fully established, the motor, sensory, and language deficits remain static or improve very little as months and years pass. If the patient is globally aphasic for a prolonged period of time, he or she will seldom ever again communicate effectively.

Occlusion of the stem of the middle cerebral artery by a thrombus, contrary to conventional teaching, is relatively infrequent (less than 10% of middle cerebral artery occlusions in our experience); cerebral embolism is a more common cause. Pathological studies over the years have shown that most carotid occlusions are thrombotic, whereas most middle cerebral occlusions are embolic. *(Ropper, chapter 34)*

**11.** **(D)** The angiogram in Figure 7-3 demonstrated basilar artery stenosis. Patients with basilar artery stenosis may develop transient vertebrobasilar ischemic attacks. Symptoms of vertebrobasilar circular insuffiency include binocular visual loss, vertigo, weakness, gait ataxia, dysarthria, and diplopia. *(Adams, 82)*

**12.** **(E)** The basilar artery supplies a wedge of the pons on either side of the midline with its paramedian branches, the lateral two third of the pons, and the middle and superior cerebellar peduncles through its short circumferential branches, the cerebellar hemispheres through its long circumferential branches, and the high midbrain and medial subthalamic regions through its several paramedian branches.

Basilar artery occlusion due to thrombosis may arise from occlusion of the basilar artery

itself, occlusion of both vertebral arteries, and occlusion of a single vertebral artery when it is the only one of adequate size. When there is embolism, the clot usually lodges at the upper bifurcation of the basilar or in one of the posterior cerebral arteries. The syndrome of basilar artery occlusion reflects damage to the corticospinal and corticobulbar tracts, cerebellum, middle and superior cerebellar peduncles, medial and lateral lemnisci, spinothalamic tracts, medial longitudinal fasciculi, pontine nuclei, vestibular and cochlear nuclei, descending hypothalamospinal sympathetic fibers, and the third through eighth cranial nerves (the nuclei and their segments within the brainstem). *(Ropper, chapter 34)*

**13.** **(B)** In this vignette, the patient woke up with right side weakness after 9 hours of sleep. For a patient who awakens with symptoms, the time of onset is considered to be the time when the patient went to bed, which in this case is outside the time range for intravenous or intra-arterial thrombolytic therapy. In two large randomized trials, the use of aspirin (160 or 300 mg/day) initiated within 48 hours after the onset of stroke and continued for 2 weeks or until discharge led to reduced rates of death or dependency at discharge or at 6 months, probably by means of reducing the risk of recurrent ischemic stroke. In both trials, the routine use of aspirin was recommended as secondary prevention after the first few weeks. Although the benefit was small (77 patients would need to be treated to prevent a poor outcome in 1 patient), aspirin is inexpensive, has a good safety profile, and appears to be effective across the range of patients with ischemic stroke. *(CAST, 1641–1649; Chen 1240–1249; International Stroke Trial Collaborative Group, 1569–1581)*

**14.** **(A)** Subhyaloid hemorrhage is seen in association with subarachnoid hemorrhage (SAH). The combination of SAH and subhyaloid hemorrhage is known as Terson syndrome. It was defined by the occurrence of vitreous hemorrhage in association with subarachnoid hemorrhage. Terson syndrome now encompasses any intraocular hemorrhage associated with intracranial hemorrhage and elevated intracranial pressure. Intraocular hemorrhage includes the development of subretinal, retinal, preretinal, subhyaloidal, or vitreal blood. The classic presentation is in the subhyaloidal space. Reports have shown an incidence of 10% to 50% of intraocular hemorrhage with subarachnoid hemorrhage. This association is statistically associated with the severity of the subarachnoid hemorrhage based on the Hunt–Hess classification system of subarachnoid hemorrhages. The incidence of vitreous hemorrhage is much lower (3% to 13%). Several mechanisms of subhyaloid hemorrhage have been proposed: (1) A sudden increase in intracranial pressure (ICP) forces blood from the subarachnoid space directly into the preretinal space. (2) A sudden rise in ICP is thought to decrease venous return to the cavernous sinus from the veins draining the globe. The increased retinal venous pressure results in stasis followed by vessel rupture. (3) A sudden rise in ICP obstructs both the retinochoroidal anastomoses and the central retinal vein due to a rapid effusion of CSF through the communication of the subarachnoid space with the optic nerve sheath. This produces an acute decrease in venous drainage from the retina and results in stasis and hemorrhage. *(Adams, 85; Castano-Duque, 1081–1083)*

**15.** **(E)** The association of monocular transitory visual loss with the presence of a fibrin platelet embolus in a branch of the retinal artery on fundoscopic examination is suggestive of amaurosis fugax. It is the most specific symptom of transient ischemia in the carotid circulation. The usual cause the transitory visual loss is embolization to the central retinal artery or its branches. *(Adams, 85)*

**16.** **(E)** Radiological and postmortem studies indicate that perioperative strokes are predominantly ischemic and embolic. In a study of 388 patients with stroke after coronary artery bypass grafting (CABG), hemorrhage was reported in only 1% of patients; 62% had embolic infarcts. The timing of embolic strokes after surgery had a bimodal distribution. Approximately 45% of perioperative strokes were identified within the first day after surgery. The remaining 55% occurred after uneventful recovery from anesthesia from the second postoperative day onward. Early embolism results especially

from manipulation of the heart and aorta or release of particulate matter from the cardiopulmonary bypass pump. Delayed embolism is often attributed to postoperative atrial fibrillation, myocardial infarction resulting from an imbalance between myocardial oxygen supply and demand, and coagulopathy. Surgical trauma and associated tissue injury result in hypercoagulability. *(Selim, 706–713; Likosky, 2830–2834)*

**17. (D)** Nontraumatic subarachnoid hemorrhage is a neurological emergency characterized by the extravasation of blood into the spaces covering the central nervous system that are filled with cerebrospinal fluid. The leading cause of nontraumatic subarachnoid hemorrhage is rupture of an intracranial aneurysm, which accounts for about 80% of cases and is associated with a high rate of death and complications. It accounts for 2% to 5% of all new strokes and affects 21,000 to 33,000 people each year in the United States. The incidence of the disorder has remained stable over the past 30 years, and although it varies from region to region, the aggregate worldwide incidence is about 10.5 cases per 100,000 person-years. The incidence increases with age, with a mean age at presentation of 55 years. The risk for women is 1.6 times that of men, and the risk for blacks is 2.1 times that of whites. The average case fatality rate for subarachnoid hemorrhage is 51%, with approximately one third of survivors needing lifelong care. Most deaths occur within 2 weeks after the ictus, with 10% occurring before the patient receives medical attention and 25% within 24 hours after the event. The major factors associated with poor outcome are the patient's level of consciousness on admission, his or her age, and the amount of blood shown by initial CT of the head. The major identified modifiable risk factors include cigarette smoking, hypertension, cocaine use, and heavy alcohol use. Patients with a family history of first-degree relatives with subarachnoid hemorrhage are also at a higher risk. Heritable connective tissue disorders associated with the presence of intracranial aneurysm and subarachnoid hemorrhage include polycystic kidney disease, Ehlers–Danlos syndrome type IV, pseudoxanthoma elasticum, and fibromuscular dysplasia. *(Suarez, 387–396)*

**18. (C)** Intracranial aneurysms are common lesions; autopsy studies indicate prevalence in the adult population between 1% and 5%. Associated conditions include autosomal dominant polycystic kidney disease, fibromuscular dysplasia, Marfan syndrome, Ehlers–Danlos syndrome type IV, and arteriovenous malformations of the brain. An estimated 5% to 40% of patients with autosomal dominant polycystic kidney disease have intracranial aneurysms and 10% to 30% of patients have multiple aneurysms. The most frequent location of intracranial aneurysms is the anterior communicating artery (30%), followed by the posterior communicating artery (25%), middle cerebral artery (20%), internal carotid bifurcation (7.5%), basilar tip (7%), pericallosal artery (4%), and posterior inferior cerebellar artery (3%). *(Brisman, 928–939)*

**19. (E)** The brainstem is formed by three main divisions: the medulla, the pons, and the midbrain. The medulla is the rostral extension of the spinal cord. It contains the inferior olivary nucleus as well as the nucleus of the lower cranial nerves. The hypoglossal nucleus is located near the ventrolateral portion of the central canal. The nucleus ambiguus (the nucleus of the glossopharyngeal nerve, vagus nerve, and spinal accessory nerves) is located within the medullary reticular formation, ventromedial to the nucleus and spinal tract of the trigeminal nerve.

The dorsal motor nucleus of the vagus is located dorsolaterally to the hypoglossal nucleus. The nucleus of the tractus solitarius (nucleus of the sensory facial, glossopharyngeal, and vagus nerves) lies anterolateral to the motor nucleus of the vagus nerve. The posterolateral to the solitary tracts lie medial and inferior to the vestibular nuclei; caudal to them are the dorsal and ventral cochlear nuclei of the vestibulocochlear nerve. The nucleus gracilis and nucleus cuneatus are located in the posterior funiculi of the dorsal medulla and give off fibers that decussate in the medial lemniscus.

Medial medullary syndrome (Dejerine syndrome) is caused by an occlusion of the anterior spinal artery or its parent vertebral artery. The syndrome causes ipsilateral paresis of the tongue due to damage of the hypoglossal nerve, which deviates toward the lesion; contralateral

hemiplegia sparing the face due to damage of the corticospinal tract; and contralateral loss of position and vibratory sensation due to damage of the medial lemniscus.

The lateral medullary syndrome (Wallenberg syndrome) may be caused by an occlusion of the vertebral artery or posterior inferior cerebellar artery. The damage is located in the dorsolateral medulla and inferior cerebellar peduncle. The clinical features of lateral medullary syndrome include ipsilateral loss of pain and temperature sensation of the face due to damage of the descending spinal tract and nucleus of the trigeminal nerve; ipsilateral paralysis of the palate, pharynx, and vocal cords with dysarthria and dysphagia due to damage of the nuclei and fibers of the glossopharyngeal and vagus nerves; ipsilateral Horner syndrome due to damage of the descending sympathetic tract fibers; ipsilateral ataxia and dysmetria due to damage of the inferior cerebellar peduncle and cerebellum; contralateral loss of pain and temperature sensation due to damage of the spinothalamic tract; and vertigo, nausea, vomiting, and nystagmus due to damage of the vestibular nuclei.

The pons lies rostral to the medulla. It has two components: a dorsal part (the tegmentum) and a ventral part (the basis pontis). The tegmentum is largely composed of the pontine reticular formation. Cranial nerve nuclei in the pons include the nucleus of the abducens nerve (located in the dorsomedial pons, dorsolateral to the paramedian pontine reticular formation), the motor nucleus of the facial nerve (situated ventrolaterally), the main motor and sensory nucleus of the trigeminal nerve, the superior and inferior salivatory nuclei, and the lacrimal nucleus. Tracts within the pons include the medial longitudinal fasciculus, the medial lemniscus, and the corticospinal, the corticobulbar, the corticopontine, the spinothalamic, the ventral spinocerebellar, the rubrospinal, and the lateral tectospinal tracts.

The basilar artery is the principal source of blood flow to the pons. It gives off three types of branches: the paramedian arteries, the short circumferential arteries, and the long circumferential arteries (which supply the pontine tegmentum and the dorsolateral quadrant of the pons, together with the anterior inferior cerebellar arteries and the superior cerebellar arteries). The ventral pontine syndrome (Millard–Gubler syndrome) is caused by paramedian infarction of the pons. This results in ipsilateral paresis of the lateral rectus from damage to the abducens nerve, causing diplopia; in addition, there is ipsilateral paresis of the upper and lower face from damage to the facial cranial nerve and contralateral hemiplegia from damage to the corticospinal tract.

The lower dorsal pontine syndrome (Foville syndrome) is caused by a lesion in the dorsal tegmentum of the lower pons. The affected patient may develop ipsilateral paresis of the upper and lower halves of the face from damage to the nucleus or fibers of the facial nerve and ipsilateral horizontal gaze palsy from damage of the paramedian pontine reticular formation and/or the abducens nerve nucleus. The upper dorsal pontine syndrome is caused by obstruction of the long circumferential branches of the basilar artery and results in ipsilateral ataxia and coarse intention tremor (the superior and middle cerebellar peduncles). There is also contralateral body sensory loss to all modalities from damage to the medial lemniscus and spinothalamic tract. When the lesion extends to the ventral part of the pons, contralateral hemiparesis, including the face, occurs from damage to the corticospinal tract. *(Afifi, 141–146, 179–186, 227–234; Rolak, 112–121)*

**20.** **(E)** The midbrain, which is the smallest and the most rostral component of the brainstem, plays an important role in the control of eye movements and coordination of visual and auditory reflexes. The midbrain may be divided into three parts: the tectum, the tegmentum, and the cerebral peduncles. The dorsal tectum contains the corpora quadrigemina, made up of four rounded eminences arranged in pairs, the superior and inferior colliculi. The tegmentum contains ascending and descending tracts, reticular nuclei, and well-delineated nuclear masses. The cerebral peduncles are ventral and contain corticopontine fibers in their medial fifth, corticospinal tract fibers in their middle three-fifths, and temporopontine fibers in their lateral fifth. The substantia nigra is a pigmented layer possessing melanin granules; dorsal to the peduncle and ventral to the red nucleus, it is composed of the dorsal zona compacta and ventral zona

reticulata. The nucleus of the trochlear nerve is located in the ventral part of the central gray matter at the level of the inferior colliculus. The nucleus of the oculomotor nerve lies rostral to the trochlear nucleus beneath the superior colliculus. Mesencephalic tracts include the crus cerebri, the dentatorubrothalamic tract, the medial tegmental tract, the posterior commissure, the median longitudinal fasciculus, the spinothalamic tract, and the median lemniscus. The vascular supply of the midbrain includes the paramedian and circumferential branches of the basilar artery.

Dorsolateral midbrain syndrome is caused by infarction of the territory of the circumferential arteries and results in (1) ipsilateral Horner syndrome; (2) ipsilateral severe tremor from damage to the superior cerebellar peduncle; and (3) contralateral loss of all sensory modalities from damage to the spinothalamic and medial lemniscus tracts. *(Afifi, 141–146, 179–186, 227–234; Rolak, 112–121)*

**21.** **(C)** Ventral midbrain syndrome (Weber syndrome) is caused by an occlusion of median and paramedian perforating branches and may result in ipsilateral oculomotor paresis, ptosis, and dilated pupils from damage to the fascicle of the third nerve. In addition, there is a contralateral hemiplegia, including the lower face, from damage to the corticospinal tract. Dorsal midbrain syndrome (Moritz–Benedikt syndrome) results from a lesion in the midbrain tegmentum caused by occlusion of the paramedian branches of the basilar or posterior cerebral arteries or both. It results in ipsilateral oculomotor paresis, ptosis, and dilated pupil from damage to the third nerve. Contralateral involuntary movements also occur, such as intention tremor, ataxia, and chorea, from damage to the red nucleus. There is a contralateral hemiparesis with extension of the lesion ventrally and contralateral hemianesthesia with extension of the lesion laterally to the spinothalamic tracts and the medial lemniscus. *(Afifi, 141–146, 179–186, 227–234; Rolak, 112–121)*

**22.** **(E)** Spontaneous dissection of the carotid or vertebral artery accounts for about 2% of all ischemic strokes. Its annual incidence in some studies ranges from 2.5% to 3% per 100,000. However, in young and middle-aged populations, it accounts for 10% to 25% of ischemic strokes. Spontaneous dissections of the carotid and vertebral arteries affect all age groups, but there is a distinct peak in the fifth decade of life. Although there is no overall sex-based predilection, women are, on average, about 5 years younger than men at the time of the dissection. *(Schievink, 898–906)*

**23.** **(E)** Cranial nerves are affected in about 12% of carotid artery dissections. The hypoglossal nerve is the most commonly affected cranial nerve, followed by other lower cranial nerves. The oculomotor nerve, trigeminal nerve, and facial nerve are less affected. *(Schievink, 898–906)*

**24.** **(D)** The patient described in this vignette has a triad of signs and symptoms that include unilateral headache, unilateral oculosympathetic palsy, and transient monocular blindness (which may be considered in this context as a sign of retinal ischemia). The occurrence of this constellation of signs and symptoms after chiropractic manipulation is highly suggestive of carotid artery dissection. Hyperextension or rotation of the neck may also precipitate carotid dissection. It is estimated that about 1 in 20,000 of spinal manipulations are associated with a stroke by carotid or vertebral artery dissection.

Unilateral headache develops in two thirds of patients. It may mimic a migraine headache or a subarachnoid hemorrhage, but most commonly it is a frontotemporal headache with gradual onset, often above the ipsilateral eye. Miosis and ptosis reflect oculosympathetic palsy and are seen in less than 50% of patients with carotid dissection. A cranial nerve lesion is detected in only 12% of cases of carotid artery dissection. The hypoglossal nerve is the most frequently affected cranial nerve. Transient monocular blindness is the most common sign of retinal ischemia seen in patients with spontaneous carotid dissection. Permanent blindness from ischemic optic neuropathy or occlusion of the retinal artery is rare. Symptoms and signs of retinal or cerebral ischemia are reported in 50% to 95% of carotid artery dissections. Ultrasound or MR angiography of the carotid artery is useful for an initial assessment, but carotid angiography remains the gold standard. *(Schievink, 898–906)*

**25.** **(B)** Diffusion-weighted imaging is a technique that permits in vivo measurement of the translational mobility of water along the particular direction of the used diffusion-sensitizing gradient in tissue. The apparent diffusion coefficient that quantifies water mobility is reduced in ischemic tissue. The drop in brain perfusion caused by an acute ischemic event induces an energy deficit, with failure of the sodium/potassium pump. This results in the accumulation of sodium inside the neural and glial cells, which causes an intracellular influx of water inside these cells. This influx of water from the extracellular space into the intracellular space causes swelling of the neuronal and glial cells and a reduction of the extracellular volume space. Thus, water mobility is hindered as a consequence of the production of longer diffusion paths and the apparent diffusion coefficient of water is decreased. *(Schievink, 898–906)*

**26.** **(A)** Lacunar strokes are small infarcts of the noncortical parts of the cerebellum and the brain stem that result from occlusion of penetrating branches of large cerebral arteries, most commonly the middle cerebral, basilar, and posterior cerebral arteries and less commonly the anterior cerebral and vertebral arteries. The size of a lacunar stroke ranges from 3 mm to 2 cm. Pathological studies show that the penetrating vessels might be obstructed either by small embolic particles or lipohyalinosis. Signs of lacunar stroke depend on the anatomical location of the ischemic lesion. Hemiballismus is caused by an infarct or hemorrhage in the subthalamic nucleus. Pure motor hemiparesis involves the face, arm, and leg without sensory deficit, aphasia, agnosia, apraxia, or visual field defect. The most frequent location of the lesion is the posterior limb of the internal capsule and less frequently the corona radiata, pons, and medullary pyramid. Infarction of the basis pontis at the junction of the upper third and inferior two thirds from obstruction of the paramedian branch of the basilar artery causes dysarthria clumsy hand syndrome. Ataxia hemiparesis results from a lacunar lesion located in the corona radiata, internal capsule, or pons. *(Fisher, 871–876; Fisher and Bogousslavsky, 108)*

**27.** **(D)** The typical presentation of subarachnoid hemorrhage includes a sudden onset of severe headache, frequently described as the worst headache of the patient's life. Nausea, vomiting, transient loss of consciousness, or leg buckling may accompany the headache. Physical examination may show nuchal rigidity, retinal hemorrhages, papilledema, third nerve palsy (in case of posterior communicating artery aneurysm), sixth nerve palsy, bilateral weakness in legs (or abulia in case of aneurysm of the anterior communicating artery), and/or aphasia hemiparesis (or left-sided visual neglect in the case of a middle cerebral artery aneurysm). Arrythmias are a frequent complication of subarachnoid bleeding. Andreoli and coworkers reported arrhythmias in 91% of patients diagnosed with spontaneous subarachnoid hemorrhage and investigated prospectively with 24-hour Holter monitoring. This study did not demonstrate a correlation between the frequency and severity of cardiac arrhythmias and the neurologicl condition, the site and extent of intracranial blood on CT scan, or the location of the ruptured vessel.

CT scan of the head without contrast and with thin cuts through the base of the brain is the first recommended test. In retrospective studies, the sensitivity of modern third-generation CT scanners for detecting subarachnoid hemorrhage is 100% in the first 12 hours and 93% in the first 24 hours. Although MRI technology is continually advancing and can detect aneurysms, standard MRI is inferior to CT for the detection of acute subarachnoid hemorrhage. Lumbar puncture should be performed in a patient whose clinical presentation suggests subarachnoid hemorrhage and whose CT scan is negative, equivocal, or technically inadequate. After aneurysmal hemorrhage, erythrocytes invade the subarachnoid space and then gradually lyse to release hemoglobin, which is metabolized to the pigmented molecules, oxyhemoglobin (reddish pink) and bilirubin (yellow), resulting in xanthochromia. The presence of xanthochromia is considered by many authors to be the primary criterion for a diagnosis of subarachnoid hemorrhage in patients with negative CT scans, although some authors assert that the presence of erythrocytes, even in the absence of xanthochromia, is more accurate. *(Andreoli, 558–564; Edlow, 29–36)*

**28.** **(E)** WARSS was a multicenter, double blind, randomized trial that compared the effect of warfarin (at a dose adjusted to produce an international normalized ratio of 1.4 to 2.8) and aspirin (325 mg per day) on the combined primary endpoints of recurrent ischemic stroke or death from any cause within 2 years. The two randomized study groups were similar with respect to baseline risk factors. No significant differences were found between the treatment groups in any of the outcomes measured. The rates of major hemorrhage were low (2.22 per 100 patient-years in the warfarin group and 1.49 per 100 patient-years in the aspirin group). Also, there were no significant treatment-related differences in the frequency of major hemorrhage according to the cause of the initial stroke. The authors concluded that over a 2-year period, there was no difference between aspirin- and warfarin-treated patients in the rate of major hemorrhage or in the prevention of recurrent ischemic stroke (for a population with noncardioembolic stroke) or death. *(Mohr, 1444–1451)*

**29.** **(A)** Hypertension is reported to be the most consistently powerful predictor of stroke. It is found to be a contributing factor in about 70% of strokes. Hypertension promotes stroke by aggravating atherosclerosis in the aortic arch and cervicocerebral arteries, causing arteriosclerosis and lipohyalinosis in the small-diameter, penetrating end arteries of the cerebrum. For people of all ages and both sexes, higher levels of both systolic and diastolic blood pressure have been associated with an increased incidence of ischemic and hemorrhagic stroke. Treatments not only for severe hypertension but also mild-to-moderate hypertension have been associated with a decrease in the incidence of stroke.

Cigarette smoking is also a major cause of both ischemic and hemorrhagic stroke. The relative risk of stroke for smokers, as compared with nonsmokers, is estimated to be close to 1.51. Cigarette smoking may increase the risk of stroke by modifying blood coagulability (increasing blood levels of fibrinogen and other clotting factors, increasing platelet aggregability and hematocrit), modifying the lipid profile of smokers (decreasing the high-density lipoprotein cholesterol level), and promoting atherosclerosis by direct endothelial damage. Tobacco may promote arterial rupture by increasing blood pressure.

Diabetes may increase the risk of stroke independently of hypertension, dyslipoproteinemia, and obesity. Diabetes may increase the risk of stroke by promoting atherogenesis. Obesity, elevated serum cholesterol, and lack of physical activity are also risk factors for stroke. *(Bronner, 1392–1400)*

**30.** **(B)** rt-PA is produced endogenously in physiological concentrations by endothelial cells. It is relatively fibrin-specific. The NINDS trial randomized 624 patients (312 each to placebo and intravenous rt-PA) within 3 hours after stroke symptom onset. The trial had two parts: Part 1 (in which 301 patients were enrolled) tested whether rt-PA demonstrated a clinical effect within 24 hours of the onset of stroke (primary endpoint). Part 2 (in which 333 patients were enrolled) used a global test statistic to assess clinical outcome at 3 months. There was no significant difference between the drug treatment and placebo groups in the percentages of patients with neurological improvement at 24 hours. A benefit was observed for the rt-PA group at 3 months for all outcome measures. For every 100 patients treated with rt-PA, an additional 11 to 13 patients will have a favorable outcome as compared with 100 not treated with rt-PA. The benefit did not vary by stroke subtype at baseline because not only cardioembolic strokes but also small-vessel ischemic strokes benefited from thrombolytic treatment. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4% of patients given rt-PA but only in 0.6% of patients given placebo ($p < 0.001$). Nevertheless, severe disability and death were higher in the nontreated group. *(Schellinger, 1812–1818)*

**31.** **(D)** A prospective population-based cohort study of patients without a history of stroke who were followed for a median of 9.9 years identified homocysteine level as an independent risk factor for stroke. This relative risk increases with the level of homocysteine up to 1.82. Homocysteine may act by inducing endothelial dysfunction and altering the antithrombotic

properties of the endothelium with enhancement of the activity of factors XII and V. It may also have a mitogenic effect on vascular smooth muscle cells. Statins do not lower homocysteine levels, but dietary folic acid may reduce the level of homocysteine by approximately 25% and vitamin $B_{12}$ may reduce it by an additional 7%. It remains unknown whether lowering homocysteine prevents important atherosclerotic vascular events. However, an uncontrolled study has shown that lowering homocysteine through the combination of folic acid 2.5 mg/day, vitamin $B_6$ 25 mg/day, and vitamin $B_{12}$ 250 μg/day reduces the progression of atherosclerosis as measured by carotid plaque area. *(Hankey, 95–102)*

**32.** **(D)** PET classifies three regions within the disturbed vascular territory. The core zone of ischemia, which usually becomes necrotic, has blood flow below 12 mL/100 gr per minute and a cerebral metabolic rate for oxygen ($CMRO_2$) below 60 μmol/100 gr per minute. The penumbral region has a flow rate between 12 and 22 mL/100 gr per minute (it is a dynamic area where the tissue is still viable but can either become necrotic or recover; it is characterized by increased oxygen extraction fraction). The third region is an area of hypopofusion (flow >22 mL/100 gr per minute), which is not primarily damaged by the lack of blood supply. *(Heiss, 67–75)*

**33.** **(A)** Hypertension is the most important risk factor for spontaneous intracerebral hemorrhage. It increases the risk of intracerebral hemorrhage, particularly in untreated people 55 years of age or younger and those who smoke. Excessive use of alcohol also increases the risk of intracerebral hemorrhage by impairing coagulation and directly affecting the integrity of cerebral vessels. Low serum cholesterol (less than 4.1 mmol/L), especially when associated with hypertension or hypercoagulable status, is a less well established risk factor for intracerebral hemorrhage. Cerebral amyloid angiopathy, which is characterized by the deposition of (beta)-amyloid protein in the blood vessels of the cerebral cortex and leptomeninges, is another risk factor for intracerebral hemorrhage, particularly in elderly persons with (epsilon)2 and (epsilon)4 alleles of the apolipoprotein E gene. *(Qureshi et al., 1450–1460)*

**34.** **(D)** Several days after intracerebral hemorrhage, the patient may develop obstructive hydrocephalus from the mass effect caused by the hematoma and the edematous tissue surrounding it. The resulting increased intracranial pressure may subsequently cause central nervous system herniation, which remains the chief secondary cause of death in the first few days after intracerebral hemorrhage. Marked elevation of the intracranial pressure occurs with massive intracerebral hemorrhages because the intracranial volume cannot expand. However, localized intracerebral hemorrhage may occur without significant increase in global intracranial pressure.

The use of hyperventilation and osmotic agents is discouraged in the absence of evidence of a critical rise in intracranial pressure and should be reserved for patients with impending cerebral herniation. This strategy is supported by some experimental studies showing improvement of the blood flow and cerebral metabolism when high intracranial pressure is lowered in cases of intracranial herniation but no benefit with moderate pressure elevations. Corticosteroids should be avoided because randomized trials have failed to demonstrate their efficacy in patients with an intracerebral hemorrhage.

Surgical evacuation of a hematoma is indicated to reduce the mass effect. However, there is no sustained benefit from evacuation of basal ganglionic, thalamic, and pontine hemorrhages.

Cerebellar hematomas are unique from a surgical perspective because they can be approached without causing substantial damage to higher cortical or primary motor pathways. Thus early craniotomy is recommended in patients with a cerebellar hematoma that causes compression of the brainstem because the rate of neurologic deterioration after cerebellar hemorrhage is very high and unpredictable. Most patients with intracerebral bleed do not require long-term antiseizure medications, since most seizures occur at the onset of the hemorrhage or in the first 24 hours. Anticonvulsants can usually be discontinued after the first month in patients who have had no further seizures.

Patients who have a seizure more than 2 weeks after the onset of an intracerebral hemorrhage are at higher risk for further seizures and may require long-term prophylactic treatment with anticonvulsants. *(Qureshi et al., 1450–1460)*

**35.** **(E)** Intracranial hemorrhage is the most common clinical presentation of arteriovenous malformation, with a reported frequency ranging from 30% to 82%. Several factors increase the risk of a first hemorrhage: a small malformation, exclusively deep venous drainage, and high intracranial pressure resulting in high pressures to the feeding arteries or restriction of venous outflow. Seizures that are not caused by hemorrhage are the initial symptom in 16% to 53% of patients. The majority of seizures are partial or complex partial; grand mal seizures account for 27% to 35% of seizures. Headache is the presenting symptom in 7% to 48% of patients, without distinctive features such as frequency, duration, or severity. Focal neurological deficits without signs of underlying hemorrhage have been reported in 1% to 40% of patients, and only a few of them (4% to 8%) have well-documented progressive neurological deficits. *(Anonymous, 1812–1818)*

**36.** **(A)** Magnetic resonance spectroscopy (MRS) is a noninvasive in vivo technique that allows the measurement of histochemical cell components. Specific cell types or structures have metabolites that give a change in proton MRS peaks that may reflect a loss of a specific cell component. The methyl resonance of N-acetyl aspartate (NAA) produces a sharp peak at 2.01 ppm. It acts as a specific neuronal marker and reflects neuronal integrity. In cases of acute ischemia, the NAA peak declines, reflecting neuronal loss. Creatine and phosphocreatine have specific MRS signals. They are found in both neurons and glial cells and act as a phosphate transporter system and energy buffer within the cell. In acute ischemic stroke, there is a reduction in the peak of creatine and phosphocreatine, reflecting the disturbance of cellular energy metabolism. The trimethylamine resonance of the choline-containing component is present in 3.2 ppm. It is a marker of cell membrane integrity. Also, in acute ischemia, the choline peak may increase, decrease, or remain unchanged. A lactate doublet peak is seen at 1.33 ppm. It is not normally detected within the brain. Its concentration rises when the glycolytic rate exceeds the tissue's capacity to catabolize or remove it from the brain and into the circulation. The presence of lactate may thus represent a perfusion mismatch and may possibly point to salvageable tissue. *(Saunders, 334–345)*

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CHAPTER 8

# Infections of the Nervous System
## Questions

**1.** Which of the following pathological features correlates best with the severity of AIDS dementia?

(A) The number of nodules containing macrophages, lymphocytes, and microglia
(B) Multinucleated giant cells
(C) Cortical atrophy
(D) Neuronal loss
(E) Macrophage activation

**2.** A 40-year-old man diagnosed with HIV-associated dementia is able to perform basic activities of self-care but cannot work or maintain the more demanding aspects of daily life. He is able to ambulate. In which stage of HIV-associated dementia Memorial Sloan Kettering (MSK clinical staging system) can the patient be classified?

(A) Stage 0
(B) Stage 1
(C) Stage 2
(D) Stage 3
(E) Stage 4

**3.** Neuropsychological tests in the initial stage of AIDS dementia may show

(A) selective memory loss; impaired retrieval
(B) severe attention deficit
(C) impaired calculation
(D) language impairment
(E) preservation of manipulation of acquired knowledge

**4.** A 35-year-old HIV-positive man consults the neurologist because of increasing difficulty walking over the last 6 months. He reports progressively worsening stiffness in his lower extremities. He has also noticed increasing urinary frequency and urgency over the last 6 months. On neurological examination, the patient displays mild paraparesis of lower extremities with spasticity and brisk reflexes in the left knee and ankle as well as bilateral Babinski signs. Sensory examination shows moderate loss of proprioception in the legs without a sensory level.

CSF (CSF) analysis shows a protein level of 63 mg/dL, WBCs at 5/$mm^3$, 100% lymphocytes, and glucose 50 mg/dL. CSF viral and bacteriologic studies are normal. Vitamin $B_{12}$ level is normal. Magnetic resonance imaging (MRI) of the cervical, thoracic, and lumbar spine with gadolinium enhancement is normal. Somatosensory evoked potentials show a prolongation of the central conduction time. The most likely diagnosis is

(A) lymphoma
(B) cytomegalovirus myelopathy
(C) AIDS-associated vacuolar myelopathy
(D) HIV myelitis
(E) bacterial paraspinal abscess

**5.** The most common type of peripheral neuropathy in AIDS patients is

(A) distal symmetric polyneuropathy
(B) acute inflammatory demyelinating polyneuropathy
(C) mononeuropathy multiplex
(D) autonomic neuropathy
(E) progressive polyradiculopathy

**6.** Which of the following drugs causes a pure sensory neuropathy as a neurotoxic side effect?

(A) Stavudine
(B) Isoniazide
(C) Vinca alkaloids
(D) Ethambutol
(E) Dapsone

**7.** Which of the following statements is true of progressive multifocal leukoencephalopathy?

(A) SV 40 virus is the most frequent cause of the disease.
(B) Approximately 50% of patients with AIDS will develop progressive multifocal leukoencephalopathy during the course of their disease.
(C) The parietooccipital region is the site of predilection for progressive multifocal leukoencephalopathy.
(D) Gait disturbance is the most frequent clinical manifestation of progressive multifocal leukoencephalopathy.
(E) Polymerase chain reaction (PCR) testing of the CSF has low specificity for the diagnosis of progressive multifocal leukoencephalopathy.

**8.** A 31-year-old right-handed man with a history of HIV infection developed headaches and right-sided weakness progressing over 1 week. Physical examination demonstrates mild right hemiparesis with increased deep tendon reflexes, right Babinski sign, and a fever of 38.5°C. MRI of the head with contrast shows a single ring-enhanced lesion in the left basal ganglia and internal capsule surrounded by edema. The lesion is hypoactive on thallium-201 single photon emission computed tomography (SPECT). The patient's CD4 lymphocyte count is 10/μL. *Toxoplasmsa gondii* serology is positive. The most appropriate approach to the treatment of this patient is to

(A) start corticosteroids alone
(B) schedule a stereotactic biopsy
(C) start radiation therapy
(D) start antitoxoplasmosis therapy without corticosteroids
(E) start empirical treatment for toxoplasmosis combined with corticosteroids

**9.** Which of the following CSF features is commonly found in cryptococcal meningitis in HIV patients?

(A) Decreased opening pressure
(B) Hypoglycorrhachia
(C) Cryptococcal antigen
(D) Increased protein
(E) Visualization of *Cryptococcus neoformans* organisms on India ink smear

**10.** The most commonly affected cranial nerve in tuberculosis in non-HIV-infected patients is the

(A) oculomotor nerve
(B) abducens nerve
(C) trochlear nerve
(D) facial nerve
(E) vestibulocochlear nerve

**11.** A 24-year-old man with a history of HIV infection consults the neurologist because of a chronic headache. Neurological examination is normal. Computed tomography (CT) scan of the head with contrast shows a ring-enhancing lesion in the left parietal area, which is confirmed by magnetic resonance imaging (MRI) of the head with gadolinium enhancement. The most appropriate diagnosis or therapeutic approach is to

(A) proceed to a biopsy to establish the diagnosis
(B) start the patient on corticosteroids
(C) start empirical antibiotic therapy
(D) start empirical antitoxoplasmosis treatment
(E) start the patient on intravenous acyclovir

**12.** The most frequent presenting symptom of primary central nervous system (CNS) lymphoma in HIV patients is

(A) impaired cognition
(B) seizures
(C) hemiparesis
(D) aphasia
(E) cranial nerve palsy

**13.** The most common cause of an intracranial space-occupying mass with contrast enhancement in AIDS patients is

(A) primary CNS lymphoma
(B) bacterial abscess
(C) fungal abscess
(D) toxoplasmosis
(E) metastatic brain tumor

**14.** The most frequent abnormal finding on retinal examination in AIDS patients is

(A) cotton-wool spots
(B) cytomegalovirus (CMV) retinitis
(C) optic atrophy
(D) swollen optic nerve
(E) toxoplasmal retinitis

**15.** The abnormal findings most frequently noted in eastern equine encephalitis are located in the

(A) brainstem
(B) cerebellum
(C) periventricular white matter
(D) basal ganglia
(E) meninges

**16.** Which of the following statements is true about subacute sclerosing panencephalitis?

(A) It is a slow CNS infection with herpes simplex virus.
(B) The onset of the disease is characterized by a rapid onset of dementia.
(C) Myoclonic jerks are seen in the second stage of the disease.
(D) Brain biopsy, if performed in the early stage of the disease, shows a mild inflammation limited to the cortex area.
(E) The electroencephalogram (EEG) normalizes in the myoclonic phase.

**17.** The most frequent cause of bacterial meningitis among children aged less than 3 months is

(A) group B *Streptococcus*
(B) *Listeria monocytogenes*
(C) *Streptococcus pneumoniae*
(D) *Haemophilus influenzae*
(E) *Neisseria meningitides*

**18.** Which of the following is true of leprosy?

(A) *Mycobacterium leprae* has a preference for body parts with higher temperature than the core body.
(B) Loss of light touch is the first manifestation of sensory impairment.
(C) Peripheral nerve thickening results from bacterial multiplication within the neuron.
(D) The median nerve is the most frequently affected peripheral nerve in tuberculoid leprosy.
(E) Impaired cell-mediated immunity causes lepromatous leprosy.

**19.** Which of the following is true of botulism?

(A) Toxin production by *Clostridium botulinum* colonizing the gut is the most frequent cause of adult botulism.
(B) Botulism toxin blocks acetylcholine receptors.
(C) The N-terminal of the heavy chain of botulinum toxin governs the internalization of the toxin into the motor neuron.
(D) Cognition is usually affected in the early stage of the disease.
(E) Sensory examination is typically altered.

**20.** Which of the following is true of tetanus?

(A) Tetanospasmin inhibits glutamate release in the spinal cord.
(B) Tetanus toxin travels to the anterior horn cells by retrograde axonal transport.
(C) The heavy chain of tetanus toxin blocks exocytosis.
(D) Spasms are caused by sympathetic blockade.
(E) Autonomic dysfunction rarely complicates the course of the disease.

**21.** The most common cause of viral encephalitis in the United States is

(A) arbovirus
(B) herpesvirus
(C) measles virus
(D) mumps virus
(E) enterovirus

**22.** Repetitive sharp wave complexes over the temporal lobe are commonly seen in

(A) HIV encephalitis
(B) subacute sclerosing panencephalitis
(C) herpes simplex encephalitis
(D) Creutzfeldt–Jakob disease
(E) renal failure

**23.** The most frequent neurological manifestation of poliovirus infection is

(A) transverse myelitis
(B) paralytic illness
(C) cerebellitis
(D) aseptic meningitis
(E) seizures

**24.** The most likely cause of bacterial meningitis in a 40-year-old man with a history of splenectomy is

(A) *Streptococcus pneumoniae*
(B) *Haemophilus influenzae* type b
(C) *Staphylococcus aureus*
(D) *Acinetobacter calcoaceticus*
(E) *Listeria monocytogenes*

**25.** The most likely cause of bacterial meningitis in a 56-year-old man with a history of heavy ethanol abuse is

(A) *Streptococcus pneumoniae*
(B) *Haemophilus influenzae* type b
(C) *Staphylococcus aureus*
(D) *Acinetobacter calcoaceticus*
(E) *Listeria monocytogenes*

**26.** The most likely cause of bacterial meningitis in a 60-year-old woman with a history of heart transplantation is

(A) *Streptococcus pneumoniae*
(B) *Haemophilus influenzae* type b
(C) *Staphylococcus aureus*
(D) *Acinetobacter calcoaceticus*
(E) *Listeria monocytogenes*

**27.** The most common cause of bacterial meningitis in an immunocompetent adult is

(A) *Streptococcus pneumoniae*
(B) *Haemophilus influenzae* type b
(C) *Staphylococcus aureus*
(D) *Acinetobacter calcoaceticus*
(E) *Listeria monocytogenes*

**28.** The most likely cause of bacterial meningitis in a 40-year-old man 2 days after undergoing a ventriculostomy is

(A) *Streptococcus pneumoniae*
(B) *Haemophilus influenzae* type b
(C) *Staphylococcus aureus*
(D) *Acinetobacter calcoaceticus*
(E) *Listeria monocytogenes*

**29.** What is the most appropriate antibiotic therapy for the treatment of hospital-acquired meningitis in a 55-year-old man with severe neutropenia?

(A) Ceftriaxone 2 gr every 12 hours
(B) Vancomycin 0.5 gr every 6 hours and ampicillin 2 gr every 4 hours
(C) Cefotaxime 2 gr every 4 hours and vancomycin 0.5 gr every 6 hours
(D) Vancomycin 0.5 gr every 6 hours and ceftazidine 2 gr every 8 hours
(E) Ampicillin 2 gr every 4 hours and gentamicin 6 mg/kg per day

**30.** The presence of "owl eye" intranuclear inclusions, with focal necrosis in the basal ganglia and thalamus is highly suggestive of

(A) herpes encephalitis
(B) CMV encephalitis
(C) Epstein–Barr meningoencephalitis
(D) varicella zoster encephalitis
(E) La Crosse virus encephalitis

**31.** The most frequent cause of viral meningitis is

(A) enterovirus
(B) CMV virus
(C) herpesvirus
(D) arbovirus
(E) West Nile virus

**32.** The most common cause of epidural abscess in immunocompetent patients is

(A) *Klebsiella pneumoniae*
(B) *Staphylococcus*
(C) *Streptococcus*
(D) fungal infection
(E) *Mycobacterium tuberculosis*

**33.** The most frequent sign of neurocysticercosis is

(A) seizure
(B) headache
(C) visual disturbance
(D) hemiplegia
(E) ataxia

**34.** The most common neurological complication of chronic Chagas infection is

(A) seizure
(B) irritability
(C) stupor
(D) dementia
(E) cardioembolic stroke

**35.** Which of the following HIV complications is the *least* affected by antiretroviral therapy?

(A) Progressive multifocal leukoencephalopathy
(B) AIDS dementia
(C) CNS toxoplasmosis
(D) Cryptococcal meningitis
(E) CMV polyradiculopathy

**36.** Hemorrhagic meningitis is caused by the organism leading to

(A) botulism
(B) brucellosis
(C) Q fever
(D) anthrax
(E) Venezuelan equine encephalitis

**37.** Which of the following statements is true about Creutzfeldt–Jakob disease?

(A) The cerebrospinal fluid (CSF) opening pressure is usually high.
(B) CSF protein 14-3-3 has a high sensitivity and specificity for patients with the diagnosis of progressive dementia.
(C) The CSF protein level is higher than 100 mg/dL.
(D) Brain MRI may show hypersignal in the internal capsule in 80% of cases.
(E) Early in the course of the disease, the EEG usually shows triphasic synchronous sharp-wave complexes.

**38.** Which of the following statements is true of varicella zoster virus?

(A) The virus can be cultured from human ganglia during the latent period.
(B) Neurons are the primary site of the latent virus.
(C) The incidence of recurrent zoster is around 30%.
(D) The abducens cranial nerve is the cranial nerve most commonly affected by varicella zoster virus.
(E) Facial Ramsay–Hunt syndrome has a better prognosis for recovery than Bell's palsy.

**39.** Which of the following is true of fatal insomnia?

(A) Cognitive function is affected early in the course of the disease.
(B) EEG typically shows periodic discharges.
(C) The absence of spongiform changes on neuropathology excludes the diagnosis.
(D) PET scan shows decreased blood flow in the thalamus early in the course of the disease.
(E) Sleep studies are not necessary for the diagnosis of fatal insomnia as the disease is always clinically obvious.

**40.** Which of the following is true of Japanese encephalitis?

(A) The disease is limited to the pediatric population.
(B) Ninety percent of patients affected by Japanese encephalitis will recover fully.
(C) The thalamus and basal ganglia are the sites of intense inflammation in affected patients.
(D) Serologic tests in Japanese encephalitis have a low sensitivity and specificity.
(E) A progressive ascending paralysis is the most frequent form of Japanese encephalitis seen in children.

**41.** A 40-year-old man developed progressive worsening of anxiety and depressed mood, with auditory and visual hallucinations. Neurological examination demonstrated mild bilateral cerebellar syndrome. His clinical status deteriorated progressively over the next 13 months, with decreased cognitive function and chorea followed by myoclonus. The most likely diagnosis is

(A) Creutzfeldt–Jakob diseas
(B) Gerstmann–Straussler–Scheinker (GSS) disease
(C) Kuru
(D) variant Creutzfeldt–Jakob disease
(E) none of the above

**42.** A 20-year-old man died after 12 months of progressive cerebellar ataxia without alteration of the cognitive function until the late stage of the disease, when the patient was obtunded. The most likely diagnosis is

(A) Creutzfeldt–Jakob disease
(B) GSS disease
(C) Kuru
(D) variant Creutzfeldt–Jakob disease
(E) none of the above

**43.** A 60-year-old woman developed a progressive onset of fatigue, insomnia, and ill-defined pain over several weeks. This was followed by progressive mental deterioration and myoclonus. Neurological examination demonstrated cerebellar ataxia and bilateral pyramidal syndrome. Over the next 3 months, the patient progressed to akinetic mutism. She died 5 months after the onset of symptoms. The most likely diagnosis is

(A) Creutzfeldt–Jakob disease
(B) GSS disease
(C) Kuru
(D) variant Creutzfeldt–Jakob disease
(E) none of the above

**44.** A 40-year-old man died after 4 years of progressive cerebellar ataxia, pyramidal syndrome, and dementia. Postmortem examination showed an abundant prion protein (PrP), amyloid plaques in cerebral and cerebellar cortexes, as well as multicentric prion–protein amyloid plaques. The most likely diagnosis is

(A) Creutzfeldt–Jakob disease
(B) GSS disease
(C) Kuru
(D) variant Creutzfeldt–Jakob disease
(E) none of the above

**45.** The most common cause of brain abscess in immunocompetent patients is

(A) anaerobic bacteria
(B) *Staphylococcus aureus*
(C) fungi
(D) *Pseudomonas aeruginosa*
(E) protozoa

**46.** The gold standard method for the diagnosis of herpes encephalitis is

(A) brain MRI
(B) brain MRI spectroscopy
(C) brain biopsy
(D) polymerase chain reaction (PCR) testing of the CSF for herpes DNA
(E) culture of the herpesvirus in the CSF

**47.** The most common cause of spinal epidural abscess is

(A) *Staphylococcus aureus*
(B) *Candida albicans*
(C) *Salmonella*

(D) *Nocardia asteroides*
(E) *Escherichia coli*

**48.** Which of the following is a classic CSF abnormality in tuberculous meningitis?

(A) Hemorrhagic CSF
(B) Low CSF opening pressure
(C) Lymphocytic pleocytosis
(D) Elevated CSF glucose concentration
(E) Normal CSF protein concentration

**49.** The most frequent cause of viral meningitis is

(A) La Crosse virus
(B) West Nile virus
(C) echovirus
(D) herpes simplex virus
(E) mumps virus

**50.** The most common neurological complication of HIV infection is

(A) seizure
(B) CNS toxoplasmosis
(C) myelopathy
(D) distal sensory polyneuropathy
(E) progressive multifocal leukoencephalopathy

# Answers and Explanations

1. **(E)** Cerebral atrophy involving the frontotemporal areas is a common finding in patients with HIV dementia. It does not correlate with the severity of the dementia. Multiple microglial nodules containing macrophages, lymphocytes, and microglia may be seen in HIV dementia. Scattered in the gray and white matter of the brain, they are more common in the white matter, subcortical gray of the thalamus, basal ganglia, and brainstem. They are not specific to HIV dementia and do not correlate with its severity. Other neuropathological findings include neuronal loss, dendritic changes, myelin pallor (which corresponds to changes of the blood–brain barrier), and multinucleated giant cells. The presence of these cells correlates with the degree of dementia and the detection of HIV-1 DNA. However, the intensity of macrophage activation does appear to correlate best with the severity of dementia. *(Glass, 2230–2237; Glass, 755–762)*

2. **(C)** In 1988, Price and colleagues developed the following clinical staging of the severity of HIV-associated dementia:

   - Stage 0: normal mental and motor function.
   - Stage 0.5 (equivocal subclinical): absent, minimal, or equivocal symptoms without impairment of work or capacity to perform activities of daily life. Mild signs such as snout response, slowed ocular, or extremity movements may be present. Gait and strength are normal.
   - Stage 1 (mild severity): ability to perform all but the most demanding activities of daily life with unequivocal evidence of functional intellectual or motor impairment. The patient can walk without assistance.
   - Stage 2 (moderate severity): ability to perform basic activities of self-care but cannot work or maintain the more demanding aspects of daily life. The patient may ambulate independently.
   - Stage 3 (severe disability): major intellectual or motor incapacity.
   - Stage 4: nearly vegetative status. *(Price and Brew, 1079–1083)*

3. **(B)** Neuropsychological testing adds to the neurological evaluation of suspected HIV dementia by virtue of being sensitive to mild or early symptoms of HIV-related cognitive impairment. In addition to quantifying the severity of any cognitive symptoms, it can also provide information regarding the overall pattern of cognitive impairment. Attention, calculation, and language are not usually affected in HIV dementia in its initial stage, fitting with the subcortical pattern of involvement. Impaired memory (verbal and nonverbal), impaired manipulation of acquired knowledge, memory loss selective for impaired retrieval, and deficits in psychomotor speed are characteristic of HIV dementia and are typically more severe than deficits in other cognitive domains. *(McArthur, 129–150)*

4. **(C)** The patient described in the vignette demonstrates clinical evidence of an insidiously progressive thoracic or high lumbar myelopathy because of the spastic paraparesis, bladder dysfunction, and corticospinal and posterior column signs without a sensory level and normal spinal cord MRI. The differential diagnosis includes:

   - CMV myelopathy: a rare cause of myelopathy in HIV patients. It usually presents as an acute

or subacute radiculomyelitis involving the lower lumbar sacral roots and cauda equina. It is characterized clinically by the acute or subacute development of a flaccid paraplegia and incontinence. The patient in this case did not have signs of radiculopathy and had slow progression of his symptoms, which make the diagnosis of CMV myelopathy unlikely.

- HIV myelitis may appear as an acute or subacute complication of AIDS. A rare complication of AIDS, it is characterized by features of transverse myelitis with CSF pleocytosis. It is unlikely to be the diagnosis in this clinical case considering the clinical picture, especially the CSF results.
- AIDS-associated vacuolar myelopathy is a slowly progressive disease of the spinal cord. It is prevalent in more than 30% in pathological series, although only a minority of these patients are symptomatic. Pathological features of the disease include the presence of intramyelinic and periaxonal vacuoles in the lateral and posterior columns of the spinal cord. It appears late in the course of the illness. The patient may report erectile or bladder dysfunction and mild paraparesis in the early stage of the disease. Neurological examination typically demonstrates a spastic asymmetric paraparesis, increased deep tendon reflexes in the lower extremities, hyperreflexia, and the absence of a sensory level. MRI may be normal or may show atrophy of the thoracic and cervical spinal cord. CSF examination may show mild pleocytosis or increased protein level. Somatosensory evoked potentials may show increased central conduction time. The patient described in the vignette does have signs of AIDS-associated vacuolar myelopathy.
- Other causes of lower extremity weakness in HIV patients—such as syphilis, tuberculosis, cryptococcosis, aspergillosis, vitamin $B_{12}$ or folate deficiency, and lymphoma—are unlikely to be the diagnosis in this case considering the clinical features and the results of ancillary tests. *(DiRocco, 151–155)*

**5. (A)** Distal symmetric polyneuropathy is the most common form of peripheral neuropathy in HIV-infected patients. The proposed mechanisms of this neuropathy include direct HIV infection, injury from cytokine effects, metabolic abnormalities, or the medications used to control the HIV infection. *(Simpson, 769–785)*

**6. (A)** Toxicity from drugs used to treat HIV infection is among the major causes of peripheral neuropathy in these patients. Didanosine, stavudine, and zalcitabine are antiretroviral drugs that may cause a sensory neuropathy. Isoniazid and ethambutol cause sensorimotor neuropathy. Vinca alkaloids and dapsone cause a mixed motor more than a sensory neuropathy. *(Simpson, 769–785)*

**7. (C)** Progressive multifocal leukoencephalopathy was initially described on the basis of its distinctive neuropathological features of demyelination, giant astrocytes, and oligodendrocytes with abnormal nuclei. Subsequently, a papovavirus referred to as JC virus was identified in affected oligodendrocytes and astrocytes. JC virus infection typically remains latent until there is impairment of cellular immunity. Approximately 5% of all AIDS patients will develop progressive multifocal leukoencephalopathy. Its clinical manifestations are dependent on the location of the infection. Hemiparesis is the most common clinical manifestation of progressive multifocal leukoencephalopathy in AIDS patients. Other common clinical manifestations are gait disturbance, speech and language disorders, cognitive dysfunction, and cortical blindness. MRI of the head is the most sensitive technique to show the demyelinating lesion involving the white matter in the subcortical U fibers with a predilection for the parietooccipital areas. The lesions are not typically enhancing, although up to 9% may have peripheral enhancement around them. PCR of the CSF for the diagnosis of progressive multifocal leukoencephalopathy has high sensitivity and specificity that reaches 100%. The prognosis of progressive multifocal leukoencephalopathy is ominous. Death occurs between 1 and 18 months after the onset of symptoms. *(Berger, 59–68)*

**8. (D)** In this vignette, the differential diagnosis is of a single brain lesion in an HIV patient with positive toxoplasmosis serology. The main differential diagnoses are toxoplasmosis encephalitis and

primary CNS lymphoma. Although this patient's head MRI does not present the classic multiple space-occupying enhancing lesions of toxoplasmosis encephalitis, the combination of a positive serology of toxoplasmosis, a CD4+ cell count of less than 200/μL, and decreased thallium-201 SPECT imaging that is more suggestive of toxoplasmosis encephalitis than lymphoma. The recommendations of the American Academy of Neurology Qualified Standards Subcommittee are to institute empirical antibiotic therapy for the presumptive toxoplasmosis and obtain a follow-up imaging study. If the patient shows a clinical and radiological response to this treatment, he or she can be presumed to have CNS toxoplasmosis. The patient should be maintained on suppressive antibiotics for life after finishing the induction therapy. If the patient does not show improvement on antibiotics after 2 weeks, he or she is eligible for stereotactic biopsy. The empirical use of corticosteroids is not recommended for toxoplasmosis treatment. The addition of corticosteroids has not been shown to improve neurological outcome and may interfere with the assessment of a possible primary CNS lymphoma. *(Anonymous, 21–26)*

**9.** **(A)** CSF abnormalities in cryptococcal meningitis in HIV patients may be subtle. The opening pressure is elevated in two thirds of cases and may exceed 400 mm $H_2O$. Mild pleocytosis is seen in 6% to 30% of cases. Hypoglycorrhachia is found in 8% to 76% of cases. Increased protein is observed in 35% to 70% of cases. Visualization of organisms on India ink smear is seen in 72% to 94% of cases. Successful culture of *C. neoformans* in and visualization of cryptococcal antigen in the CSF may be seen in up to 100% of cases. *(Churck, 794–799)*

**10.** **(B)** Cranial nerves are affected in 15% to 40% of immunocompetent patients with tuberculosis. The abducens nerve is the most commonly affected, followed in descending order by the oculomotor, trochlear, facial, optic, vestibulocochlear, vagus, accessory, and hypoglossal nerves. *(Lincoln, 807–823)*

**11.** **(D)** The presence of a ring-enhancing mass on CT scan of the head in an HIV patient should raise the possibility of CNS toxoplasmosis. The diagnostic workup should include a toxoplasmosis antibody titer of the serum and the CSF; also, if possible, a thallium SPECT study should be done to rule out a hyperactive lesion (more suggestive of lymphoma). The most appropriate therapeutic approach is to start the patient on antitoxoplasmosis therapy for 2 weeks and thereafter assess the patient clinically and radiologically. In case of improvement, the patient should be maintained on prophylactic antibiotics for life after completion of the induction therapy. If there is no improvement, stereotactic biopsy should be considered. The use of corticosteroids has not been shown to be beneficial for the treatment of CNS toxoplasmosis and may delay the diagnosis of primary CNS lymphoma. It should be used with caution and rapidly tapered. *(Luft, 211–222)*

**12.** **(A)** The most frequent presenting symptom of central nervous lymphoma is cognitive or mental status impairment, which is seen in 60% of cases. Hemiparesis or aphasia is seen in 35% of cases. Seizures are seen in 15% of cases at presentation. Cranial nerve palsy is seen in only 10% of cases at presentation. *(Baumgartner, 206–211)*

**13.** **(D)** Toxoplasmosis is the most common cause of an intracranial space-occupying mass in AIDS patients, followed by primary CNS lymphoma. Toxoplasmosis lesions are most frequently found in the cerebral cortex, basal ganglia, and gray–white matter junction. *(Chinn, 694–654)*

**14.** **(A)** The most frequent retinal lesion in AIDS patients is cotton-wool spots, seen in 75% of these cases. It is a buildup of exoplasmic material at the site of a nerve fiber layer infarct. When these spots are coupled with hemorrhage or capillary abnormalities, it is called AIDS retinopathy. Axonal loss in the optic nerve has been estimated at 40% in patients dying from AIDS in the absence of opportunistic infection of the retina. CMV retinitis may affect 25% to 35% of patients with AIDS. Toxoplasmosis retinitis, optic atrophy, and optic edema are less frequently seen. *(Gagliuso, 63–86)*

**15.** **(D)** Eastern equine encephalitis is a life-threatening mosquito-borne arboviral infection found

principally along the East and Gulf Coasts of the United States. Cases have occurred sporadically and in small epidemics. Diagnosing eastern equine encephalitis is difficult because its symptoms are nonspecific and confirmation requires either specific serologic findings or the isolation of the virus in CSF or brain tissue. Neuroradiographic abnormalities are common and best visualized by MRI. The abnormal findings include focal lesions in the basal ganglia (found in 71% of patients on MRI and in 56% on CT), thalami (found in 71% on MRI and in 25% on CT), and brain stem (found in 43% on MRI and in 9% on CT). Periventricular white matter changes and cortical lesions as well as meningeal enhancement are less common. *(Deresiewicz et al., 1867–1874)*

**16.** **(C)** Subacute sclerosing panencephalitis (SSPE) is a slowly progressing CNS infection caused by measles virus that results in progressive inflammation and sclerosis of the brain. The incidence of the disease in the United States fell from 0.61 case per million for persons under the age of 20 years to 0.06 case in 1980, most likely related to measles vaccination. Patients with subacute sclerosing panencephalitis generally have a history of typical measles with full recovery. The symptoms of SSPE follow on average by about 7 years. The clinical course of the disease is divided arbitrarily into four stages. Its onset is usually insidious, marked by subtle changes in behavior and deterioration of school or work, followed by a frank dementia. The appearance of massive repetitive myoclonic jerks marks the onset of stage 2 of the disease. Cerebellar ataxia, dystonia, retinopathy, and optic atrophy may appear. As the disease progresses, the myoclonic jerks tend to disappear, while the dementia progresses to stupor and coma. Death occurs after a mean of 18 months. Brain biopsy in the early stages may show mild inflammation of the meninges and a panencephalitis involving cortical and subcortical gray as well as white matter. EEG is useful in supporting the diagnosis of SSPE. Early in the course of the disease, it may be normal or show moderate nonspecific slowing. In the myoclonic phase, the EEG shows suppression-burst episodes. Later in the course of the disease, the EEG becomes increasingly disorganized, with high amplitude and random dysrhythmic slowing. *(Garg, 63–70)*

**17.** **(A)** The likelihood of infection with a specific pathogen in cases of bacterial meningitis is related in large part to the age of the patient. Group B *Streptococcus* is the most frequent pathogen among immunocompetent patients aged less than 3 months. *Neisseria meningitidis* is the predominant pathogen among children aged 2 to 18 years, and *Streptococcus pneumoniae* is most likely among adults. *(Schuchat, 970–976)*

**18.** **(E)** Leprosy, a primary peripheral nerve and skin infection, is caused by the acid-fast bacterium *Mycobacterium leprae*. *M. leprae* has a preference for parts of the body with a temperature of 7°C to 10°C lower than the core body temperature. It has a long incubation period, between 6 months and 40 years. Sensory impairment proceeds in a predictable sequence, with loss of temperature sensation first, followed by pain and then touch. Vibration and proprioception are spared. Impaired cell-mediated immunity causes lepromatous leprosy, a more disseminated infection than the tuberculoid leprosy of patients with conserved cellular immunity. Nerve damage results from bacterial multiplication within Schwann cells or granulomatous damage to the perineurium. The ulnar nerve is the most frequently affected in cases of tuberculoid leprosy. *(Bradley, 1332–1334)*

**19.** **(C)** Botulism is caused by the blockade of peripheral cholinergic transmission by a neurotoxin (secreted by *Clostridium botulinum*). It can be acquired either by contaminated food or by an infected wound spreading the toxin in the bloodstream. Gut colonization by *C. botulinum* causes infantile botulism and less commonly adult botulism. Botulinum toxin blocks acetylcholine release from the presynaptic membrane, leading to the paralytic and autonomic symptoms. Botulinum toxin is formed by heavy and light chains. The C-terminal region of the heavy chain binds tightly and specifically to the presynaptic membrane, whereas the N-terminal domain governs internalization of the toxin into the motor neuron, which protects the toxin from neutralizing antibodies. After translocation into the cytosol,

the liberated light chain (a zinc endopeptidase) targets various protein-mediating exocytoses, causing irreversible blockade at peripheral cholinergic synapses. The early symptoms of botulism include diplopia, ptosis, dysarthria, and dysphagia. Respiratory muscles as well as extraocular and limb muscles are affected symmetrically. Cognitive function is conserved unless there are metabolic changes from respiratory failure. Sensation is typically normal. Reflexes are decreased or absent. *(Bradley, 1384)*

**20.** **(B)** *Clostridium tetani* secretes tetanospasmin, a neurotoxin that inhibits the release of GABA and glycine (which are inhibitory neurotransmitters) in the brainstem and spinal cord. Tetanus neurotoxin is formed by heavy and light chains linked together by a disulfide bond. The light chain, a zinc endopeptidase, is responsible for blocking exocytosis. Tetanus neurotoxin travels to the anterior horn cells of the spinal cord by retrograde axonal transport, penetrates the intrasynaptic space, and enters inhibitory neurons. Impaired exocytosis in these spinal inhibitory neurons and in the intermediolateral column of the spinal cord causes muscle contractions and autonomic dysfunction, respectively. The cardinal clinical features of tetanus include muscle rigidity and spasms, which may be triggered by a sensory stimulus, movement, or emotion. Autonomic dysfunction is frequent in tetanus and includes fever, tachycardia, hypertension, and other signs of sympathetic irritation. *(Bradley, 1340–1342)*

**21.** **(B)** The most common cause of focal viral encephalitis in the United States is herpes simplex virus type 1. Other causes of viral encephalitis are varicella zoster virus (VZV), enterovirus, mumps, measles, and Lacrosse virus. *(Bradley, 1358–1359)*

**22.** **(C)** The EEG in acute viral encephalitis may show patterns suggesting a specific diagnosis. Repetitive sharp-wave complexes over the temporal lobes or periodic lateralized epileptiform discharges are recorded in herpes simplex type 1 encephalitis and rare cases of infectious mononucleosis encephalitis. Periodic slow-wave complexes occur in subacute sclerosing panencephalitis. Triphasic waves at higher periodic frequency are seen in Creutzfeldt–Jakob disease. *(Bradley, 1358)*

**23.** **(D)** Poliovirus one of the most virulent members of the enterovirus group, is the causative agent of acute anterior poliomyelitis. It has a tropism for motor neurons of the spinal cord and brainstem. The most frequent clinical manifestation of poliovirus is aseptic meningitis (seen in 8% of cases). Paralytic illness is seen in 1% of all cases. Other less frequent clinical manifestations include cerebellitis, transverse myelitis, and facial paresis. *(Bradley, 1991–1994)*

**24.** **(B)** *Haemophilus influenzae* type b causes meningitis in immunocompromised patients (e.g., postsplenectomy and in chronic lung diseases). *(Roos, 1–2; 2002)*

**25.** **(D)** *Acinetobacter calcoaceticus* and other gram-negative bacilli cause meningitis in alcoholic patients. *(Roos, 1–2; 2002)*

**26.** **(E)** *Listeria monocytogenes* causes meningitis in immunosuppressed patients (e.g., after organ transplantation). *(Roos, 1–2; 2002)*

**27.** **(A)** The most common causative organisms of community-acquired bacterial meningitis are *Streptococcus pneumoniae* and *Neisseria meningitidis*. *(Roos, 1–2; 2002)*

**28.** **(C)** *Staphylococcus aureus* causes meningitis following invasive neurosurgical procedures such as ventriculostomy. *(Roos, 1–2; 2002)*

**29.** **(D)** Bacterial meningitis is a medical emergency. The goal is to begin antibiotic therapy within 60 minutes of a patient's arrival in the emergency room. Empiric antimicrobial therapy is initiated in patients with suspected bacterial meningitis before the results of CSF Gram's stain and culture are known. *S. pneumoniae* and *N. meningitidis* are the most common etiological organisms of community-acquired bacterial meningitis. Because resistant *S. pneumonia* appeared after the development of penicillin,

empiric therapy of community-acquired bacterial meningitis should include a third-generation cephalosporin (e.g., ceftriaxone or cefotaxime) or a fourth-generation cephalosporin (cefepime) and vancomycin. Ampicillin and gentamicin should be added to the empiric regimen for coverage of *Listeria monocytogenes* in individuals with impaired cell-mediated immunity due to chronic illness, organ transplantation, pregnancy, AIDS, malignancies, or immunosuppressive therapy. In hospital-acquired meningitis and particularly meningitis following neurosurgical procedures, staphylococci and gram-negative organisms (including *P. aeruginosa*), are the most common etiological organisms. In these patients, empiric therapy should include a combination of vancomycin and ceftazidime. Ceftazidime should be substituted for ceftriaxone or cefotaxime in neurosurgical patients and in neutropenic patients, as *P. aeruginosa* may be the meningeal pathogen, and ceftazidime is the only cephalosporin with sufficient activity against *P. aeruginosa* in the CNS. *(Roos, 7–10; 2005)*

**30. (B)** CMV meningoencephalitis is largely a disease of congenitally infected newborns and immunocompromised individuals, including organ transplant recipients and those with advanced HIV infection. In immunocompromised individuals, infection results predominantly from reactivation of latent virus. It is generally associated with evidence of CMV infection in other organs, including the eye, lungs, gastrointestinal tract, and other organs. In individuals infected with AIDS, CMV can produce multifocal CNS disease with involvement of the spinal cord, nerve roots, ventricular and subependymal regions, and both gray and white matter. Infection often shows a predilection for deep gray structures, including basal ganglia and thalamus, producing regions of focal necrosis and hemorrhage. Microglial nodules (dense focal aggregates of microglial cells and macrophages) and Cowdry type A intranuclear inclusions are characteristic of CMV, although both are seen in a variety of other infections. "Owl's eye" inclusions (large basophilic intranuclear inclusions separated from the nuclear membrane by a thin halo) are virtually diagnostic of CMV infection. *(McCutchan, 747–754)*

**31. (A)** Enteroviruses are responsible for the overwhelming majority (85% to 95%) of cases of acute viral meningitis. Less commonly, enteroviruses produce encephalitis or polio-like flaccid paralysis. Most infections occur in the summer and early fall (May through October), although sporadic cases occur all year round. Children are more frequently infected than adults, although infections in older individuals tend to be more severe. *(Rotbart, 971–981)*

**32. (B)** *Staphylococcus aureus* has been traditionally and remains the main pathogen in epidural abscess, accounting for over 60% of the isolates. Other gram-positive pathogens that may cause epidural abscess less frequently include *Staphylococcus epidermidis*, streptococci (alpha and beta hemolytic), and anaerobes. Gram-negative pathogens are increasing in frequency (second to *Staphylococcus*), perhaps reflecting an increasing proportion of iatrogenic infections. *Mycobacterium tuberculosis* and pathogenic fungi also account for a significant percentage of cases. *(Bradley, 1238–1329)*

**33. (A)** Neurocysticercosis infection is pleomorphic owing to individual differences in the number and location of lesions and in the severity of the host's immune response to the parasites. Seizures are the most common clinical manifestation of the disease, occurring in more than 70% of cases. Indeed, in endemic regions, the presence of adult-onset epilepsy is highly suggestive of neurocysticercosis. Focal neurological signs (pyramidal tract signs, sensory deficits, cerebellar ataxia, signs of brainstem dysfunction, and involuntary movements) occur in 20% to 30% of patients with neurocysticercosis. These manifestations usually follow a subacute or chronic course, making the differential diagnosis with neoplasms or other infections of the CNS difficult on clinical grounds. However, focal signs may occur abruptly in patients who develop a cerebral infarct as a complication of cysticercotic angiitis. Some patients present with intracranial hypertension that may be associated with seizures, focal neurological signs, or intellectual deterioration. Hydrocephalus is the most common cause of this syndrome. In these cases, clinical manifestations have a

subacute onset and a slowly progressive course that may be punctuated by episodes of sudden loss of consciousness related to movements of the head when the cause of hydrocephalus is a fourth ventricle cyst. Intracranial hypertension also occurs in patients with cysticercotic encephalitis, a severe form of the disease resulting from a massive cysticercal infection of the brain parenchyma that induces an intense immune response from the host. *(Bradley, 1392–1393)*

**34.** **(E)** Acute Chagas disease is usually characterized by an inoculation chagoma in the orbital region (Romaña's sign) and mild constitutional symptoms. However, some children, HIV-infected individuals, and immunosuppressed patients may develop severe encephalitis during the acute phase of the disease. Chagasic encephalitis is characterized by irritability, stupor progressing to coma, seizures, focal neurological signs (related to granuloma formation), and a mononuclear pleocytosis in the CSF. Most of these patients die during the acute disease, and survivors are usually left with epilepsy and intellectual impairment. In patients with chronic infection, the most common neurologic complication is a cardioembolic stroke related to the development of cardiac arrhythmias or ventricular aneurysms. The territory of the middle cerebral artery is the most frequently affected, and infarcts may be located in the parietal, frontal, and temporal lobes or in the basal ganglia. The actual prevalence of stroke in Chagas disease is unknown; however, some studies have shown that between 9% and 36% of patients with chagasic cardiomyopathy develop a cerebral infarct. *(Bradley, 1392–1393)*

**35.** **(B)** Potent antiretroviral therapy may be less effective in preventing HIV-1–associated dementia than other HIV-1-related complications. A study from Australia compared the effect of highly active antiretroviral therapy (HAART) against AIDS dementia complex (ADC) relative to its effect on other initial AIDS-defining illnesses (ADIs). The study demonstrated a proportional increase in ADC compared with other ADIs. A marked increase in the median CD4 cell count at ADC diagnosis has occurred since the introduction of HAART in Australia. Poor penetration of antiretroviral medication in the CNS is suggested by the study as a possible explanation for the modest impact of HAART on ADC. *(Dore, 1249–1253)*

**36.** **(D)** Anthrax meningitis is a rare complication that can occur with any form of anthrax. Meningeal symptoms are usually accompanied by fever, myalgias and vomiting and less frequently by seizures or delirium. The CSF is typically hemorrhagic and culture for *Bacillus anthracis* is positive. Imaging of the CNS may reveal subarachnoid, intracerebral, or intraventricular hemorrhage with leptomeningeal enhancement, while pathology reveals hemorrhage of the leptomeninges known as a "cardinal's cap."

Brucellosis is associated with low back pain in 60% of infected people and can be associated with vertebral osteomyelitis, intervertebral disk infection, sacroiliac infection, or paravertebral abscess. The nervous system is involved in approximately 5% of people with brucellosis; the condition is then referred to as neurobrucellosis. Acute neurobrucellosis typically includes symptoms of meningeal irritation and may be accompanied by seizures or coma. Chronic neurobrucellosis may include meningoencephalitis, demyelination, cranial neuropathy (most often involving the vestibulocochlear nerve), myeloradiculitis, or cerebral arteritis. The CSF examination in neurobrucellosis almost always reveals a moderate elevation of protein and a lymphocytic pleocytosis.

Severe headache is present in most people with symptomatic Q fever, but infection of the nervous system is uncommon. Infection of the CNS usually manifests as an acute aseptic meningitis and/or encephalitis and may be accompanied by cranial nerve palsy, seizures, mental status change, or coma. Examination of the CSF typically reveals a pleocytosis (usually lymphocytic, but it can also be neutrophilic) in 50% of patients as well as an elevated protein and negative bacterial culture in nearly all patients. Neuroimaging may reveal hypodense lesions in the subcortical white matter.

Botulism typically presents with bilateral cranial nerve palsies and symmetric descending paralysis. Symptoms often include blurred vision, diplopia, dry mouth and throat, dysphagia, and dysphonia. Sensory deficits do not

occur. Deep tendon reflexes may be present or absent. Respiratory failure is a common complication. CSF examination should be normal. Venezuelan equine encephalitis (VEE) causes encephalitis in only 4% of children and less than 1% of adults, and typically occurs after a few days or a week of prodromal illness. CSF examination typically reveals a lymphocytic pleocytosis. *(Bradley, 1346)*

**37. (B)** Study of the CSF in Creutzfeldt–Jakob disease shows that it has a normal opening pressure, does not have an increase in cells or abnormal levels of immunoglobulin, and has a normal or mildly elevated protein content. Partial sequencing of these proteins has shown that they matched a normal brain protein known as 14-3-3, and a rapid CSF immunoassay for the protein has proved useful in the diagnosis. The sensitivity of the test is 96% and the specificity is 99%. Elevated levels of this protein are found in the CSF of patients with viral encephalitis and during the first month after a cerebrovascular accident. Early in the course of the disease, the EEG may be normal or show nonspecific slowing. Later in the disease, periodic biphasic or triphasic synchronous sharp-wave complexes are superimposed on a slow background rhythm in most patients, but these characteristic complexes may disappear as the myoclonus subsides in the terminal phase of the disease. The results of brain imaging are usually normal in the early stages of the disease. MRI may show hyperintense signals in the basal ganglia on T2-weighted images. *(Johnson, 1994)*

**38. (B)** After it has produced chickenpox, VZV becomes latent in ganglia along the entire neuraxis. The virus cannot be cultured from human ganglia, although viral DNA was detected by PCR in human trigeminal and thoracic ganglia. Most studies indicate that neurons are the primary or possibly exclusive site of latent virus. Other studies have detected the presence of the virus in the perineuronal satellite cells. The incidence of recurrent zoster in immunocompetent patients is less than 5%. The trigeminal nerve is the most common cranial nerve affected by VZV. When the ophthalmic division of the trigeminal nerve is affected, it is frequently accompanied by keratitis, which is a potential cause of blindness if not recognized and treated promptly. When the seventh cranial nerve is involved, there is weakness of all facial muscles on one side, along with rash in the ipsilateral external ear (zoster oticus) or hard palate. Zoster oticus and peripheral facial weakness together constitute the Ramsay–Hunt syndrome. Recovery from facial weakness or paralysis is reported to be less complete than in idiopathic Bell's palsy. Palsies of other cranial nerves occur less frequently. *(Gilden, 635–645)*

**39. (D)** In its most characteristic presentation, fatal insomnia causes an untreatable condition that sometimes lasts for weeks or months. The insomnia is followed by dysautonomia, ataxia, and variable pyramidal and extrapyramidal signs, with relative sparing of cognitive function until late in the course. The dysautonomias may include episodic alterations in blood pressure, heart rate, temperature, respiratory rate, and secretions. The EEG shows diffuse slowing rather than periodic discharges. A sleep study is valuable to document a shortening of total sleep time if insomnia is not clinically obvious. Positron emission tomography (PET) shows a reduction in metabolic activity or blood flow to the thalamus relatively early in the disease. The neuropathologic features of fatal insomnia include neuronal loss and astrogliosis within the thalamus, inferior olives and, to a lesser degree, the cerebellum. The lack of spongiform changes does not exclude the diagnosis. The protease-resistant prion protein (PrP) is detectable in the brains of affected patients but is usually present only in small amounts and is often restricted to specific regions such as the thalamus and temporal lobe. *(Mastrianni, 337–352)*

**40. (C)** Japanese encephalitis (JE) virus is one of the most important causes of viral encephalitis worldwide, with an estimated 50,000 cases and 15,000 deaths annually. The clinical manifestations appear predominantly in children and young adults. Older adults seem to be affected when epidemics occur in new locations. The clinical features include a nonspecific prodromal stage followed by headaches, nausea, vomiting, behavioral changes, altered state of consciousness, and often seizures. A dull mask-like

face with wide, staring eyes, tremor, choreoathetosis, head nodding, and rigidity are also found. Approximately one third of patients die, and 50% of the survivors have severe neuropsychiatric sequelae. In addition, Japanese encephalitis virus was recently found to cause acute flaccid paralysis in Vietnamese children. The weakness is usually asymmetric, and the lower extremities are more often affected than the upper. Electrophysiological studies have localized the site of damage to the anterior horn cells. The clinical and pathological features are therefore similar to those of poliomyelitis. The diagnosis of JE infection is made serologically. The presence of anti-JE virus immunoglobulin M in the CSF has a sensitivity and specificity in excess of 95%. Pathological studies demonstrate that the thalamus, basal ganglia, and midbrain are heavily affected, providing anatomical correlates for the tremor and dystonias that characterize Japanese encephalitis. *(Hinson, 369–374; Solomon, 405–415)*

**41.** **(D)** Variant Creutzfeld–Jakob disease has a clinical presentation in which behavioral and psychiatric disturbances predominate; in some cases, there are marked sensory phenomena. Initial referral is often to a psychiatrist and the most prominent feature is depression, but anxiety, withdrawal, and behavioral changes are also frequent. Other features include delusions, emotional lability, aggression, insomnia, and auditory and visual hallucinations. In most patients, a progressive cerebellar syndrome develops, with gait and limb ataxia. Dementia usually develops later in the clinical course. Myoclonus is seen in most patients, in some cases preceded by chorea. The most remarkable neuropathological feature of variant Creutzfeld–Jakob disease are the abundant PrP amyloid plaques in the cerebral and cerebellar cortexes. *(Collinge, 519–550)*

**42.** **(C)** Kuru affects both sexes, and onset of disease ranges from the age of 5 years to over 60 years. The mean clinical duration of illness is 12 months, with a range of 3 months to 3 years; the course tends to be shorter in children. The central clinical feature is progressive cerebellar ataxia. In sharp contrast to Creutzfeld–Jakob disease, dementia is often absent, although in the terminal stages the faculties of many patients are impaired. *(Collinge, 519–550)*

**43.** **(A)** The classic (sporadic) Creutzfeld–Jakob disease is a rapidly progressive multifocal dementia, usually with myoclonus. Onset usually occurs in individuals between 45 and 75 years of age, with peak onset between 60 and 65 years. Around 70% of those afflicted die less than 6 months after onset of symptoms. Prodromal features are seen in approximately one third of cases and include fatigue, insomnia, depression, weight loss, headaches, general malaise, and ill-defined pain. In addition to mental deterioration and myoclonus, frequent additional neurological features include extrapyramidal signs, cerebellar ataxia, pyramidal signs, and cortical blindness. *(Collinge, 519–550)*

**44.** **(B)** The presence of chronic cerebellar ataxia with pyramidal signs and dementia is highly suggestive of GSS. This diagnosis is supported by the presence of multicentric PrP amyloid plaques. *(Collinge, 519–550)*

**45.** **(A)** Most brain abscesses in immunocompetent patients are bacterial in origin. The most common etiologic organisms are microaerophilic streptococci and anaerobic bacteria. Other common organisms include *S. aureus*, *Clostridium*, Enterobacteriaceae, *P. aeruginosa* and *Haemophilus.* *(Roos, 30)*

**46.** **(D)** The actual gold standard for the diagnosis of herpes encephalitis is CSF PCR for herpes simplex virus DNA, replacing brain biopsy. CSF viral cultures for herpesvirus are almost always negative. CSF herpes PCR studies have been reported negative in the first few days of infection. If the diagnosis of herpes encephalitis is strongly suspected clinically, CSF PCR should be repeated if the first test was negative. *(Roos, 70)*

**47.** **(D)** About half of subdural empyemas are due to *S. aureus*, which represent the most common cause of spinal epidural abscess. *(Roos, 345)*

**48. (C)** The classic cerebrospinal findings in tuberculosis meningitis include:

- an elevated opening pressure.
- a lymphocytic pleocytosis of 10 to 500/mm$^2$.
- a reduced glucose concentration.
- an elevated protein concentration. *(Roos, 345)*

**49. (C)** Enteroviruses are the most common cause of viral meningitis. The enteroviruses include the coxsackieviruses, echoviruses, polioviruses, and human enteroviruses 68 to 71. *(Roos, 55)*

**50. (D)** HIV-associated distal sensory polyneuropathy is the most common neurological complication of HIV infection affecting over 30% of patients during their lives, with pathological evidence of neuropathy in most patients at autopsy. *(Roos, 103)*

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CHAPTER 9

# Neuroimmunology
## Questions

**1.** Which of the following statements is true of relapsing–remitting multiple sclerosis (MS)?

(A) The female predominance is approximately 4 to 1.
(B) Slowly evolving upper motor neuron syndrome of the legs is typical of the relapsing–remitting form of MS.
(C) An increase in body temperature may exacerbate symptoms.
(D) The presence of oligoclonal bands reduces the risk of recurrence.
(E) Women with predominantly sensory symptoms have a more serious prognosis.

**2.** Which of the following statements is true of the influence of genetic factors in MS?

(A) The concordance rate of MS in monozygotic twins is equal to that among dizygotic twins.
(B) The absolute risk of MS in the first-degree relative of a patient with MS is not different from the risk in the general population.
(C) The HLA DR2 allele increases the risk of MS.
(D) The mode of transmission of MS is autosomal recessive.
(E) HLA DR and DQ polymorphisms are associated with the course and severity of the disease.

**3.** Demyelinating lesions in MS are *least* likely to occur in the

(A) thalamus
(B) optic nerve
(C) cerebellum
(D) brainstem
(E) periventricular white matter

**4.** Which of the following is true of the mechanism of action of interferon in MS?

(A) It decreases the antigen presentation.
(B) It decreases cytokine production governed by type 2 helper T cells.
(C) It reduces the secretion of interferon 10.
(D) It competes with myelin basic protein for presentation on MHC class I molecules.
(E) It increases the passage of the immune cells across the blood–brain barrier.

**5.** Which of the following is characteristic of chronic inactive MS plaques?

(A) They are hypercellular infiltrates mainly composed of macrophages, T lymphocytes, and microglia.
(B) They have well-demarcated areas of hypocellularity with myelin pallor.
(C) Shadow plaques are seen in the center of the demyelinating lesion.
(D) B lymphocytes tend to concentrate in the periventricular region
(E) Local precipitation of immunoglobulin and complement is seen in areas of myelin damage.

**6.** Once autoreactive T cells have gained entry into the central nervous system (CNS), they invade the extracellular matrix aided by their secretion of

(A) metalloproteinases
(B) adhesion molecules
(C) tumor necrosis factor (TNF)-α
(D) interleukin (IL)-6
(E) TNF-β

**7.** Autoreactive T lymphocytes respond to putative MS antigens through the formation of a molecular complex involving all of the following *except*

(A) oligodendrocytes
(B) macrophages
(C) T lymphocytes
(D) perivascular monocytes
(E) microglia

**8.** Which of the following agents has been suggested to cause immunological injury in MS?

(A) HIV virus
(B) Herpesvirus
(C) *Escherichia coli*
(D) Cytomegalovirus (CMV)
(E) JC virus

**9.** Which of the following is true of axonal injury in MS?

(A) Less than 10% of axons are lost in chronically demyelinating cervical spinal cord plaque.
(B) Acute active MS plaque does not demonstrate axonal transection.
(C) Axonal loss may underlie the neurological deficit during primary or secondary progressive MS.
(D) The accumulation of amyloid precursor protein identifies intact axons in actively demyelinating MS.
(E) Acute axonal injury correlates with the number of CD4+ T lymphocytes.

**10.** Transected axons are identified during the progression of MS as early as

(A) 2 weeks
(B) 1 year
(C) 5 years
(D) 10 years
(E) 20 years

**11.** Which of the following mechanisms does not contribute to the clinical remission in relapsing–remitting MS?

(A) Resolution of inflammation
(B) Redistribution of axolemmal sodium channels
(C) Remyelination
(D) Accumulation of amyloid precursor proteins
(E) Compensatory adaptation of the CNS

**12.** Which of the following is the most likely determinant of disability in MS?

(A) Number of enhancing lesions on T1 magnetic resonance imaging (MRI) with contrast
(B) Number of T2 MRI lesions
(C) Positron emission tomography studies of brain activity
(D) Number of T1 hypodense lesions in the brain
(E) Total white matter axonal status

**13.** In MR spectroscopy, axonal integrity correlates with which of the following peaks?

(A) Choline
(B) Lactate
(C) N-acetylaspartate
(D) Creatinine
(E) None of the above

**14.** The decrease in NAA peak on MR spectroscopy in MS is a marker of

(A) axonal regeneration
(B) axonal loss
(C) demyelination
(D) astrocyte activity
(E) oligodendrocyte activity

**15.** Which of the following is true of neurophysiological tests in MS?

(A) EEG studies are abnormal in less than 10% of patients with MS.
(B) In case of cognitive deficit, electroencephalography (EEG) may show increased β activity in the frontal lobe.
(C) P 300 event-related potential latency correlates with the degree of white matter disease.
(D) Evoked potentials are very sensitive in detecting the spatial distribution of MS lesions.
(E) The evaluation of middle latency auditory evoked potentials does not affect the sensitivity of brainstem auditory evoked potentials.

**16.** Which of the following is not associated with unfavorable prognosis in MS?

(A) Male sex
(B) Younger age of onset
(C) Motor or cerebellar signs at onset
(D) Early disability
(E) Incomplete remission after the first attack

**17.** The first line of treatment of spasticity in MS is

(A) the use of reciprocal motion exercises
(B) baclofen
(C) clonidine
(D) cyproheptadine
(E) dantrolene

**18.** Which of the following antispasticity medications acts as an α2 sympathetic agonist with effects on polysynaptic reflexes?

(A) Tizanidine
(B) Dantrolene
(C) Baclofen
(D) Cyproheptadine
(E) Phenol

**19.** Which of the following drugs is used to improve fatigue in MS?

(A) Carbamazepine
(B) Pregabalin
(C) Amantadine
(D) Gabapentil
(E) Duloxetine

**20.** Which of the following myelin sheath proteins is found in the CNS as well as in the peripheral nervous system?

(A) Protein zero (P0)
(B) Peripheral myelin protein 22 (PMP22)
(C) Myelin basic protein
(D) Proteolipid protein
(E) Oligodendrocyte specific protein

**21.** Which of the following cytokines is *not* produced by Th2 lymphocytes?

(A) IL-4
(B) IL-5
(C) Interferon (IFN)-γ
(D) IL-10
(E) IL-13

**22.** Upregulation of IL-4 is most likely seen in which phase of experimental autoimmune encephalitis?

(A) Induction
(B) Demyelination
(C) Relapse
(D) Epitope spreading
(E) Remission

**23.** Which of the following is a proinflammatory cytokine?

(A) IL-4
(B) IL-10
(C) TNF-α
(D) IFN-β
(E) TGF-β

**24.** Which of the following is the correct combination of a paraneoplastic syndrome and the antineuronal antibody associated with that syndrome?

(A) Lambert–Eaton myasthenic syndrome/anti-MAG
(B) Myasthenia gravis (MG)/anti-CV2
(C) Limbic encephalitis/anti-Ma2
(D) Peripheral neuropathy/antiamphiphysin
(E) Cerebellar degeneration/anti-MAG

**25.** Which of the following paraneoplastic antibodies is not associated with small cell lung cancer (SCLC)?

(A) Anti–P/Q type VGCC antibody
(B) Anti-Hu antibody
(C) Anti-MAG antibody
(D) Antiamphiphysin antibody
(E) Anti-Ri antibody

**26.** MG is associated with

(A) anti–P/Q type voltage-gated calcium channels
(B) antiacetylcholine receptor antibody
(C) anti-Hu antibody
(D) anti–voltage-gated potassium channel antibody
(E) anti-Yo antibody

**27.** Neuromyotonia is associated with

(A) anti–P/Q type voltage-gated calcium channels
(B) antiacetylcholine receptor antibody
(C) antiamphiphysin antibody
(D) anti–voltage-gated potassium channel antibody
(E) anti-Yo antibody

**28.** Anti-Ri antibodies are associated with

(A) cerebellar degeneration
(B) Lambert–Eaton myasthenic syndrome
(C) testicular cancer limbic encephalitis
(D) chronic inflammatory demyelinating polyneuropathy–like (CIDP-like) neuropathy
(E) opsoclonus

**29.** Demyelinating polyneuropathy is associated with

(A) anti-Ri antibody
(B) antiamphiphysin antibody
(C) anti-CV2 antibody
(D) anti-Ma2 antibody
(E) anti-MAG antibody

**30.** Anti-CV2 antibody is associated with

(A) thymoma related sensory neuronopathy
(B) cerebellar degeneration
(C) Lambert–Eaton myasthenic syndrome
(D) testicular cancer limbic encephalitis
(E) demyelinating neuropathy

**31.** Antiamphiphysin antibody is most commonly associated with

(A) MG
(B) neuromyotonia
(C) stiff-man syndrome
(D) SCLC–related encephalomyelitis
(E) thymoma-related sensory neuronopathy

**32.** Cerebellar degeneration is most commonly associated with

(A) antiacetylcholine receptor antibody
(B) anti-Hu antibody
(C) anti–voltage-gated potassium channel antibody
(D) anti-Yo antibody
(E) anti-Ri antibody

**33.** Anti-Ma2 antibody is commonly associated with

(A) cerebellar degeneration
(B) Lambert–Eaton myasthenic syndrome
(C) testicular cancer limbic encephalitis
(D) demyelinating neuropathy
(E) opsoclonus

**34.** Lambert–Eaton myasthenic syndrome is commonly associated with

(A) anti–P/Q type voltage-gated calcium channels
(B) anti-acetylcholine receptors antibody

(C) anti-Hu antibody
(D) anti–voltage-gated potassium channel antibody
(E) anti-Yo antibody

**35.** The most frequent cause of anti-Yo antibodies is

(A) breast cancer
(B) ovarian cancer
(C) SCLC
(D) bladder cancer
(E) uterine cancer

**36.** Which of the following is true of paraneoplastic encephalomyelitis?

(A) It usually antedates the diagnosis of breast cancer.
(B) It is commonly associated with anti-CV2 antibodies.
(C) It is frequently associated with irregular, continuous large-amplitude conjugate saccades in all directions of gaze.
(D) It may be associated with central hypoventilation.
(E) Patients with paraneoplastic encephalomyelitis may develop seizures but not nonconvulsive status.

**37.** Anti-Hu antibodies are seen most frequently in

(A) SCLC
(B) breast cancer
(C) prostate cancer
(D) neuroblastoma
(E) sarcoma

**38.** Opsoclonus seen in conjunction with abnormalities in ocular motility is most commonly associated with

(A) anti-Ma antibody
(B) anti-Yo antibody
(C) anti-Hu antibody
(D) anti-Ri antibody
(E) antiamphiphysin antibody

**39.** Which of the following antineuronal antibodies is associated with testicular cancer?

(A) Anti-Tr antibodies
(B) Antiacetylcholine receptors antibodies
(C) Anti-CV2 antibodies
(D) Amphiphysin antibodies
(E) Anti-Ma2 antibodies

**40.** Which of the following antineuronal antibodies is not associated with limbic encephalitis?

(A) Anti-Hu antibodies
(B) Anti-Ma2 antibodies
(C) Anti-CV2 antibodies
(D) Anti-PCA2 antibodies
(E) Anti-Yo antibodies

**41.** A 60-year-old right-handed woman came to the emergency room because she had recently developed an unsteady gait, dizziness, and double vision, progressing over several weeks. Neurological examination showed generalized severe ataxia, more prominent in the trunk, and mild dysarthria. Ocular examination showed opsoclonus ocular flutter and abnormal visual tracking. MRI of the head was normal. Laboratory evaluation showed the presence of antineuronal antibodies. Which of the following is true of the patient condition?

(A) Diffuse loss of pyramidal cells is the pathological hallmark of the patient's condition.
(B) Anti-Hu antibody is the most likely type of antineuronal antibody found in this patient.
(C) SCLC is the most likely malignancy that is causing this patient's symptoms.
(D) Inflammatory infiltrate involving the tegmentum of the pons and mesencephalon may be seen with cerebellar degeneration.
(E) Immunosuppressive treatment does not reverse these symptoms.

**42.** A 50-year-old man developed a progressive increase of muscle stiffness, rigidity, lumbar lordosis, and urinary incontinence. If his symptoms are caused by a paraneoplastic syndrome, which of the following is true?

(A) The use of clonazepam will not improve the rigidity.
(B) SCLC is the major cause of the syndrome.
(C) Antiamphiphysin antibodies are the major antineuronal antibodies found in the serum of this patient.
(D) Antiglutamic acid decarboxylase (GAD) is found in 70% of patients with a similar paraneoplastic condition.
(E) Treatment of the primary tumor will not improve the patient's neurological symptoms.

**43.** In acute inflammatory demyelinating polyneuropathy, the most frequently detected antigangliosides antibody is

(A) IgG antibody against $G_{M1}$
(B) antibody against GQ1b
(C) antibody antiglycolipids
(D) anti-EVB antibody
(E) anti-GD1a antibody

**44.** Which of the following is suggestive of the mechanism of action of intravenous immunoglobulins in the treatment of demyelinating polyneuropathy?

(A) Downregulation of Th2 cytokine production
(B) T-cell activation
(C) Complement activation
(D) Immunoglobulin Fab receptor blockade
(E) Stimulation of immunoglobulin production

**45.** Anti-N-methyl-D-aspartate (NMDA) receptor–associated encephalitis is usually seen in conjunction with

(A) SCLC
(B) lymphoma
(C) ovarina teratoma
(D) neuroblastoma
(E) breast cancer

**46.** In children, the most frequent cause of opsoclonus–myoclonus syndrome is

(A) lymphoma
(B) neuroblastoma
(C) SCLC
(D) thymoma
(E) breast cancer

**47.** Antiglial nuclear antibody is commonly seen in

(A) SCLC
(B) astrocytoma
(C) oligodendroglioma
(D) lymphoma
(E) glioblastoma multiforme

**48.** Which of the following is true of dermatomyositis?

(A) It is the most common inflammatory myopathy after the age of 50 years.
(B) There is asymmetric muscle involvement.
(C) It is associated with the diagnosis of malignancy in 45% of cases.
(D) It affects men 3 times more than women.
(E) Irregular rimmed vacuoles are present in up to 70% of muscle fibers.

**49.** According to the McDonald criteria, what additional data are needed to confirm the diagnosis of MS in a 45-year-old woman who developed two partially reversible attacks of blurred vision, ataxic gait, and left leg weakness over 3 months?

(A) A third clinical attack
(B) Two brain MRI-detected lesions
(C) None
(D) Presence of oligoclonal bands on cerebrospinal fluid (CSF) examination
(E) Abnormal visual evoked potentials

**50.** Which of the following is the strongest genetic factor influencing susceptibility to MS?

(A) HLA DRB1
(B) APOE gene
(C) Alpha synuclein gene
(D) Dystrophin gene
(E) Merlin gene

**51.** Which of the following infectious agents is most likely to play a contributory role in the pathogenesis of MS?

(A) HIV virus
(B) Epstein–Barr virus
(C) *Campylobacter jejuni*
(D) Mumps virus
(E) Rubella virus

**52.** Which of the following medications acts by blocking CD20 receptor on circulating B cells?

(A) Rituximab
(B) Intravenous immunoglobulin
(C) Glatiramer
(D) IFN-β
(E) Corticosteroids

**53.** Which drug has the following mechanism of action: stimulation of anti-inflammatory cytokine production and inhibition of synthesis and transport of matrix metalloproteinases?

(A) Rituximab
(B) Intravenous immunoglobulin
(C) Glatiramer
(D) IFN-β
(E) Mitoxantrone

**54.** Which medication acts by intercalating with DNA and suppressing lymphocytes?

(A) Rituximab
(B) Intravenous immunoglobulin
(C) Glatiramer
(D) IFN-β
(E) Mitoxantrone

**55.** Which drug has activity against circulating immune cell integrins?

(A) Rituximab
(B) Intravenous immunoglobulin
(C) Glatiramer
(D) Natalizumab
(E) Mitoxantrone

**56.** Which of the following autoantibodies is associated with neuromyelitis optica?

(A) Aquoporin-4 antibody
(B) Antisulfatide antibody
(C) Anti-MAG antibody
(D) Anti-GAD antibody
(E) Anti-Hu antibody

**57.** Which of the following syndromes has the *least* likely chance of having a paraneoplastic origin?

(A) Stiff-man syndrome
(B) Cerebellar degeneration
(C) Limbic encephalitis
(D) Motor neuron disease
(E) Brainstem encephalitis

**58.** MRI of the brain is useful in which of the following paraneoplastic syndromes?

(A) Subacute sensory neuronopathy
(B) Limbic encephalitis
(C) Lambert–Eaton myasthenic syndrome
(D) Stiff-man syndrome
(E) Brain stem encephalitis

**59.** Which of the following differentiates MS from postinfectious encephalomyelitis?

(A) Commonly monophasic
(B) Equal gender incidence
(C) Seizure seen in 50% of cases
(D) Optic neuritis
(E) Preserved level of consciousness

**60.** Which of the following factors may increase the risk of developing MS after isolated transverse myelitis?

(A) Complete transverse myelitis
(B) Asymmetric sensory and motor deficit on neurological examination
(C) Normal CSF examination.
(D) Limited nonconfluent intramedullary lesions on spinal MRI
(E) Normal multimodality evoked potentials

# Answers and Explanations

**1. (C)** In relapsing–remitting MS, the type of MS present in 80% of patients, symptoms and signs typically progress over a period of several days, stabilize, and then often improve spontaneously or in response to corticosteroids within weeks. Relapsing–remitting MS typically begins in the second or third decade of life and has a female predominance of approximately 2 to 1. The tendency for corticosteroids to speed recovery from relapses often diminishes with time. Persistent signs of CNS dysfunction may develop after a relapse, and the disease may progress between relapses. Twenty percent of affected patients have primary progressive MS, which is characterized by a gradually progressive clinical course and a similar incidence among men and women. Relapsing–remitting MS typically starts with sensory disturbances, unilateral optic neuritis, diplopia (internuclear ophthalmoplegia), Lhermitte's sign, limb weakness, clumsiness, gait ataxia, and neurogenic bladder and bowel symptoms. Many patients describe fatigue that worsens in the afternoon and is accompanied by physiological increases in body temperature. Prominent cortical signs (aphasia, apraxia, recurrent seizures, visual-field loss, and early dementia) and extrapyramidal phenomena only (chorea and rigidity) rarely dominate the clinical picture.

Patients who have primary progressive MS often present with a slowly evolving upper motor neuron syndrome of the legs. Typically, this variant worsens gradually, and quadriparesis, cognitive decline, visual loss, brain stem and cerebellar syndromes, bowel, bladder, and sexual dysfunction may develop. The diagnosis is based on established clinical and, when necessary, laboratory criteria. Advances in CSF analysis and MRI, in particular, have simplified the diagnostic process. The relapsing forms are considered clinically definite when neurological dysfunction becomes disseminated in space and time. Studies of the natural history of the disease have provided important prognostic information. Ten percent of patients do well for more than 20 years and are thus considered to have benign MS. Approximately 70% will have secondary progression. Frequent relapses in the first 2 years, progressive course from the onset, male sex, early permanent motor or cerebellar findings, and presence of oligoclonal bands in the CSF are associated with the more severe course of the disease. Women and patients with predominantly sensory symptoms and optic neuritis have a more favorable prognosis. *(Noseworthy, 938–952)*

**2. (C)** Evidence that genetic factors have a substantial effect on susceptibility to MS is unequivocal. The concordance rate of 31% among monozygotic twins is approximately 6 times the rate among dizygotic twins (5%). The absolute risk of the disease in a first-degree relative of a patient with MS is less than 5%; however, the risk in such relatives is 20 to 40 times the risk in the general population. The HLA-DR2 allele substantially increases the risk of MS. The magnitude of the relative risk depends on the frequency of the HLA-DR2 allele in the general population. The mode of transmission of genetic susceptibility to MS is complex. Most cases are sporadic, despite the clear excess risk among the relatives of patients. Investigators have used the usual genetic approaches to identify genes associated with an increased risk of MS. HLA-DR and DQ polymorphisms are not associated

with the course and severity of MS despite their substantial contribution to disease susceptibility. *(Noseworthy, 938–952)*

3. **(A)** The pathological hallmark of chronic MS is the demyelinated plaque, which consists of a well-demarcated hypocellular area characterized by the loss of myelin, relative preservation of axons, and formation of astrocytic scars. Lesions have a predilection for the optic nerves, periventricular white matter, brainstem, cerebellum, and spinal cord white matter; they often surround one or several medium-sized vessels. Although the lesions are usually round or oval, they often have finger-like extensions along the path of small- or medium-sized blood vessels ("Dawson's fingers"). Inflammatory cells are typically perivascular in location, but they may diffusely infiltrate the parenchyma. The composition of the inflammatory infiltrate varies depending on the stage of demyelination. In general, it is composed of lymphocytes and macrophages; the latter predominate in active lesions. *(Noseworthy, 938–952)*

4. **(D)** IFN-β-1a and glatiramer acetate reduce the frequency of relapses of MS. IFN-β may delay the progression of disability in patients with minor disability who have a relapsing form of MS. The specific mechanisms of action of these agents in MS are incompletely understood. The interferons reduce the proliferation of T cells and the production of TNF-α, decrease antigen presentation, alter cytokine production to favor ones governed by type 2 helper T (Th2) cells, increase the secretion of IL-10, and reduce the passage of immune cells across the blood–brain barrier by means of their effects on adhesion molecules, chemokines, and proteases. Glatiramer acetate may promote the proliferation of Th2 cytokines, compete with myelin basic protein for presentation on MHC class II molecules, alter the function of macrophages, and induce antigen-specific suppressor T cells. *(Noseworthy, 938–952)*

5. **(B)** MS plaques may be characterized as active or inactive. The presence in macrophages of activation markers and specific myelin degradation products is suggestive of active plaque. Macrophages are numerous in active lesions, which are hypercellular and contain patchy infiltrates of autoreactive T cells and antigen-nonspecific monocytes. Macrophages and lymphocytes form prominent perivascular cuffs and invade the parenchyma, whereas plasma cells and B cells tend to concentrate in the perivascular region only. Most lymphocytes within plaques are T cells, including both CD4+ (helper) and CD8+ (cytotoxic) cells. The CD4+ cells can be functionally divided into Th1 (which secrete proinflammatory cytokines, such as TNF-α and IFN-γ) or Th2 (which secrete antiinflammatory cytokines such as IL-4, -5, and -6).

   Chronic plaques display well-demarcated areas of hypocellularity with myelin pallor or loss. There are varying degrees of axonal loss, usually most obvious in the center of the lesion. There is typically a persistent but minor inflammatory response, with only a few scattered perivascular lymphocytes present, although plasma cells may occasionally be prominent. Shadow plaques are circumscribed regions where axons maintain uniformly thin myelin sheaths. They may occur within acute plaques or at the edge of chronic ones. These plaques represent areas of remyelination and are macroscopic evidence that the CNS white matter possesses the means for self-repair. Shadow plaques are seen in conjunction with actively demyelinating lesions that retain viable oligodendrocytes in the plaque center. *(Wingerchuk, 263–281)*

6. **(A)** An intact blood–brain barrier allows limited passage of T lymphocytes that may not have antigen specificity. This may be initiated by the interaction of adhesion molecules expressed on the surface of lymphocytes with complementary integrins present on the endothelium, resulting in T-cell rolling and adherence to the luminal surface. Examples of such molecules include vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM). After crossing the blood–brain barrier, activated T cells invade the extracellular matrix, aided by their secretion of matrix metalloproteinases, which degrade myelin components as well as type IV collagen matrix and regulate cytokine production. *(Wingerchuk, 263–281)*

7. **(A)** Autoreactive T cells respond to putative MS autoantigens presented by antigen-presenting

cells (APCs) through formation of a trimolecular complex involving perivascular monocytes, microglia and macrophages, parenchymal lymphocytes, and possibly astrocytes. These cells express MHC molecules. There are two principal types of MHC molecules: class I (includes HLA-A, -B, and -C) and class II (includes HLA-DR, -DP, and -DQ). These molecules bind peptide antigens as part of the processing they require for presentation to different T lymphocytes. Lymphocytes of the CD4+ type recognize antigens in conjunction with MHC class II molecules; whereas CD8+ lymphocytes recognize antigens in the context of MHC class I molecules. The trimolecular complex is completed by interaction with the T-cell receptor.

MS seems primarily to be a disease involving immune responses to antigens presented by class II molecules, although class I mechanisms are receiving increased attention. The interaction between a CD4+ T lymphocyte and an APC results in antigen-specific signaling; however, T-cell activation requires the presence of costimulatory molecules. Costimulatory molecules CD28 and CTLA-4 are present on the T-cell surface. These molecules interact with their ligands B7-1 and B7-2 to promote activation; when absent, the T cell–APC interaction results in T-cell apoptosis and limitation of the immune response. When the costimulatory molecules and their respective ligands are present, intracellular signaling pathways involving phosphorylation-dependent enzymes and second messenger systems activate secretory and proliferative mechanisms within the T lymphocyte. *(Wingerchuk, 263–281)*

**8. (B)** Dysregulation of the immune system may contribute to the initiation or propagation of a pathological state in MS by autoreactive T cells. The causative autoantigen(s) in MS is still not known; however, the leading candidates are myelin protein constituents. The role of other myelin components is less well studied. Molecular mimicry has been hypothesized to explain immunological injury in autoimmune diseases. Under this schema, antigens present in or originating from an exogenous pathogen activate T cells. These cells then induce CNS demyelination by recognizing cross-reactive myelin antigens. This explanation has been used to implicate herpesvirus in MS pathogenesis, although a latent viral infection, rather than mimicry, could also potentially result in demyelination and oligodendroglial loss. The T-cell receptor normally maintains an extremely high level of cross-reactivity, probably to balance the requirement to recognize nonself antigens and to reduce the possibility of loss of self-tolerance. The concept of molecular mimicry remains speculative. *(Wingerchuk, 263–281)*

**9. (C)** It has long been recognized that axons are relatively but not absolutely spared in MS, especially early in the disease. Recent pathological and noninvasive radiological studies have focused attention on how, early in the disease, axons may be injured or lost, the possible contribution of axonal injury to clinical disability, and the development of progressive MS. Not surprisingly, axonal density is reduced in chronic plaques. Whereas estimates of axonal number and density are challenged by the variable presence of edema, myelin loss, atrophy, and inflammatory cell infiltrates, between 50% and 80% of axons may be lost in chronically demyelinated cervical spinal cord plaques. The accumulation of β-amyloid precursor protein identifies damaged axons in actively demyelinating MS lesions. Acute, active MS plaques may also demonstrate axonal transection, swelling, formation of terminal spheroids, and regenerative sprouting.

Others have confirmed early axonal loss in the early inflammatory phases of the disease, even in the absence of demonstrable primary demyelination. Axonal loss is irreversible and probably underlies the worsening neurological deficits that accrue in the primary and secondary progressive forms of the disease; clinical progression correlates with brain atrophy in both of these forms of MS. The mechanisms of axonal injury are largely unknown. In particular, it is not clear whether inflammatory effects may damage axons directly or whether they operate primarily through a pathway that includes demyelination. Recently, it was found that acute axonal injury correlates with the number of macrophages and CD8+ T lymphocytes within plaques but not with TNF-α or nitric oxide

synthase expression. This suggests that axonal injury is not solely due to demyelination. Glutamate-driven excitotoxic mechanisms may be operative as well. *(Wingerchuk, 263–281)*

**10. (A)** Histopathologic studies of MS brains have demonstrated axonal injury in lesions undergoing inflammatory demyelination. Axonal ovoids (which are characteristic of newly transected axons) and extensive accumulation of the amyloid precursor protein (APP) have been reported in active lesions and at the border of chronic active lesions. APP is detected immunohistochemically only in axons with impaired axonal transport. This result indicates not only axonal dysfunction within inflammatory MS lesions but also suggests that many of the axons are transected. Importantly, these changes are observed in patients with a short duration of disease. A morphological investigation quantified axonal ovoids in MS brains with disease durations from 2 weeks to 27 years. The results of the study not only confirm that axonal transection is abundant during the early stages of the disease but also demonstrate that the density of transected axons correlates with inflammatory activity in the lesions. Because APP accumulation correlates with number of macrophages and CD8+ T lymphocytes but not with expression of putative mediators of demyelination such as TNF-α and inducible nitric oxide synthase, it is suggested that axonal damage in MS lesions might not be directly proportional to demyelinating activity. *(Bjartmar, 271–278; Trapp, 278–285)*

**11. (D)** Four mechanisms may contribute to clinical remission in MS: resolution of the inflammation, redistribution of axolemmal sodium channels, remyelination, and compensatory adaptation of the CNS. *(Bjartmar, 271–278)*

**12. (E)** In MS, the correlation between clinical disability and atrophy—as revealed by MRI of the cerebellum, spinal cord, and cerebrum—has been interpreted as a reflection of axonal loss. In secondary progressive MS (SP-MS), cervical spinal cord atrophy averages 25% to 30%. In a group of RR-MS patients with mild to moderate disability followed over 2 years, brain atrophy increased yearly. Axonal loss is a conceivable contributor to atrophy in MS, although demyelination and reduced axon diameter may also decrease tissue volume. Axonal pathology and loss is not restricted to MS lesions, as all axons will undergo Wallerian degeneration distal to the site of axonal transection of the MS lesion.

Axonal loss in normal-appearing white matter (NAWM) has been quantified in a number of recent autopsy studies. Axonal density was reported to be reduced by 19% to 42% in the lateral corticospinal tract of MS patients with lower limb weakness. Axonal loss was investigated in NAWM from cervical spinal cords of patients with SP-MS. The average reduction in axonal density in these samples was as much as 57%. As NAWM constitutes the greatest proportion of white matter in MS patients and as levels of the neuron-specific marker N-acetyl aspartate (NAA) in NAWM show a strong correlation with disability, the possibility has been raised that total white matter axonal status may be a more precise determinant of disease progression than the presence and characteristics of individual lesions. *(Bjartmar, 271–278)*

**13. (C)** The clinical importance of axonal degeneration in MS suggests that neuronal markers could be useful for noninvasive monitoring of disease progression and efficiency of therapy in these patients. In this respect, measurement of NAA by proton magnetic resonance spectroscopy (MRS) is a promising tool. NAA appears relatively specific for neurons and neuronal processes in vivo, although expression by oligodendrocyte progenitors and oligodendrocytes in vitro has been reported. Reduced levels of NAA as determined by MRS have been demonstrated in a number of neurodegenerative disorders, including MS. At acute stages of MS, reduced NAA occurs primarily in lesions, is partly reversible, and correlates with reversible functional impairment. Over time, NAA appears to decrease irreversibly in normal-appearing white matter (NAWM), indicating that axonal loss or damage occurs outside MS lesions. Reduced white matter NAA correlates with increased disability over time.

These results demonstrate a side-to-side correlation between NAA levels, motor impairment, and conduction times, conforming with

the view that axonal pathology in NAWM is a likely determinant of disease progression in MS. In theory, reduced NAA in MS tissue could reflect multiple mechanisms, including reversible neuronal/axonal damage due to inflammatory demyelination, altered neuronal metabolism related to activity, axonal atrophy, or axonal loss. In order to differentiate between these possibilities, NAA is measured by high-performance liquid chromatography at autopsy in MS spinal cord white matter and correlated with axonal loss as determined by immunohistochemistry. NAA is significantly reduced in chronic inactive MS lesions compared with MS nonlesion and control white matter, and the reduction correlates with total axonal volume and axonal density. These results demonstrate that reduced NAA levels in inactive lesions correspond to substantial axonal loss and support axonal loss as a major cause of decreased white matter NAA in secondary progressive MS. *(Bjartmar, 271–278)*

**14.** **(B)** The measurement of N-acetyl aspartate (NAA) as a neuronal marker by proton MRS is a valuable tool for assessing the progression of MS. Reduced NAA occurs in MS lesions and becomes irreversible as the disease progresses. In theory, reduced NAA in MS tissue could reflect multiple mechanisms, including reversible neuronal/axonal damage due to inflammatory demyelination, altered neuronal metabolism related to activity, axonal atrophy, or axonal loss. In order to differentiate between these possibilities, Bjartmar and colleagues studied the NAA levels in MS spinal cord white matter by high-performance liquid chromatography at autopsy. They found a correlation between the NAA level and the axonal loss as determined by immunohistochemistry. NAA was significantly reduced in chronic inactive MS lesions compared with MS white matter without lesion and control white matter. The reduction in NAA concentration was found to correlate with total axonal volume and axonal density. These results demonstrate that reduced NAA levels in inactive lesions correspond to substantial axonal loss. *(Bjartmar, 271–278)*

**15.** **(C)** In the early phases of MS, evoked potentials (EPs) are used to detect subclinical involvement of the sensory and motor pathways or to objectify vague symptoms. Previous studies indicated that in isolated syndromes, approximately one third of patients have subclinical involvement of sensory pathways revealed by EPs, mostly by visual-evoked potentials (VEPs) and somatosensory-evoked potentials (SEPs). In a study of 112 patients with isolated optic neuritis, 34.1% had abnormal extravisual EPs; however, the contribution of neurophysiological techniques in demonstrating spatial dissemination of the lesions was quite poor: only 4% of patients with abnormal extravisual EPs had normal brain MRI.

The major limiting factor on the usefulness of EPs in detecting subclinical involvement is that the presence of a lesion is revealed only if it affects pathways explored by neurophysiological investigations. Moreover, a significant proportion of the fibers must be affected to produce recordable modifications of EPs. The evaluation of middle latency AEPs complemented by brainstem AEPs (BAEP) in a group of 30 clinically definite MS patients increased the sensitivity of the test from 60% to 83%, suggesting that the validation of middle latency AEPs could establish criteria for a more comprehensive evaluation of the auditory system.

The EEG, which is the expression of multiple neuronal network interactions affected by white matter damage, may be used as an indicator of the global status of such interactions. Spectral analysis of the EEG revealed abnormalities in 40% to 79% of MS patients; the main changes were an increase of slow frequencies and decrease of the alpha band, which is related to cognitive dysfunction. Event-related potentials (ERPs) are brain waves related to stimulus processing. P300, the most widely studied ERP, is a positive wave recorded over the scalp when subjects discriminate stimuli differing in some physical dimension. It is thought to represent a closure of the evaluation process stimulus, and its latency has been proposed as an indicator of information processing speed. This process is electively affected in MS, and P300 latency is increased in MS patients. The increase in P300 latency is correlated with cognitive impairment and the degree of white matter involvement. *(Leocani, 255–261)*

**16.** **(B)** Factors associated with unfavorable prognosis in MS include:

- Male sex
- Older age at onset
- Motor or cerebellar signs at onset
- Short interval between initial and second attack
- High relapse rate in early years
- Incomplete remission after first relapses
- Early disability
- High lesion load detected by early MRI of the brain

*(Polman, 490–494)*

**17.** **(A)** Approximately 55% of patients with MS have detectable spasticity. This is defined as increased resistance to passive range of motion of the limb, which can be associated with exaggerated withdrawal to noxious stimuli, spasms, clonus, and hyperreflexia. Spasticity can interfere with volitional movement, cause pain, and disrupt sleep or activities of daily living. The first line of treatment of spasticity involves simple physical measures including stretching, use of reciprocal motion exercises such as exercycling, and, for some patients, passive standing in a standing frame.

When these measures fail, orally administered pharmacological agents may be necessary and in most cases are sufficient to manage the negative manifestations of increased muscle tone. The classically used medications include baclofen, benzodiazepines, and dantrolene sodium. The first two drugs can cause drowsiness, and all three can increase fatigue and weakness. Careful dose titration is therefore critical. The dose of baclofen, a gamma-aminobutyric acid (GABA) agonist, should be titrated slowly because patients with MS may be more sensitive than other patients to the side effects of drowsiness and weakness. If the response to baclofen is insufficient or if this drug causes intolerable side effects, diazepam or dantrolene may be substituted or added. In patients with fatigue or drowsiness from baclofen, diazepam may exacerbate these symptoms.

Use of diazepam should be avoided in those patients with a tendency toward depression or a history of substance abuse. Dantrolene can then be used but may cause weakness because of its direct muscle effect of preventing excitation–contraction coupling. If use of dantrolene is continued, liver function should be monitored at least every 3 months; liver toxicity can occur in rare instances. If the usual antispasticity medications fail or are contraindicated, various other medications can be tried. Clonidine hydrochloride or cyproheptadine hydrochloride (Periactin), serotonin, acetylcholine, and histamine antagonists have been reported to reduce MS-related spasticity. Selective botulinum toxin injections are also used. *(Stolp-Smith, 1184–1196)*

**18.** **(A)** Tizanidine is a centrally acting α-2-sympathetic agonist pharmacologically similar to clonidine with effects on polysynaptic reflex arcs. Tizanidine has been shown to reduce spasticity in several placebo-controlled clinical trials and has had efficacy similar to that of baclofen. Muscle weakness occurs less frequently with tizanidine than with baclofen. The most common side effects are drowsiness, dry mouth, and orthostatic hypotension. Liver function abnormalities rarely occur. *(Stolp-Smith, 1184–1196)*

**19.** **(C)** Fatigue is a common problem for patients with MS. Pharmacological therapy may be helpful when other medical problems that may cause fatigue, such as anemia or hypothyroidism, are excluded. Amantadine hydrochloride is the most widely used medication for MS-related fatigue. Its mechanism of action in MS is unknown, but the drug has central dopaminergic activity that may be relevant. Pemoline, also used for MS-related fatigue, has had a response rate of approximately 50% in some studies.

In a prospective open label study, modafanil was found to significantly improve fatigue and sleepiness in patients with MS. Unlike the higher-dose regimen required in narcolepsy, a low-dose regimen of modafinil was found to be effective and well tolerated by MS patients. Potassium channel blocking agents, such as 4-aminopyridine and 3,4-diaminopyridine, may also prove to be effective for MS-related fatigue. With use of these agents, the major toxic effect of these drugs at high serum levels is the occasional occurrence of generalized tonic–clonic seizures. Patients may experience increased fatigue and a decline in neurological function due to warm

environments (Uhthoff's phenomenon). Thus, remaining in a cool environment can enhance function. *(Stolp-Smith, 1184–1196; Zifko, 983–987)*

**20. (C)** The myelin sheaths of the CNS and peripheral nervous system contain distinct sets of proteins, but myelin basic protein is found in the myelin sheaths of both. In the peripheral nervous system, the compact myelin contains protein 0 (P0), peripheral myelin protein (PMP22), and myelin basic protein (MBP); whereas the noncompact myelin contains ecadherin, myelin-associated glycoprotein (MAG), and connexin 32 (Cx32). In the CNS, myelin contains proteolipid protein (PLP), oligodendrocyte-specific protein (OSP), myelin–oligodendrocyte basic protein, and myelin basic protein. *(Arroyo, 1–18)*

**21. (C)** As CD4+ lymphocyte responses develop in response to immune stimulation and T-cell populations become divided toward the production of Th1 or inflammatory cytokines versus Th2 or regulatory cytokines. The paradigmatic Th1 cytokine is IFN-γ, IL-4 being the defining Th2 cytokine. IL-12 is implicated in driving responses toward Th1 cytokine patterns: IFN-γ, IL-2, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-12 itself, and the B cells and macrophage cytokines. IL-4 implicated in Th2 cytokine patterns switch: IL-3, IL-5, IL-10, and IL-13. *(Ransohoff, 13–14)*

**22. (E)** Experimental autoimmune encephalitis may pursue a relapsing–remitting course. The remission may be caused by natural termination of the T-cell response through apoptosis or the action of regulatory cytokines, including upregulation of Th2 cytokines such as IL-4. *(Ransohoff, 24)*

**23. (C)** Proinflammatory cytokines include IL-1α,β, IL-2, IL-3, IL-6 (which has pro- and anti-inflammatory proprieties), IL-12, TNF-α, IFN-γ, LT-α, G-CSF, and GM-CSF. Anti-inflammatory cytokines include IL-4, IL-10, IL-13, IFN-β, and TGF-β. *(Ransohoff, 37)*

**24. (C)** A new family of paraneoplastic antigens (the Ma proteins) has recently been identified. There are at least five Ma proteins, the best characterized being Ma1 and Ma2. The expression of these proteins is highly restricted to neurons and spermatogenic cells of the testis. The anti-Ta (anti-Ma2) antibodies are present in the serum and spinal fluid of patients with paraneoplastic limbic and brainstem encephalitis associated with testicular cancer. These antibodies recognize epitopes mainly contained in Ma2 (a 40-kDa neuronal protein). Limbic encephalitis is frequently associated with small cell lung cancer (SCLC) and is characterized clinically by subacute confusion, amnesia, and psychiatric symptoms. MRI usually reveals increased signal in the medial temporal lobes on T2-weighted images and CSF may show a mild lymphocytic pleocytosis. Limbic encephalitis can occur as an isolated syndrome or as part of a multifocal disorder associated with cerebellar, brainstem, spinal cord, and dorsal root ganglion involvement. The largest study of paraneoplastic limbic encephalitis revealed that anti-Hu antibodies only occurred in 50% of the patients who had an associated SCLC. The antibody-positive patients are more likely to have involvement of other areas of the nervous system and to die from the neurological disorder rather than progression of the cancer. *(Dalmau, 405–408; Rees, 633–637)*

**25. (C)** SCLC is by far the tumor most commonly associated with paraneoplastic encephalomyelitis (PEM). Nearly all patients display signs and symptoms of multifocal involvement of the CNS and dorsal root ganglia. The most common clinical manifestation of PEM is a disabling subacute sensory neuronopathy (SSN). A high percentage of patients with PEM/SSN have polyclonal IgG anti-Hu antibodies. These antibodies produce diffuse staining of the nuclei and, to a lesser degree, the cytoplasm of all neurons in the brain, spinal cord, dorsal root ganglia, and autonomic ganglia.

Ninety percent of patients with paraneoplastic cerebellar degeneration (PCD) have SCLC, Hodgkin lymphoma, or carcinomas of the breast, ovary, or female genital tract. Patients typically have a subacute onset and progression of pancerebellar dysfunction. In addition to the cerebellar deficits, many patients show symptoms or signs of multifocal PEM, including

lethargy, cognitive deterioration, bulbar palsy, and limb weakness.

The most prevalent autoantibodies in patients with PCD are high-titer and polyclonal IgG anti-Purkinje cell antibodies (also called anti-Yo antibodies). Anti-Ri antibodies are seen in paraneoplastic opsoclonus. SCLC and breast carcinoma together account for approximately 70% of adults with paraneoplastic opsoclonus. Antiamphiphysin antibodies have been detected in the serum and CSF of a few patients with SCLC and PEM mainly manifesting as SSN without rigidity.

Lambert–Eaton myasthenic syndrome (LEMS) occurs in around 2 of every 1,000 cancer patients and is characterized by limb weakness, usually of the lower limbs; it is commonly associated with autonomic dysfunction. The deep tendon reflexes are reduced but show facilitation after exercise. Sixty percent of all cases are associated with underlying malignancy; in 40%, the LEMS occurs as an autoimmune condition in its own right. Nonparaneoplastic cases of LEMS occur more commonly in middle-aged women. When cancer is identified, it is usually SCLC, although cancer of the prostate or cervix has been described. Antibodies against voltage-gated calcium channels are present in most patients. Anti-MAG (myelin-associated glycoprotein) antibodies have been seen in Waldenström macroglobulinemia and are associated with peripheral neuropathy. Immunoglobulin M antibodies seem to have a higher pathogenicity for polyneuropathy than immunoglobulin G or immunoglobulin A antibodies. *(Dropcho, 246–261)*

**26. (B)** Myasthenia gravis (MG) is associated with three types of acetycholine receptor antibodies: binding, blocking, and modulating. The binding antibody test is the most sensitive; 90% of patients with generalized MG and 50% of those with ocular myasthenia have positive tests. If the test yields a negative result, then an acetycholine receptor–modulating antibody may increase the diagnostic yield slightly; however, the test suffers higher rates of false positives. Acetycholine receptor–blocking antibodies do not help in making the diagnosis of MG because they are found in only 1% of MG patients without acetycholine receptor binding antibodies, making them of limited diagnostic utility. *(Kusner, 231–239)*

**27. (D)** Neuromyotonia arises from peripheral nerve hyperexcitability. Patients present with muscle twitching and myokymia—a continuous undulating, rippling of the muscles described as a "bag of worms." Other features include stiffness, painful cramps worsened by attempted muscle contraction, hyperhidrosis, muscle hypertrophy, and pseudomyotonia, a myotonic-like slow relaxation of muscle after voluntary contraction without percussion myotonia. Neuromyotonia on needle EMG is demonstrated by spontaneous, continuous, high- frequency (150 to 300 Hz) doublet, triplet, or multiplet single motor unit discharges. Acquired neuromyotonia is considered an autoimmune or paraneoplastic syndrome. Antibodies to voltage-gated potassium channel antibody (VGKC) are often present and seem to result in motor nerve hyperexcitability and increased acetylcholine release, acting at the distal motor nerve, terminal arborization, or both. Paraneoplastic neuromyotonia primarily occurs with thymoma and occasionally with MG. It is also seen in SCLC and rarely in Hodgkin disease. VGKC-Abs are frequently present, but neuomyotonia is also reported with anti-Hu antibodies and SCLC. *(Toothaker, 21–33)*

**28. (E)** Opsoclonus–myoclonus (OM) comprises myoclonic jerks of the limbs and trunk, with opsoclonus—involuntary, arrhythmic, high-amplitude, multidirectional saccades. Opsoclonus may be constant, even during sleep, and may cause oscillopsia or blurring and oscillation of vision. OM is often associated with cerebellar ataxia, most often in children; it is commonly referred to as OM–ataxia syndrome, although adult forms exist. Pediatric OM etiology is diverse, including para- and postinfectious, toxic, and paraneoplastic causes. Pediatric OM is paraneoplastic in 40% of patients, always associated with neuroblastoma. Some 2% to 3% of neuroblastoma patients develop OM. Among adults, paraneoplastic OM and anti-Ri antibodies are associated, usually in women with underlying breast cancer. The Ri antibody recognizes the RNA-binding protein Nova, which is strictly neuron-specific and may regulate neuronal RNA metabolism. *(Toothaker, 21–33)*

**29.** **(E)** In approximately 50% of patients with neuropathy and IgM monoclonal gammopathy, the M-protein reacts with the myelin-associated glycoprotein (MAG) and other glycoconjugates in nerves bearing the carbohydrate epitope HNK-1. High titers of anti-MAG IgM antibodies are almost invariably associated with a chronic, slowly progressive, predominantly sensory demyelinating neuropathy. *(Nobile-Orazio, 710–717; Gondim, 902–904; Ropper, 1601–1605)*

**30.** **(A)** Anti-CV2 is seen in thymoma or SCLC, causing sensory neuronopathy or encephalomyelitis. *(Ransohoff, 94–104)*

**31.** **(C)** Stiff-man syndrome has both a nonparaneoplastic and paraneoplastic variant, both autoimmune. Glutamic acid decarboxylase (GAD) antibodies are associated with the nonparaneoplastic variant, usually in patients with other autoimmune diseases, particularly the diabetes mellitus type. Paraneoplastic stiff-man syndrome is clinically similar to the nonparaneoplastic form, although arm involvement may be more prominent. Amphiphysin antibodies are most commonly detected in paraneoplastic stiff-man syndrome, usually in breast cancer patients, although SCLC and Hodgkin disease are also reported. *(Toothaker, 21–33)*

**32.** **(D)** Paraneoplastic cerebellar degeneration (PCD) was the first paraneoplastic syndrome to be recognized. Cerebellar symptoms, including truncal and appendicular ataxia, nystagmus, and dysarthria begin abruptly, progress over weeks to months, and then stabilize, usually leaving the patient significantly impaired, unable to walk or sit unassisted, and unable to perform fine motor tasks such as writing or eating. The degree and probability of severe impairment correlates somewhat with the underlying cancer and type of antineuronal antibody present. Malignancies commonly associated with PCD include gynecologic cancers, such as breast and ovarian, SCLC, and Hodgkin disease. Breast or gynecological cancer is usually detected with anti-Yo positivity. It targets the cdr2 antigen, normally expressed on Purkinje cells in the cerebellum and aberrantly expressed in ovarian and breast cancers. Present in 38% of patients in whom antibodies are detected, anti-Yo is the most common antibody in PCD. With anti-Yo, cerebellar symptoms are usually present in isolation, often leaving patients with significant long-term disability resulting from irreversible Purkinje cell destruction. *(Toothaker, 21–33)*

**33.** **(C)** Limbic or brainstem encephalitis may be seen with testicular cancer and is associated with the synthesis of anti-Ma2 antibodies. *(Ransohoff, 94–104)*

**34.** **(A)** Lambert–Eaton myasthenic syndrome is seen in SCLC and is associated with the synthesis of anti-P/Q type voltage-gated calcium channel antibodies. *(Ransohoff, 94–104)*

**35.** **(B)** Anti-Yo antibodies are markers of paraneoplastic cerebellar degeneration. The associated tumors include ovarian cancer (60%) and other gynecologic tumors (5%), breast cancer (30%), and other cancers (5% lung and bladder). Low titers of anti-Yo antibodies may also be detected in less than 5% of patients with ovarian cancer without neurological symptoms. The target antigens of the anti-Yo antibodies are several 34- and 62-kDa proteins expressed predominantly in the cytoplasm of Purkinje cells of the cerebellum and to a lesser degree in neurons of the molecular layer and large neurons in the brainstem. *(Ransohoff, 102)*

**36.** **(D)** Paraneoplastic encephalomyelitis (PEM) is characterized by neuronal loss and inflammatory infiltrates in multiple areas of the nervous system. PEM antedates the diagnosis of cancer, almost always a SCLC; the majority of patients harbor serum and CSF Hu (ANNA-1) antibodies and, less frequently, CV2 (CRMP5), amphiphysin, Ri (ANNA-2), and other less well characterized onconeural antibodies. PEM may present with classic neurological syndromes, such as limbic encephalitis, or less frequently with symptoms that do not initially raise the suspicion of a paraneoplastic syndrome. In this setting, the detection of onconeural antibodies is crucial to make the diagnosis. Patients with PEM and Hu antibodies may present with epilepsia partialis continua or nonconvulsive status epilepticus as the first and predominant manifestation. Acquired

central hypoventilation leading to loss of automatic respiration with preserved voluntary breathing ("Ondine's curse") occurs with medullary lesions. Less than 5% of PEM patients with Hu antibodies never develop cancer after long-term follow up. Whether PEM patients without detectable cancer represent true paraneoplastic cases in which the tumor is destroyed by the immune response is presently unclear. *(Graus, 732–737)*

**37. (A)** Anti-Hu antibodies are markers of paraneoplastic encephalomyelitis, sensory neuronopathy, and autonomic dysfunction. The detection of these antibodies in patients with focal symptoms, such as limbic encephalopathy or cerebellar dysfunction, indicates that although these areas are the main targets of the immune response, the neuropathological substrate is a more diffuse encephalomyelitis. Since in 80% of patients with an anti-Hu–associated syndrome the causal tumor is a SCLC, a chest CT scan is mandatory for patients with anti-Hu antibodies and an as yet undiagnosed cancer. Rarely, other tumors have been found to be associated with anti-Hu antibodies, including breast cancer, prostate cancer, neuroblastoma, and small cell cancer of unknown origin. The targets antigens of the anti-Hu antibodies are a family of neuronal specific RNA-binding proteins expressed predominantly in the nuclei of neurons of the central and peripheral nervous system. *(Ransohoff, 102)*

**38. (D)** Anti-Ri antibodies are associated with paraneoplastic cerebellar and brainstem encephalopathy characterized by opsoclonus and other abnormalities of ocular motility. The most commonly associated tumor is breast cancer. The anti-Ri antibodies react with neuronal proteins located in the nuclei of neurons in the CNS but not in the peripheral nervous system. *(Ransohoff, 103)*

**39. (E)** Anti-Ma and anti-Ma2 antibodies are markers of paraneoplastic syndromes involving the limbic region, brainstem, and cerebellum. The target antigens are a family of brain cancer testicular proteins that include Ma1, Ma2, and several other uncharacterized members. These proteins are highly homologous to each other and are encoded by different genes. Ma1 is expressed in brain and testis, while Ma2 is expressed only in the brain. Antibodies that react with both Ma1 and Ma2 are called anti-Ma. Anti-Ma antibodies are associated predominantly with brainstem and cerebellar dysfunction and several types of cancer, including lung, breast, colon, and parotid glands. Antibodies that react only with Ma2 are called anti-Ma2 or anti-Ta. The detection of anti-Ma2 antibodies is usually associated with limbic and brainstem encephalitis; 80% of these patients have germ cell tumors and 20% have other tumors, including lung and breast cancers. Anti-CV2 antibodies are associated with paraneoplastic cerebellar degeneration and encephalomyelitis. The causal tumors are SCLC and thymoma. The target antigen of anti CV2 antibodies is a set of 62- to 66-kDa proteins expressed in neurons and oligodendrocytes. The detection of antiamphiphysin in patients with neurological symptoms of unknown cause is suggestive of a paraneoplastic origin. Antiamphiphysin antibodies may be seen in breast cancer and SCLC. Amphiphysin is a major antigen associated with paraneoplastic stiff-man syndrome, although some patients develop paraneoplastic encephalomyelitis and sensory neuronopathy. Anti-Tr antibodies are associated with paraneoplastic cerebellar degeneration and Hodgkin lymphoma. In adult brain, the Tr antigen is expressed predominantly in the Purkinje cell cytoplasm and dendrites. Antiacetylcholine receptors antibodies are associated with thymoma. *(Ransohoff, 103)*

**40. (E)** Paraneoplastic–limbic encephalitis is a disorder characterized by the subacute development of depression, irritability, seizures, and short-term memory loss. Symptoms usually precede or lead to the diagnosis of the primary tumor. Typical MRI findings of paraneoplastic limbic encephalitis include uni- or bilateral mesial temporal lobe abnormalities that are best seen on T2-weighted images.

The tumor most frequently involved is lung cancer. Other tumors include germ-cell tumors of the testis, breast cancer, thymoma, and immature teratoma of the ovary. Antineuronal antibodies associated with limbic encephalitis include anti-Hu, anti-Ma2, anti-CV2, and anti-PCA2

antibodies. Pathological findings include perivascular and interstitial inflammatory infiltrates, neuronal loss, and microglial proliferation that predominates in the limbic system. Neurological symptoms usually develop over days or weeks; they then stabilize, leaving the patient with severe short-term memory loss. In contrast to other paraneoplastic diseases of the CNS, this disorder may improve with treatment of the tumor. *(Ransohoff, 107)*

**41.** **(D)** The patient described in this vignette has symptoms of cerebellar and mesencephalic dysfunction. The presence of antineuronal antibodies is suggestive of paraneoplastic syndrome affecting the brainstem and cerebellum. Antineuronal antibodies associated with paraneoplastic cerebellar dysfunction include anti-Ri, anti-Tr, anti-Yo, anti-Ma, anti-CV2, anti-GluR1α, and anti-PCA2 antibodies. A number of clinical immunology correlates have been suggested for some of these antibodies.

The patient in this case has distinctive clinical findings suggestive of an association with anti-Ri antibodies. Up to 75% of patients with anti-Ri antibodies have opsoclonus, ocular flutter, and dysmetria, the latter two developing when the opsoclonus subsides. Patients may also develop nystagmus and abnormal visual tracking. Ataxia predominates in the trunk and may cause severe gait difficulty and multiple falls. Treatment of the primary tumor, which is usually a breast cancer, or the use of immune suppression may result in neurological improvement. Pathological examination may show perivascular and interstitial inflammatory infiltrates involving the tegmentum of the pons and mesencephalon, with extensive degeneration of cerebellar Purkinje cells.

Patients with paraneoplastic cerebellar degeneration and anti-Yo antibodies generally present with progressive disabling cerebellar syndrome over a few days or weeks. The most frequent cause of this syndrome is ovarian and other gynecological cancers, followed by breast cancer. Treatment of the primary tumor rarely improves the cerebellar symptoms. Cerebellar syndrome associated with anti-Hu antibodies is generally caused by SCLC. Treatment of the tumor may improve the symptoms. Hodgkin lymphoma may cause the production of anti-Tr antibodies, leading to cerebellar degeneration in relatively young patients. Improvement of symptoms may result from treatment of the lymphoma. *(Ransohoff, 107–109)*

**42.** **(C)** The patient described in this vignette has symptoms highly suggestive of stiff-man syndrome with sphincter dysfunction. The syndrome may be idiopathic or a paraneoplastic manifestation of breast, colon, and Hodgkin lymphoma. When the syndrome is not associated with a cancer, the major autoantigen is GAD and around 70% of patients develop diabetes. When the syndrome is caused by paraneoplastic manifestation of a cancer, antiamphiphysin antibodies are often found in the serum and the CSF of affected patients. The use of clonazepam or diazepam may improve the rigidity. Some authors include the improvement of rigidity with the use of diazepam as the diagnostic criteria to maintain stiff-man syndrome as the diagnosis of such rigidity. The treatment of the primary tumor, as well as the use of steroids, may cause definitive improvement of the stiff-man syndrome. *(Ransohoff, 113)*

**43.** **(A)** The improvement of symptoms of acute inflammatory demyelinating polyneuropathy (AIDP) by plasmapheresis, the presence of circulating antibodies directed against peripheral nerve antigens, and the deposition of immunoglobulins and complements in the myelinated fibers are highly suggestive of humoral factors involved in the pathogenesis of this polyneuropathy. Several circulating antibodies against myelin have been found in patients with AIDP. The anti-GM1 antibody is the most frequent antiganglioside antibody detected in serum of patients with AIDP. Some authors reported increased titers of anti-GD1a in the axonal form of AIDP. The anti-GM1β antibody has been reported in the motor form of AIDP as well as in acute motor axonal polyneuropathy. Anti-GQ1β antibodies are invariably associated with the Miller–Fisher variant of AIDP. Antiglycolipide antibodies have been associated with AIDP, including antibodies against *Campylobacter jejuni*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, cytomegalovirus, and Epstein-Barr virus. *(Ransohoff, 126)*

**44.** **(A)** The therapeutic effect of intravenous immunoglobulin on demyelinating polyneuropathy has been established. The suggested mechanisms are downregulation of Th2 cytokine production, immunoglobulin Fc receptors blockade, inhibition of T-cell activation, nonspecific binding of activated complement, and anti-idiopathic suppression of autoantibodies. *(Ransohoff, 128)*

**45.** **(C)** Anti-N-methyl-D-aspartate (NMDA) receptor–associated encephalitis is a recently described disorder that usually affects young women with teratoma of the ovary. A few days after prodromic fever or headache, most patients develop a syndrome that predictably evolves in stages, including prominent psychiatric symptoms (agitation, delusional thoughts, hallucinations) or, less frequently, short-term memory loss, seizures, progressive unresponsiveness (catatonia-like stage), central hypoventilation, autonomic instability (fluctuations of blood pressure, temperature, and cardiac rhythm), orofacial dyskinesias, limb choreoathetosis, and dystonia. The tumor (mature or immature teratoma) is often missed or mistaken for a benign or physiological cyst of the ovary. Detection of CSF and serum antibodies to NR1/NR2 heteromers of the NMDA receptor is characteristic of this disorder. The disorder can also occur in men or women without a detectable tumor. *(Graus, 732–737)*

**46.** **(B)** Opsoclonus is a disorder of the ocular motility characterized by irregular, continuous, large-amplitude conjugate saccades in all directions of gaze. Paraneoplastic opsoclonus–myoclonus may be the presenting symptom in about 2% to 5% of children with neuroblastoma. In adults, paraneoplastic opsoclonus usually affects women with breast or fallopian cancer in association with Ri antibodies and patients with SCLC without any characteristic antibodies. Children with idiopathic or paraneoplastic opsoclonus–myoclonus syndrome develop antibodies against unknown membrane antigens of neuroblastoma cell lines and cerebellar granular neurons detected by flow cytometry. *(Graus, 732–737)*

**47.** **(A)** Lambert–Eaton myasthenic syndrome (LEMS) is a disorder of neuromuscular transmission mediated by voltage-gated potassium channel (VGCC) antibodies. The predominant initial symptoms include proximal weakness of the lower limbs, dry mouth, and transient ptosis. SCLC is detected in up to 50% of LEMS patients. At present, there are no biological markers that can determine which LEMS patients are paraneoplastic. However, a previous study conducted by Graus and colleagues showed that 43% of patients with LEMS and SCLC had an antibody, called antiglial nuclear antibody (AGNA), defined by the immunoreactivity with the nuclei of the Bergmann glia of the cerebellum. While the frequency of AGNAs was higher than expected in LEMS patients with SCLC, no patient with idiopathic LEMS had these antibodies. *(Graus, 732–737)*

**48.** **(C)** Inclusion body myositis (IBM) is the most common inflammatory myopathy after the age of 50 years. It is characterized by an insidious onset of asymmetric weakness involving the quadriceps, volar forearm muscles, and ankle dorsiflexors. Up to 25% of patients with IBM have an associated autoimmune disease, but there is no increased association with malignancy or lung and heart abnormalities. IBM affects men three times more often than women, whereas non-paraneoplastic varieties of dermatomyositis and polymyositis affect women twice as often as men. Paraneoplastic dermatomyositis, however, is slightly more frequent in men than women. Polymyositis is associated with the diagnosis of malignancy in up to 28% of patients; dermatomyositis is associated with malignancy in up to 45% of cases. In IBM, pathological examination shows irregular rimmed vacuoles in up to 70% of muscle fibers. Eosinophilic inclusions are found in the cytoplasm and nuclei, and CD8+ T-cell endomysial infiltrate may be seen in the muscle fibers. In dermatomyositis, pathological findings are characterized by perivascular and perifascicular infiltrates, predominantly formed by B lymphocytes, macrophages, and CD4+ T cells. Early and prominent capillary changes in dermatomyositis suggest the importance of humoral factors in the pathogenesis of the disease. *(Ransohoff, 135–138)*

**49.** **(C)** The McDonald criteria allow for the diagnosis of MS based on clinical presentation alone

if multiple attacks accompanied by clinical evidence of at least two lesions can be identified. The definition of an attack is generally accepted to be the development of neurologic symptoms likely caused by an inflammatory demyelinating lesion, lasting at least 24 hours, and supported by objective findings. When there are two or more attacks with objective clinical evidence of two or more lesions, there is no need for additional data when the McDonald criteria are used. Although the patient in this vignette does not need additional tests to confirm her diagnosis, extreme caution is needed before making the diagnosis of MS if tests such as head MRI and CSF examination are undertaken and are negative. Since many patients early in the disease course may not meet the strict clinical definition for MS, the McDonald criteria allow for the use of ancillary testing such as MRI, CSF analysis, and visual evoked potentials to satisfy the requirements for dissemination in space and time. *(Rinker, 13–34)*

**50.** **(A)** The HLA-DRB1 gene located within the major histocompatibility complex (MHC) superlocus on chromosome 6p21 is the strongest genetic factor identified as influencing MS susceptibility. The association of MS with HLA genes, specifically DRB1*1501 allele, has been a consistent finding across nearly all populations. Studies in multicase families confirm the known association with the HLA class II DR2 haplotype (HLA-DRB1*1501-DQA1*0102-DQB1*0602), primarily in populations of northern European descent. The exact mechanisms by which the DRB1 gene influences susceptibility to MS remain undefined but are likely related to the physiological function of HLA molecules, including antigen binding and presentation, and T-cell repertoire determination by negative selection of high-avidity autoreactive T cells within the embryonic thymic environment. *(Oksenberg, 375–387; Rinker, 13–34)*

**51.** **(B)** Among possible infectious agents suggested to play a role in MS pathogenesis, Epstein–Barr virus (EBV) currently appears the most likely to play a contributory role. First, almost all patients with MS are seropositive for EBV antibodies, while 5% to 10% of the general population is seronegative. In addition, some investigators have found that EBV antibody titers are higher during MS relapses. Among individuals seropositive for EBV capsid antigen, almost three times more patients with MS recalled having had clinical infectious mononucleosis. Furthermore, patients who report having had infectious mononucleosis before age 18 have an eightfold higher risk of MS than those who did not recall having had infectious mononucleosis. *(Green, 63–85)*

**52.** **(A)** Rituximab is a mouse–human chimeric antibody directed against the CD20 precursors. It induces antibody-dependent cell- and complement-mediated cytotoxicity in these cells and therefore prevents the formation of new antibody-secreting cells and reduces titers of autoantibodies. *(Onrust, 79–88)*

**53.** **(D)** The mechanism of action of IFN-β in MS is not completely understood. IFN-β receptor binding induces the expression of numerous proteins (including neopterin, $\beta_2$-microglobulin, MxA, IL-10) responsible for the pleiotropic bioactivities of IFN-β. Immunomodulatory effects of IFN-β include the enhancement of suppressor T-cell activity, reduction of proinflammatory cytokine production, downregulation of antigen presentation, inhibition of lymphocyte trafficking into the CNS, and reduction of matrix metalloproteinase production.

IFN-β is a polypeptide, normally produced by fibroblasts, that has antiviral and antiproliferative effects. Binding of IFN-β to its receptor induces a complex transcriptional response. In immune cells (the most likely target of IFN-β's therapeutic effect in MS), IFN-β reduces antigen presentation and T-cell proliferation, alters cytokine and matrix metalloproteinase (MMP) expression, reduces proinflammatory cytokine production, inhibits lymphocyte trafficking into the CNS, and restores suppressor function. *(Markowitz, S8–S11)*

**54.** **(E)** Mitoxantrone is an anthracenedione compound that intercalates with DNA and modulates the immune system through a variety of mechanisms. It has potent anti-inflammatory and immunomodulating properties. It suppresses

both B and T lymphocytes and has more effects on helper subsets than on suppressor subsets, resulting in a downregulation of the inflammatory cascade. Effects on B cells lead to a decrease in the rate and magnitude of B-cell function, thereby decreasing antibody formation. In addition, mitoxantrone has a marked suppressive effect on macrophage function. Because macrophages are found in large numbers in acute lesions, their suppression may be associated with a decrease in the extent of tissue damage caused by inflammation. *(Jeffery, 19–24)*

**55.** Natalizumab (Tysabri) is a humanized monoclonal antibody specifically designed for use in MS. Natalizumab binds to the $\alpha_4$ subunit of $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins that are present on most leukocytes other than neutrophils. Antibody binding blocks the interaction with complementary endothelial molecules known as vascular cell adhesion molecules and thereby inhibits the migration of leukocytes across the blood–brain barrier. *(Mehta, 144–180)*

**56.** **(A)** Neuromyelitis optica (NMO) is a severe autoimmune inflammatory demyelinating disease of the CNS that predominantly affects the spinal cord and optic nerves. The recent description of NMO-IgG, a highly disease-specific autoantibody found in NMO and NMO-related diseases (i.e., relapsing optic neuritis and longitudinally extensive transverse myelitis) but absent in the classic form of MS, convincingly demonstrated that NMO is a specific disease and not just a subtype of MS. In contrast to prototypical MS, NMO active lesions displayed perivascular immunoglobulin deposition, complement activation, and polymorphonuclear (neutrophils and eosinophils) infiltration, thus supporting the importance of antibody-mediated pathogenesis in NMO.

The target antigen of NMO-IgG was identified as aquaporin-4 (AQP4), the main water channel protein in the CNS, expressed on astrocyte end-feet at the blood–brain barrier (BBB) and the brain–CSF barrier. *(Lennon, 473–477; Saikali, 132–135)*

**57.** **(D)** Paraneoplastic stiff-man syndrome is associated with the production of antiamphiphysin antibodies and is seen in Hodgkin's disease as well as in breast and colon cancers. Paraneoplasticlimbic encephalitis is associated with the synthesis of anti-Hu, anti-MA-2, anti-CV2, and anti-PCA2 antibodies and is seen in SCLC and germ cell tumor of testis. Brainstem encephalitis may be seen in testis cancer, whereas cerebellar degeneration is associated with anti-Yo antibodies and is seen in breast and ovarian cancers. Motor neuron syndrome is rarely reported to be associated with malignancies. *(Ransohoff, 94–113)*

**58.** **(B)** Limbic encephalitis is the most consistent paraneoplastic disorder associated with MRI abnormalities. On T2-weighted images, abnormal signals may be seen in the mesiotemporal lobes unilaterally or bilaterally. On T1 sequences, the temporal limbic regions may be hypointense and atrophic and may sometimes enhance with contrast injection. *(Ransohoff, 106–107)*

**59.** **(E)** Postinfectious encephalomyelitis is an acute disseminated encephalomyelitis and a monophasic polyregional syndrome; it is temporally related to an infection or vaccination and is most common in children. Compared with MS, patients with postinfectious encephalomyelitis have a monophasic course and 70% have reported a precipitating event in the weeks preceding the acute phase, whereas in MS the time course of the disease is multiphasic and preceding events are uncommon. MS most commonly affects young adults, with female predominance, whereas postinfectious encephalomyelitis affects both male and female children equally.

Clinically, postinfectious encephalomyelitis has an abrupt onset. Bilateral optic neuritis is more commonly seen than unilateral optic neuritis, seizures are seen in 50% of patients, and the level of consciousness is frequently affected. Complete transverse myelitis with areflexia is seen more in postinfectious encephalomyelitis than in the incomplete transverse myelitis more frequently seen in MS. The disease onset of MS has a subacute pattern: seizures are seen in less than 5% of cases, the level of consciousness is generally conserved, and optic neuritis occurs unilaterally rather than bilaterally. Head MRI commonly shows a conservation of the periventricular

area in postinfectious encephalomyelitis, whereas in MS, a periventricular area is frequently affected. Increased cell count may be seen in both postinfectious encephalomyelitis and MS, whereas oligoclonal bands are more commonly seen in MS. *(Burks, 91)*

**60. (D)** Transverse myelitis may be an isolated clinical syndrome where the affected patient has an increased risk of developing MS. Certain features of transverse myelitis are helpful in predicting the likelihood of MS. Complete transverse myelitis carries a risk lower than 14%, whereas incomplete transverse myelitis carries a risk that approximates 70%. Other features that increase the risk of developing MS after transverse myelitis include asymmetric sensory or motor findings, abnormal CSF or brain MRI findings, spinal MRI showing limited nonconfluent intramedullary lesions, and abnormal multimodality-evoked potentials. *(Burks, 93)*

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CHAPTER 10

# Neuropharmacology and Neurochemistry Questions

**1.** Which of the following substances is not an amino acid or biogenic amine neurotransmitter?

(A) Dopamine
(B) Acetylcholine
(C) Histamine
(D) Glycine
(E) Epinephrine

**2.** Which of the following drugs blocks the transport of acetylcholine into vesicles?

(A) Curare
(B) Soman
(C) Dimethylphenyl piperazinium
(D) Oxotemorine
(E) Vesamicol

**3.** Which of the following drugs promotes the release of acetylcholine from vesicles?

(A) Atropine
(B) Physostigmine
(C) Hemicolinium-3
(D) Botulinum toxin
(E) Beta-bungarotoxin

**4.** Which of the following drugs blocks the release of acetylcholine from vesicles?

(A) Atropine
(B) Physostigmine
(C) Hemicolinium-3
(D) Botulinum toxin
(E) Beta-bungarotoxin

**5.** Which of the following drugs blocks postsynaptic nicotinic cholinergic receptors?

(A) Curare
(B) Soman
(C) Dimethylphenyl piperazinium
(D) Oxotemorine
(E) Vesamicol

**6.** Which of the following drugs is a nicotinic receptor agonist?

(A) Curare
(B) Soman
(C) Dimethylphenyl piperazinium
(D) Oxotemorine
(E) Vesamicol

**7.** Which of the following drugs is a muscarinic receptor antagonist?

(A) Atropine
(B) Physostigmine
(C) Hemicolinium-3
(D) Botulinum toxin
(E) Beta-bungarotoxin

**8.** Which of the following drugs is a presynaptic muscarinic agonist?

(A) Curare
(B) Soman
(C) Dimethylphenyl piperazinium
(D) Oxotemorine
(E) Vesamicol

**9.** Which of the following drugs is a reversible acetylcholinesterase inhibitor?

(A) Atropine
(B) Physostigmine
(C) Hemicolinium-3
(D) Botulinum toxin
(E) Beta-bungarotoxin

**10.** Which of the following drugs is an irreversible acetylcholinesterase inhibitor?

(A) Curare
(B) Soman
(C) Dimethylphenyl piperazinium
(D) Oxotemorine
(E) Vesamicol

**11.** Which of the following drugs is a competitive inhibitor of choline uptake?

(A) Atropine
(B) Physostigmine
(C) Hemicolinium-3
(D) Botulinum toxin
(E) β-bungarotoxin

**12.** The rate-limiting step for the synthesis of dopamine is

(A) tyrosine hydroxylase
(B) aromatic amino acid decarboxylase
(C) pteridine reductase
(D) dopamine β-hydroxylase
(E) phenylethanolamine-N-methyl transferase

**13.** Serotonin is derived from

(A) histidine
(B) tryptophan
(C) dopamine
(D) tyrosine
(E) glutamate

**14.** Ligand-gated channel opening for acetylcholine does not depend on

(A) the value of the membrane potential
(B) the probability that the channel is open
(C) the conduction of each open channel
(D) the driving force that acts on ions
(E) the total number of endplate channels

**15.** Which of the following blocks the action of gamma aminobutyric acid (GABA) at postsynaptic receptors?

(A) Allylglycine
(B) Flumazenil
(C) Phenobarbital
(D) Diazepam
(E) Picrotoxin

**16.** Which of the following is a GABA A agonist at postsynaptic receptors?

(A) Gabaculine
(B) Muscimol
(C) Nipecotic acid
(D) Baclofen
(E) Phaclofen

**17.** Which of the following is a GABA transaminase inhibitor?

(A) Gabaculine
(B) Muscimol
(C) Nipecotic acid
(D) Baclofen
(E) Phaclofen

**18.** Which of the following inhibits glutamic acid decarboxylase?

(A) Allylglycine
(B) Flumazenil
(C) Phenobarbital
(D) Diazepam
(E) Picrotoxin

**19.** Which of the following drugs increases the frequency of GABA A receptor opening?

(A) Allylglycine
(B) Flumazenil
(C) Phenobarbital
(D) Diazepam
(E) Picrotoxin

**20.** Which of the following drugs prolongs the duration of opening of the GABA A receptors?

(A) Allylglycine
(B) Flumazenil
(C) Phenobarbital
(D) Diazepam
(E) Picrotoxin

**21.** Which of the following drugs reverses the action of benzodiazepine agonists and has no pharmacological effect when administered alone?

(A) Allylglycine
(B) Flumazenil
(C) Phenobarbital
(D) Diazepam
(E) Picrotoxin

**22.** Which of the following drugs is a GABA B receptors agonist?

(A) Gabaculine
(B) Muscimol
(C) Nipecotic acid
(D) Baclofen
(E) Phaclofen

**23.** Which of the following drugs is a GABA B receptor antagonist?

(A) Gabaculine
(B) Muscimol
(C) Nipecotic acid
(D) Baclofen
(E) Phaclofen

**24.** Which of the following drugs is a GABA uptake inhibitor?

(A) Gabaculine
(B) Muscimol
(C) Nipecotic acid
(D) Baclofen
(E) Phaclofen

**25.** Which of the following statements is true of the molecular mechanism of cocaine addiction?

(A) Methadone is a powerful medication against cocaine addiction.
(B) Cocaine, by blocking the dopamine reuptake transporter, increases the postsynaptic concentration of dopamine.
(C) The dopamine transporter system is not necessary for the mechanism of cocaine addiction.
(D) D1 dopamine agonists stimulate cocaine-seeking behavior.
(E) D2 receptor agonists may decrease episodes of craving for cocaine.

**26.** A 10-year-old boy was treated with ethosuximide for several months because of absence seizures. Which of the following side effects might this patient develop?

(A) Hyponatremia
(B) Megaloblastic anemia
(C) Acute pancreatitis
(D) Fatigue
(E) Ataxia

**27.** A 45-year-old man was treated with phenytoin for several years because of a seizure disorder. Which of the following side effects might this patient develop?

(A) Hyponatremia
(B) Megaloblastic anemia
(C) Acute pancreatitis
(D) Fatigue
(E) Ataxia

**28.** A 25-year-old man, diagnosed with primary generalized seizures, was recently switched to valproic acid. His valproic acid level is 50 μg/mL. Which of the following side effects might this patient develop?

(A) Hyponatremia
(B) Impotence
(C) Acute pancreatitis
(D) Fatigue
(E) Ataxia

**29.** A 55-year-old man was started on primidone for the treatment of an essential tremor. Which of the following side effects might this patient develop?

(A) Hyponatremia
(B) Impotence
(C) Acute pancreatitis
(D) Megaloblastic anemia
(E) Ataxia

**30.** A 60-year-old man was started on phenobarbital 4 months ago after undergoing brain surgery for astrocytoma. Which of the following side effects might this patient develop?

(A) Hyponatremia
(B) Impotence
(C) Acute pancreatitis
(D) Dupuytren contracture
(E) Ataxia

**31.** A 35-year-old man with a history of complex partial seizure was being treated with carbamazepine. She consulted the neurologist because of chronic headache and blurred vision. Which of the following side effects might this patient develop?

(A) Hyponatremia
(B) Impotence
(C) Acute pancreatitis
(D) Dupuytren contracture
(E) Ataxia

**32.** Which of the following drugs decrease the serum level of carbamazepine?

(A) Phenytoin
(B) Valproic acid
(C) Verapamil
(D) Erythromycin
(E) Isoniazid

**33.** Phenytoin may reach a toxic level in the serum of a patient using _____ at the same time.

(A) valproic acid
(B) ethosuximide
(C) cyclosporine
(D) cimetidine
(E) prednisone

**34.** Which of the following antiepileptic drugs can have its concentration increased by the concomitant administration of aspirin?

(A) Phenobarbital
(B) Valproic acid
(C) Carbamazepine
(D) Lamotrigine
(E) Primidone

**35.** Which of the following drugs is a tyrosine hydroxylase inhibitor?

(A) Pargyline
(B) Amphetamine
(C) Phentolamine
(D) Tropolone
(E) Alpha methyltyrosine

**36.** Which of the following drugs causes norepinephrine storage depletion?

(A) Tropolone
(B) Alpha methyltyrosine
(C) Clonidine
(D) Desipramine
(E) Reserpine

**37.** Release of norepinephrine is caused by

(A) pargyline
(B) amphetamine
(C) phentolamine
(D) tropolone
(E) alpha-methyltyrosine

**38.** Which of the following drugs is a presynaptic $\alpha 2$ adrenergic autoreceptor stimulator?

(A) Tropolone
(B) Alpha methyltyrosine
(C) Clonidine
(D) Desipramine
(E) Reserpine

**39.** Which of the following drugs is a postsynaptic α-adrenergic receptor blocker?

(A) Pargyline
(B) Amphetamine
(C) Phentolamine
(D) Tropolone
(E) Alpha methyltyrosine

**40.** Which of the following drugs is a norepinephrine reuptake inhibitor?

(A) Tropolone
(B) Alpha methyltyrosine
(C) Clonidine
(D) Desipramine
(E) Reserpine

**41.** Which of the following drugs is a monoamine oxidase (MAO) inhibitor?

(A) Pargyline
(B) Amphetamine
(C) Phentolamine
(D) Tropolone
(E) Alpha methyltyrosine

**42.** Which of the following drugs is a catechol-O-methyl transferase inhibitor?

(A) Pargyline
(B) Amphetamine
(C) Phentolamine
(D) Tropolone
(E) Alpha methyltyrosine

**43.** D1 dopamine receptors exceed the number of D2 dopamine receptors as well as the number of other types of dopamine receptors in the

(A) substantia nigra
(B) caudate nucleus
(C) hippocampus
(D) amygdala
(E) ventral tegmental area

**44.** For a patient with seizures and acute porphyria, the most appropriate antiepileptic drug is

(A) felbamate
(B) topiramate
(C) lamotrigine
(D) tiagabine
(E) gabapentin

**45.** The mechanism of action of cocaine in the central nervous system is

(A) inhibition of tyrosine hydroxylase
(B) inhibition of the storage of dopamine
(C) inhibition of dopamine reuptake
(D) inhibition of monoamine oxidase
(E) inhibition of catechol-O-methyltransferase

**Questions 46 through 53**

Link the following:

(A) D1 dopamine receptors
(B) D2 dopamine receptors
(C) Both
(D) Neither

**46.** Stimulation of adenylate cyclase.

**47.** Enhancement of potassium conductance.

**48.** The number of dopamine receptors increases in cases of tardive dyskinesia.

**49.** Postmortem studies have shown an increased number of dopamine receptors in schizophrenic patients.

**50.** It has the highest affinity to quinpirol.

**51.** It has the highest affinity to clozapine.

**52.** Bromocriptine is an agonist.

**53.** Sulpiride is an antagonist.

**54.** Which of the following is true of amyloid precursor protein (APP)?

(A) The dominant isoform of APP contains the protease inhibitor region.
(B) APP undergoes a fast axonal transport to the synaptic region to interact with the extracellular matrix.
(C) APP α secretase is associated with the amyloidogenic form of APP.
(D) Beta secretases cleave the C terminal of APP and do not participate in the amyloidogenic process.
(E) Normal cellular metabolism does not synthesize the A β region of APP.

**55.** Compared with the nigrostriatal system, the mesoprefrontal dopamine system is characterized by

(A) the presence of dopamine autoreceptors
(B) lack of development of biochemical tolerance following chronic antipsychotic drug administration
(C) greater increase in the responsiveness to dopamine agonists
(D) a lower turnover rate of transmitter dopamine
(E) a lower rate of physiological activity

**56.** Which of the following is true of the serotoninergic receptors?

(A) The 5-HTA2 A receptors are densely located in the raphe nuclei.
(B) The activation of 5-HT1 receptors induces an increase of adenylate cyclase.
(C) The inhibitory effect of serotonin in the central nervous system is mediated by 5-HT1 receptors.
(D) The activation of 5-HT2 receptors induces the opening of potassium channels.
(E) The 5-HT3 receptors mediate fast excitation requiring a coupling to G protein.

**57.** The most serious side effect of clozapine is

(A) tardive dyskinesia
(B) neuroleptic malignant syndrome
(C) acute dystonia
(D) agranulocytosis
(E) akathisia

**58.** Which of the following is true of the pharmacological properties of clozapine?

(A) It has a higher affinity to D2 than to D1 dopamine receptors.
(B) It is a potent D4 dopamine receptor blocker.
(C) It inhibits c-fos expression.
(D) It has serotonin agonist activity.
(E) It activates the same dopaminergic neurons stimulated by haloperidol.

**59.** What is the mechanism of action of buspirone?

(A) It interacts with 5-HT1A receptors.
(B) It inhibits serotonin reuptake.
(C) It interacts with 5-HT2 receptors.
(D) It blocks histamine reuptake.
(E) It is a potent D1 dopamine receptor antagonist.

**60.** Which of the following drugs does *not* increase the level of lithium when both are administrated concomitantly?

(A) Ibuprofen
(B) Furosemide
(C) Aspirin
(D) Lisinopril
(E) None of the above

**61.** The primary neurotransmitter of postganglionic sympathetic neurons for sweat glands is

(A) acetylcholine
(B) norepinephrine
(C) glutamate
(D) aspartate
(E) serotonin

**62.** Stimulation of the dorsomedial nucleus of the hypothalamus results in

(A) aggressive behavior
(B) decreased feeding
(C) increased feeding
(D) increased blood pressure
(E) adjustment of the circadian clock phase

**63.** Corticotropin-releasing hormone is produced by which of the following hypothalamic nuclei?

(A) Anterior nucleus
(B) Arcuate nucleus
(C) Dorsomedial nucleus
(D) Supraoptic nucleus
(E) Medial preoptic nucleus

**64.** The inhibitory neurotransmitter of the cerebellar superficial stellate cell is

(A) dopamine
(B) serotonin
(C) taurine
(D) aspartate
(E) acetylcholine

**65.** Which of the following neurotransmitters is released by the axons of cerebellar Purkinje cells?

(A) Dopamine
(B) GABA
(C) Glutamate
(D) Aspartate
(E) Serotonin

**66.** The suprachiasmatic nucleus of the hypothalamus plays an important role in

(A) drinking behavior
(B) sexual arousal
(C) the sleep–wake cycle
(D) temperature regulation
(E) parasympathetic activation

**67.** The component of the magnetic resonance imaging (MRI) signal that depends on the direction of diffusion of water protons within the central nervous system tissue produces

(A) T1-weighted images
(B) T2-weighted images
(C) functional MRI
(D) diffusion-weighted MRI
(E) MR spectroscopy

**68.** Functional MRI is based on

(A) measuring changes in the oxygenation state of hemoglobin within a local brain region
(B) computing the distribution of radiolabeled compounds involved in neuronal metabolism or cerebral blood flow
(C) T1 relaxation time
(D) T2 relaxation time
(E) water protons activity in the brain tissue

**69.** Which of the following cerebellar cells is an excitatory interneuron?

(A) Basket cell
(B) Stellate cell
(C) Golgi cell
(D) Granule cell
(E) Pyramidal cell

**70.** Which of the following is a catecholamine neurotransmitter?

(A) Glutamate
(B) Dopamine
(C) Acetylcholine
(D) Serotonin
(E) Glycine

**71.** In the adult central nervous system, new neurons are continuously being generated in the

(A) frontal lobe
(B) hippocampal dentate gyrus
(C) thalamus
(D) caudate nucleus
(E) cerebellum

**72.** Differentiation of NSCs in neurospheres into neurons could be increased by

(A) leukemia inhibitory factor
(B) platelet derived growth factor
(C) activation of the Notch signaling pathway
(D) fibroblast growth factors
(E) transfection with v-*myc* oncogenes

**73.** In glial cell membranes, the vast majority of resting channels are permeable to

(A) sodium ions only
(B) potassium ions only
(C) chloride ions only
(D) calcium ions only
(E) calcium and chloride ions

**74.** Which of the following is true of the nerve's absolute refractory period?

(A) It follows the relative refractory period.
(B) It is caused by reduced opening of potassium channels.
(C) It results from residual inactivation of sodium channels.
(D) It results from the opening of chloride channels.
(E) An action potential may be triggered during the absolute refractory period, when a stimulus stronger than those normally required to reach threshold is applied.

# Answers and Explanations

1. **(B)** A substrate is accepted as a neurotransmitter when it is present in the presynaptic terminal, synthesized by neurons, and released in amounts sufficient to exert an effect on the postsynaptic neurons or effector organ, mimics its endogenous action when given exogenously, and has a specific mechanism for its removal from the site of action. Biogenic amine neurotransmitters include dopamine, norepinephrine, epinephrine, serotonin, and histamine. Amino acid neurotransmitters include GABA, glycine, and glutamate. Acetylcholine is the only accepted low-molecular-weight amine transmitter that is not an amino acid or derived directly from one. *(Kandell, 280)*

2. **(E)** Acetylcholine is synthesized from the combination of Acetyl CoA and choline in a reaction catalyzed by a choline acetyltransferase. Acetylcholine is then transported in vesicles into the cholinergic synapse. This transport can be blocked by vesamicol and induces the depletion of acetylcholine from the cholinergic vesicle. *(Cooper, 151–177)*

3. **(E)** The release of acetylcholine in the cholinergic synapse is promoted by β-bungarotoxin, a form of bungarotoxin that is fairly common in some snake venom. The target of this neurotoxin is the presynaptic terminal, where—by binding to proteins, most commonly actin—it causes release of acetylcholine and subsequent exhaustion of acetylcholine stores in the nerve terminal. *(Cooper, 151–177)*

4. **(D)** The release of acetylcholine at the cholinergic synapse is inhibited by botulinum toxin and magnesium. Botulinum toxin acts by binding presynaptically to high-affinity recognition sites on the cholinergic nerve terminals and decreasing the release of acetylcholine, causing a neuromuscular blocking effect. *(Cooper, 151–177)*

5. **(A)** Nicotinic receptors are blocked by curare and hexamethonium. Curare is an example of a nondepolarizing muscle relaxant that blocks the nicotinic acetylcholine receptor. The main toxin of curare, d-tubocurarine, occupies the same position on the receptor as acetylcholine with an equal or greater affinity and elicits no response, making it a competitive antagonist. The antidote for curare poisoning is an acetylcholinesterase inhibitor such as physostigmine. By blocking acetylcholine degradation, acetylcholinesterase inhibitors raise the amount of acetylcholine at the neuromuscular junction; the accumulated acetylcholine will then correct for the effect of the curare by activating the receptors not blocked by toxin at a higher rate. *(Cooper, 151–177)*

6. **(C)** Nicotinic receptors are blocked by curare and hexamethonium, whereas dimethylphenyl piperazinium acts as ganglionic nicotinic receptors agonist. *(Cooper, 151–177)*

7. **(A)** Cholinergic receptors fall into two categories: muscarinic and nicotinic. Muscarinic receptors that exhibit a slow response time are coupled to G proteins and are linked to phosphoinositide hydrolysis or cyclic AMP as a second messenger. Presynaptic or postsynaptic muscarinic receptors are blocked by atropine. Atropine and related compounds compete with acetylcholine and other muscarinic agonists for a common binding site on the muscarinic

receptor. Based on the position of retinol in the mammalian rhodopsin structure, binding site for competitive antagonists and acetylcholine likely is in a cleft formed by several of the receptor's seven transmembrane helices. An aspartic acid present in the N-terminal portion of the third transmembrane helix of all five muscarinic receptor subtypes is believed to form an ionic bond with the cationic quaternary nitrogen in acetylcholine and the tertiary or quaternary nitrogen of the antagonists. Since antagonism by atropine is competitive, it can be overcome if the concentration of acetylcholine at receptor sites of the effector organ is increased sufficiently. *(Cooper, 151–177)*

**8.** **(D)** Oxotremorine is a presynaptic muscarinic agonist that inhibits the evoked release of acetylcholine. *(Cooper, 151–177)*

**9.** **(B)** Acetylcholine is deactivated in the cholinergic synapse when it is hydrolyzed into choline and acetate by acetylcholinesterase, which may be inhibited reversibly by physostigmine. By interfering with the metabolism of acetylcholine, physostigmine indirectly stimulates both nicotinic and muscarinic receptors. *(Cooper, 151–177)*

**10.** **(B)** Acetylcholine is deactivated in the cholinergic synapse when it is hydrolyzed into choline and acetate by acetylcholinesterase, which may be inhibited reversibly by physostigmine or irreversibly by soman. *(Cooper, 151–177)*

**11.** **(C)** Acetylcholine is synthesized from choline and a donated acetyl group from acetyl-CoA by the action of choline acetyltransferase (ChAT). Thus, decreasing the amount of choline available to a neuron will decrease the amount of acetylcholine produced. Choline reuptake, for further acetylcholine synthesis, may be inhibited by a competitive blocker such as hemicolinium-3. It is a drug that blocks the reuptake of choline by the high-affinity transporter ChAT (encoded in humans by the gene SLC5A7) at the presynapse. The reuptake of choline is the rate-limiting step in the synthesis of acetylcholine; hence, hemicholinium decreases the synthesis of acetylcholine. It is therefore classified as an indirect acetylcholine antagonist. *(Cooper, 151–177)*

**12.** **(A)** Dopamine is synthesized from the essential amino acid tyrosine pathway involving five enzymes. The first enzyme is tyrosine hydroxylase. It is an oxidase that converts tyrosine to L-dopa. This is the rate-limiting step of dopamine synthesis and requires reduced pteridine as a cofactor, which is generated from pteridine by a pteridine reductase. L-dopa decarboxylase produces dopamine after decarboxylation of L-dopa. Dopamine is converted to norepinephrine by dopamine β-hydroxylase. Norepinephrine is methylated to epinephrine by phenylethanolamine-N-methyl transferase. *(Kandell, 282–283)*

**13.** **(B)** Serotonin is derived from the hydroxylation of tryptophan by a tryptophan hydroxylase followed by decarboxylation of hydroxytryptophan by a 5-hydroxytryptophan decarboxylase. *(Kandell, 283–284)*

**14.** **(A)** The stimulation of a motor nerve releases acetylcholine into the synaptic cleft, where it diffuses to bind and activate acetylcholine receptors. The activation of postsynaptic acetylcholine produces a rapid increase in the endplate current. After deactivation of acetylcholine, the random closure of the opened channels causes the endplate current to decay smoothly. The endplate current depends on the number of acetylcholine channels available for activation. The probability that a channel will be open depends on the concentration of acetylcholine at the channel, the conduction of each open channel, and the driving force acting on the ions. The postsynaptic acetylcholine receptor channels open by the binding of acetylcholine, not by a change in voltage; therefore, the value of the membrane potential does not influence the endplate current. *(Kandell, 190)*

**15.** **(E)** GABA is formed by the decarboxylation of glutamic acid by a glutamic acid decarboxylase, an enzyme located in the central nervous system and the retina. Allyglycine is an inhibitor of glutamic acid decarboxylase. GABA is metabolized by transamination by GABA-transaminase, yielding succinic semialdehyde and regenerating glutamate. GABA receptors fall into two major types: GABA A and GABA B. When

coupled with GABA, presynaptic and postsynaptic GABA receptors cause a shift in membrane permeability to chloride primarily. This change in chloride permeability results in hyperpolarization of the receptive neurons in case of postsynaptic inhibition or depolarization in case of presynaptic inhibition. The GABA A receptor–associated channels predominantly conduct chloride ions. Since the equilibrium potential of chloride is close to the resting potential of most neurons, an increase in the permeability of chloride decreases the depolarization effect of an excitatory input, resulting in the depression of excitability. Picrotoxin is a noncompetitive antagonist at GABA A receptors and thus a convulsant. It blocks the GABA-activated chloride ionophore. Although it is most often used as a research tool, it has been used as a central nervous system stimulant and an antidote in poisoning by central nervous system depressants, especially the barbiturates. *(Kandell, 190)*

**16.** **(B)** Muscimol is a direct postsynaptic GABA agonist that passes the blood–brain barrier and is active after systemic administration. Muscimol interacts directly with GABA A receptors, causing their activation. *(Cooper, 105–127)*

**17.** **(A)** Indirect GABA agonists act to facilitate GABAergic transmission by increasing the amount of GABA that reaches the receptors or by altering the interaction between the receptor and GABA. GABA transaminase inhibitors, such as gabaculine, are indirect GABA agonists, as the availability of the neurotransmitter to the GABA receptor is increased. *(Cooper, 105–127)*

**18.** **(A)** Allylglycine is a glycine derivative and an inhibitor of the enzyme glutamate decarboxylase. Inhibition of glutamate decarboxylase blocks GABA biosynthesis, leading to lower levels of the neurotransmitter. It is used to induce convulsions in animals in scientific studies. *(Cooper, 105–127)*

**19.** **(D)** Diazepam is a benzodiazepine that binds to a specific subunit on the GABA A receptor at a site that is distinct from the binding site of the endogenous GABA molecule. The GABA A receptor is an inhibitory channel that, when activated, decreases neuronal activity. Presynaptic and postsynaptic GABA receptors cause a shift in membrane permeability to chloride primarily when coupled with GABA. This change in chloride permeability results in hyperpolarization of the receptive neurons in case of postsynaptic inhibition or depolarization in case of presynaptic inhibition. Diazepam acts by increasing the frequency of opening of the chloride channels without altering either their conduction or their duration of opening. *(Cooper, 105–127)*

**20.** **(C)** Diazepam is a benzodiazepine that acts by increasing the frequency of opening of the chloride channels without altering either their conduction or their duration of opening; however, phenobarbital, which is a barbiturate, prolongs the duration of chloride channel opening by slightly decreasing the opening frequency. *(Cooper, 105–127)*

**21.** **(B)** Flumazenil is a benzodiazepine agonist as it binds to the same site of action as benzodiazepine in GABA A receptors. When administrated alone, flumazenil has no pharmacological effect. However, when administrated with a benzodiazepine, it reverses its effect. *(Cooper, 105–127)*

**22.** **(D)** GABA B receptors are not linked to a chloride channel. Presynaptic GABA B receptors are linked through GTP-sensitive proteins to a calcium or potassium channel. The inhibitory effect of GABA B receptor activation is probably mediated through either an increase in potassium conductance or a decrease in calcium conductance. GABA B receptor activation with baclofen decreases calcium conductance and GABA release. *(Cooper, 105–127)*

**23.** **(E)** Postsynaptic GABA B receptors are indirectly coupled to a potassium channel via G proteins mediating late inhibitory postsynaptic potentials. Phaclofen is an antagonist of GABA B receptors. *(Cooper, 105–127)*

**24.** **(C)** Nipecotic acid is a GABA uptake inhibitor. It acts as an indirect GABA agonist, as the

availability of the neurotransmitter to the GABA receptor is increased. *(Cooper, 105–127)*

**25. (B)** The dopamine reuptake transporter controls the levels of dopamine in the synapse by rapidly carrying the neurotransmitter back into nerve terminals after its release. Cocaine, which binds strongly to the dopamine reuptake transporter, blocks dopamine reuptake after normal neuronal activity and increases its level at the synapses, producing the characteristic cocaine euphoria. Animal studies show that the effect of dopamine is dependent on the type of dopamine synaptic receptor with which it interacts. D1-receptor agonists suppress cocaine-seeking behavior and may diminish episodes of intense craving for cocaine, whereas D2 receptor agonists may increase the cocaine-seeking behavior. Neutralization of the dopamine reuptake transporter inhibits the psychostimulatory effect of cocaine. Methadone is an active medication against chronic addiction to heroin, whereas naloxone is used in the treatment of heroin overdose. *(Leshner, 128–129)*

**26. (E)** Antiepilepsy medication side effects can be divided into two categories: dose-related and idiosyncratic. Ethosuximide is the drug of choice for the treatment of uncomplicated absence seizures. It acts by reducing low-threshold, transient, voltage-dependent calcium conductance in thalamic neurons. Its dose-dependent side effects include nausea, vomiting, abdominal pain, agitation, headaches, lethargy, drowsiness, dizziness, and ataxia. Idiosyncratic reactions to ethosuximide are rare and include rash, erythema multiforme, Stevens–Johnson syndrome agranulocytosis, and aplastic anemia. *(Brodie, 168–175)*

**27. (B)** Phenytoin is effective in the treatment of partial and tonic–clonic seizures. It appears to act by inducing voltage and use-dependent blockade of sodium channels. Its dose-dependent side effects include nausea, vomiting, ataxia, nystagmus, depression, drowsiness, paradoxical increase of seizures, gum hypertrophy, and megaloblastic anemia. Its idiosyncratic effects are hepatotoxicity, teratogenicity, acne, Stevens–Johnson syndrome, lupus-like syndrome, coarsening of facial features, hirsutism, and Dupuytren contracture. *(Brodie, 168–175)*

**28. (C)** Valproic acid is effective in patients with all types of seizures, especially in those with idiopathic generalized epilepsy. The drug may act by limiting sustained repetitive neuronal firing through inhibition of frequency-dependent blockade of voltage-dependent sodium channels. It may also increase brain GABA concentrations. Dose-related side effects to valproic acid include tremor, weight gain, alopecia, peripheral edema, nausea, and vomiting. Idiosyncratic reactions to valproic acid include acute pancreatitis, hepatotoxicity, encephalopathy, thrombocytopenia, and teratogenicity. *(Brodie, 168–175)*

**29. (B)** Primidone is metabolized to phenobarbital and another active metabolite, phenylethylmalonamide. The efficacy of primidone is similar to that of phenobarbital, but primidone is less well tolerated. Its dose-dependent side effects include fatigue, lethargy, depression, psychosis, decreased libido, and impotence. Its idiosyncratic side effects include rash, thrombocytopenia, lupus-like syndrome, agranulocytosis, and teratogenicity. *(Brodie, 168–175)*

**30. (D)** Phenobarbital is as effective as phenytoin in abolishing partial and generalized tonic–clonic seizures. At the cellular level, it prolongs inhibitory postsynaptic potentials by increasing the mean chloride-channel opening time and hence the duration of GABA-induced bursts of neuronal activity. Its dose-related side effects include decreased cognition, fatigue, lethargy and depression in adults and irritability, distractability, hyperkinesia, and insomnia in children. Idiosyncratic reactions include maculopapular rash, toxic epidermal necrosis, hepatotoxicity, arthritis, teratogenicity, and Dupuytren contracture. *(Brodie, 168–175)*

**31. (A)** Carbamazepine is effective for the treatment of partial and generalized tonic–clonic seizures but is not effective and may even be deleterious in patients with absence or myoclonic seizures. The drug acts by preventing repetitive firing of action potentials in depolarized neurons through voltage- and use-dependent blockade

of sodium channels. Its dose-dependent side effects include hyponatremia owing to its antidiuretic hormone–like effect, neutropenia, nausea, drowsiness, headache, dizziness, and diplopia. Idiosyncratic reactions include morbilliform rash in about 10% of cases, erythema multiforme and Stevens–Johnson syndrome, agranulocytosis, aplastic anemia, hepatotoxicity, and teratogenicity. *(Brodie, 168–175)*

**32. (A)** Carbamazepine induces hepatic enzymes to accelerate the hepatic metabolism of other lipid-soluble drugs, such as oral contraceptives. In addition to inducing its own metabolism, carbamazepine not only accelerates the metabolism of valproic acid, ethosuximide, corticosteroids, anticoagulants, antipsychotic drugs, and cyclosporine but also decreases their serum levels and the potency of their therapeutic effects. However, the metabolism of carbamazepine is inhibited by the administration of phenytoin, which paradoxically induces the metabolism of carbamazepine. Thus, adding phenytoin decreases plasma carbamazepine concentrations by about a third, whereas adding carbamazepine to phenytoin increases plasma phenytoin concentrations by a similar amount. Cimetidine, propoxyphene, diltiazem, erythromycin, isoniazid, and verapamil may inhibit the metabolism of carbamazepine to the point where the drug reaches a toxic level. *(Brodie, 168–175)*

**33. (D)** Phenytoin may increase the hepatic oxidation of lipid-soluble drugs including carbamazepine, valproic acid, ethosuximide, anticoagulants, corticosteroids, and cyclosporine. Drugs that inhibit the metabolism of phenytoin include allopurinol, amiodarone, cimetidine, imipramine, and some sulfonamides. This inhibition of the metabolism of phenytoin may bring the drug concentration to a toxic level. *(Brodie, 168–175)*

**34. (B)** Aspirin displaces valproic acid from its binding sites on plasma proteins and inhibits its metabolism. *(Brodie, 168–175; Goulden, 1392–1394)*

**35. (E)** Catecholamines are synthesized from tyrosine in the brain, chromaffin cells, and sympathetic ganglia. Tyrosine is metabolized in norepinephrine in the peripheral nervous system or in dopamine, norepinephrine, or epinephrine in the brain. Tyrosine hydroxylase is the first enzyme in the biosynthesis pathway of norepinephrine, allowing the conversion of tyrosine to dopa. It requires molecular $Fe^{2+}$, oxygen, and tetrahydropteridine as cofactors. Because it is the rate-limiting step in the synthesis of norepinephrine in the brain as well as in the peripheral nervous system, pharmacological blockade at this stage would reduce norepinephrine synthesis. Alpha-methyltyrosine is an amino acid analog that competitively inhibits tyrosine hydroxylase. *(Cooper, 184–202, 216)*

**36. (E)** Norepinephrine is stored in granules in the sympathetic nerve endings as well as in the central nervous system. Reserpine interferes with the storage of norepinephrine, causing irreversible long-lasting depletion of the storage of norepinephrine. *(Cooper, 184–202, 216)*

**37. (B)** The release of norepinephrine from storage granules is calcium-dependent. Amphetamines may cause an increase in the release of norepinephrine: when norepinephrine is released into the synaptic cleft, it binds to alpha or beta adrenoceptors and elicits the expected physiological effect. The norepinephrine transporter (NET) is the principal route by which norpinephrine removal occurs. The NET, often situated on the presynaptic neuronal membrane, pumps the synaptic norepinephrine back into the neuron cell body. In the cell body, this norepinephrine may reenter the vesicles or undergo metabolism through monoamine oxidase to dihydroxy phenylglycol. Under normal circumstances, presynaptic NET inactivates and recycles norepinephrine released by vesicular fusion. Amphetamine acts as both a NET substrate and a reuptake blocker, eliciting reverse transport and blocking normal uptake, thereby increasing norepinephrine levels in and beyond the synaptic cleft. *(Cooper, 184–202, 216)*

**38. (C)** Clonidine is a potent stimulator of alpha-2 presynaptic receptors. *(Cooper, 184–202, 216)*

**39. (C)** Phentolamine is an effective adrenergic postsynaptic alpha-receptor blocking agent. *(Cooper, 184–202, 216)*

**40.** **(D)** The action of norepinephrine is ended by its reuptake into the presynaptic terminal. This reuptake may be inhibited by desipramine. *(Cooper, 184–202, 216)*

**41.** **(A)** Norepinephrine is degraded by monoamine oxidase (MAO) when it presents in a free state within the presynaptic terminal. It is inhibited by pargyline. *(Cooper, 184–202, 216)*

**42.** **(D)** Outside the presynaptic neuron, norepinephrine is inactivated by catechol-O-methyltransferase (COMT). Tropolone is an inhibitor of COMT. *(Cooper, 184–202, 216)*

**43.** **(D)** D1 dopamine receptors are densely expressed in the amygdala, whereas D2 dopamine receptors as well as D3, D4, and D5 dopamine receptors have low levels of expression. D1 and D2 dopamine receptors are highly expressed in the caudate nucleus, putamen, nucleus accumbens, and olfactory tubercle. D1 dopamine receptors are not expressed in substantia nigra, ventral tegmental area, or zona inserta. *(Cooper, 241–242)*

**44.** **(E)** Among the drugs mentioned in this question, gabapentin is the only one that has no liver metabolism, as it is entirely eliminated by the kidney. Because of this pharmacological characteristic, gabapentin may be the drug of choice in treating patients with seizure and acute intermittent porphyria. *(Bourgeois, 1181–1183)*

**45.** **(C)** Mesolimbic dopamine neurons are involved in the reinforcing properties of a variety of abused drugs such as cocaine. It acts by blocking dopamine reuptake and inducing dopamine release. *(Cooper, 232)*

**46.** **(A)**

**47.** **(B)**

**48.** **(C)**

**49.** **(B)**

**50.** **(D)**

**51.** **(D)**

**52.** **(B)**

**53.** **(B)**

**Explanations 46 through 53**

Dopamine receptors are classified on the basis of a positive coupling between the receptor and adenylate cyclase activity, mainly into D1 and D2 receptors. When activated, D1 dopamine receptors increase adenylate cyclase activity, whereas the activation of D2 receptors inhibits adenylate cyclase activity, enhances potassium conductance, and inhibits calcium entry through voltage-sensitive calcium channels. The development of molecular biology divides D2 receptor into four subtypes and D1 receptors into two subtypes. D2 receptor subtypes are D2 short, D2 long, D3, and D4. D1 receptor subtypes include D1 and D5. D5 receptors have more affinity to dopamine than D1 receptors, which is the only difference between the two dopamine receptors. D4 receptors have the highest affinity to clozapine, an atypical neuroleptic, whereas D3 receptors have the highest affinity to the dopamine agonist quinpirole. Bromocriptine is a D2 receptor agonist, whereas sulpiride is a D2 antagonist. The expression of dopamine receptors has been observed to change in disease states. In schizophrenia, postmortem studies showed a consistent elevation of D2 receptors of the brain, whereas D1 receptors remain unchanged, even in tissue obtained from patients without neuroleptic treatment. In Parkinson disease, there is an increase in the expression of both D1 and D2 dopamine receptors. The chronic administration of dopamine antagonists, such as neuroleptic drugs, may increase the expression of dopamine receptors in the striatum. The development of tardive dyskinesia after a chronic use of neuroleptic may be explained by a supersensitivity of dopamine receptors that have been chronically blocked. *(Cooper, 227–264)*

**54.** **(B)** The major characteristic of Alzheimer disease is the deposition of A-β protein in the

microvasculature. This protein is derived from amyloid precursor protein (APP), which is encoded by a single gene on chromosome 21. APP has the structure of a transmembrane receptor with an N extracellular segment and a C intracellular segment. The dominant isoform of APP does not contain a protease inhibitor region. It undergoes fast axonal transport to the synaptic region to interact with the extracellular matrix. APP may undergo a nonamyloidogenic metabolism by cleavage of the A-β region (which includes the first 28 extracellular and the following 11 to 15 transmembrane amino acids), by an α secretase or by cleavage of the A-β sequence by a β secretase in the N-terminal sequence or a χ secretase in the C-terminal region. The production of A-β protein is thought to be a minor part of the normal processing of APP. *(Blennow, 77–86)*

**55. (B)** The mesoprefrontal dopamine system is a part of the mesotelencephalic dopamine system, which also includes the mesocingulate dopamine system. The mesotelencephalic dopamine system lacks neuron autoreceptors (in contrast to other dopamine neurons possessing autoreceptors such as the mesopiriform, mesolimbic, and nigrostriatal dopamine systems), which may explain some biochemical, physiological, and pharmacological characteristics of these midbrain neurons. Compared to dopamine systems possessing autoreceptors, the mesoprefrontal dopamine cells have a higher rate of firing and more bursting, a higher turnover rate and metabolism of transmitter dopamine, a lessened response to dopamine agonists and antagonists, and a lack of biochemical tolerance following chronic drug administration. *(Cooper, 255–261)*

**56. (C)** Radioligand binding studies have identified numerous subtypes of serotonin receptors in the brain. 5-HTA1 receptors have a high density in the raphe nuclei and the hippocampus. When activated, they hyperpolarize the cell membrane via G protein by opening potassium channels, inhibiting adenylate cyclase, or closing calcium channels. 5-HTA2 receptors are highly concentrated in layer IV of the cortex and the hippocampus. When activated, they depolarize the membrane and activate phospholipase C. 5-HT3 receptors are ligand-gated ion channel receptors. They mediate fast excitation through ligand-gated cationic ion channels that do not require coupling with G proteins or a second messenger. *(Cooper, 284–287)*

**57. (D)** Agranulocytosis is the most serious side effect of clozapine use. It occurs in 0.25% to 1% of treated patients, with peak incidence in the first 4 to 18 weeks of treatment. Other side effects include increased risk of grand mal seizure, sedation, hypersalivation, and weight gain. Clozapine has a very low incidence of acute or chronic motor side effects. *(Enna, 36–38)*

**58. (B)** Clozapine modifies the action of a number of neurotransmitter systems. It is an antagonist of both D1 and D2 dopamine receptors in the brain, with higher affinity for D1 than D2 dopamine receptors. Its highest affinity is for the D4 receptor. Also, it has a serotonin receptor antagonism, especially 5HT2a, an anticholinergic and histaminergic action. Clozapine induces depolarization blockade in A10 dopamine neurons and activates c-fos expression, a marker of cellular activity in the nucleus accubens, ventral striatum, anterior cingulate, and medial prefrontal cortex. In contrast, haloperidol activates c-fos expression in regions that receive projection from A9 dopamine neurons. *(Enna, 74–75)*

**59. (A)** Buspirone is an effective treatment for generalized anxiety. It belongs to the azapirone class of drug, which have a high affinity to 5HT1A receptors. Buspirone may act as a partial agonist at 5HT1A receptors at postsynaptic sites, potentially in the hippocampus and prefrontal cortex. *(Enna, 74–75)*

**60. (C)** The coadministration of lithium with diuretics and angiotensin-converting enzymes may increase lithium serum levels by promoting sodium loss and consequently a decrease in lithium excretion. Nonsteroidal anti-inflamatory medications except for aspirin may also increase lithium serum levels. *(Enna, 126–127)*

**61.** **(A)** Except for the neurons supplying the sweat gland, where acetylcholine is used as a neurotransmitter, the postganglionic sympathetic neurons use norepinephrine as a primary neurotransmitter. *(Haines, 474)*

**62.** **(A)** The dorsomedial nucleus of the hypothalamus subserves a function related to emotional behavior. In laboratory animals, stimulation of the dorsomedial nucleus results in unusually aggressive behavior, which lasts only as long as the stimulation is present. *(Haines, 490)*

**63.** **(D)** Corticotropin-releasing hormone is produced by neuroendocrine cells in the paraventricular nucleus and supraoptic nucleus of the hypothalamus; it is released from neurosecretory terminals of these neurons into the primary capillary plexus of the hypothalamohypophyseal portal system. The portal system carries the corticotrophin-releasing hormone to the anterior lobe of the pituitary, where it stimulates corticotropes to secrete adrenocorticotropic hormone (ACTH) and other biologically active substances. *(Haines, 494)*

**64.** **(C)** Taurine is believed to be the neurotransmitter of the superficial stellate cells of the cerebellum. Taurine levels are high in the molecular layer of the cerebellum and drop substantially when the development of stellate cells is blocked by x-irradiation. *(Afifi, 214–215)*

**65.** **(B)** GABA is released from axons of the Purkinje, basket and Golgi neurons of the cerebellum; it exerts an inhibitory effect on target neurons. *(Afifi, 215)*

**66.** **(E)** Although definite delineation of a sympathetic and parasympathetic center within the hypothalamus is not feasible, it is generally held that the rostral and medial hypothalamus is concerned with parasympathetic control whereas the caudal and lateral hypothalamus is concerned with sympathetic control mechanisms. Temperature regulation is under the control of the anterior regions of the hypothalamus. Drinking behavior is under the control of the lateral and anterior regions of the hypothalamus. The preoptic nucleus of the hypothalamus has significantly greater activation than other hypothalamic nuclei during sexual arousal. Through the connections of the suprachiasmatic nucleus with the retina and brain regions related to circadian rhythm, the hypothalamus plays an important role as an internal clock, regulating cyclic variation of a number of bodily function such as temperature, sleeping and waking, and hormonal changes. *(Afifi, 274)*

**67.** **(D)** Magnetic resonance imaging (MRI) uses a powerful magnetic field to align the nuclear magnetization of hydrogen atoms in water within the body. Protons in different tissues and fluid compartments, when placed in a strong magnetic field, have slightly different properties. MRI takes advantage of such differences to construct an image of brain structure or even function. MRI relies on the simple property that protons can be made to emit signals that reflect the local tissue environment. Hence, protons in different tissues or fluid emit different signals. This is achieved by exciting protons with low levels of energy, which are carried by electromagnetic waves emitted from a coil placed over the tissue. Once excited, the protons emit a signal with three components, or parameters, that depend on tissue characteristics. The first parameter is related to proton density in the tissue. The second and third parameters are related to proton relaxation time. The two relaxation time are termed T1 and T2. When an MRI scan is generated, it can be made to be dominated by one of these parameters. T1-weighted images are dominated by T1 relaxation time, whereas T2-weighted images are dominated by T2 relaxation time. In diffusion-weighted MRI, the images are generated after performing a major modification of the basic MRI technique. This takes advantage of a component of the MRI signal that depends on the direction of diffusion of water protons within the tissue, which is highly restricted within white matter tracts. *(Martin, 46–47)*

**68.** **(A)** Functional MRI provides images of brain function by measuring changes in the oxygenation state of hemoglobin within local brain regions. Active neurons consume more oxygen and more glucose and demand more blood flow

than silent ones. Typically, functional MRI scans reflect the difference in oxygenation state of hemoglobin between the resting condition and that which obtains when the individual being scanned is engaged in a particular task. *(Martin, 51)*

**69. (D)** The cerebellar cortex consists of three layers. From the cerebellar surface to the white matter these are the molecular, Purkinje, and granular layers. Five neuron classes are found in the cerebellar cortex: the Purkinje cells, which are projection neurons of the cerebellum and are inhibitory; the granule cells, which are the only excitatory interneurons of the cerebellum; and the basket, stellate, and Golgi cells, which are also inhibitory. Pyramidal cells are located in the cerebral cortex. *(Martin, 324)*

**70. (B)** The amino acid tyrosine is the precursor of three different amine neurotransmitters that contain a chemical structure called a catechol. These neurotransmitter are collectively called catecholamines. The catecholamine neurotransmitters are dopamine, norepinephrine, and epinephrine. Catecholaminergic neurons are found in regions of the nervous system involved in the regulation of movement, mood, attention, and visceral function. *(Bear, 143)*

**71. (B)** The existence of neural stem cells with the potential for multipotent differentiation has also been reported in embryonic and adult human brains. One study has demonstrated that in a group of cancer patients who received an infusion of bromodeoxyuridine (BrdU) for diagnostic purposes and later died, BrdU-labeled proliferating cells that colabeled with neuronal markers were found in the granular layer of the hippocampal dentate gyrus. It is evident from this study that new neurons are continuously being generated in the adult human central nervous system. *(Reynolds, 1707–1710)*

**72. (C)** Differentiation of neural stem cells into neurons can be increased by treatment with NT3, NT4, and platelet-derived growth factor (PDGF). Signaling by Notch, a member of the basic helix-loop-helix (bHLH) transcription factors, is an important pathway that controls a broad spectrum of cell fates and has been shown to induce glial cells in the central nervous system. Transient activation of *NOTCH1* in the rat NSC cell line induced commitment of these cells to astrocytes. Leukemia inhibitor factor and fibroblast growth factor are growth factors used for the expansion of neural stem cells. Neural stem cells transfection with the v-*myc* oncogene is used to generate clonally derived immortalized human neural stem cell lines. *(Kim, 193–201)*

**73. (B)** In the vast majority of resting channels in the membrane of the glial cell, which has a resting potential of −75 mV, are permeable only to potassium ions. As a result, the glial cell membrane at rest is almost permeable almost only to potassium ions. *(Kandel, 128)*

**74. (C)** The action potential is followed by a brief period of diminished excitablility, or refractoriness, which can be divided into two phases. The first phase, the absolute refractory period, comes immediately after the action potential. During this period, it is impossible to excite the nerve no matter how great the stimulating current applied. This phase is followed directly by the relative refractory period, during which it is possible to trigger an action potential but only by applying stimuli that are stronger than those normally required to reach threshold. These periods of refractoriness are caused by residual inactivation of sodium channels and increased opening of potassium channels. *(Kandel, 157)*

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CHAPTER 11

# Neurogenetics
## Questions

**1.** Which of the following genes is involved in familial amyotrophic lateral sclerosis?

(A) Androgen receptor gene
(B) Dystrophin gene
(C) Calpain 3 gene
(D) Caveolin gene
(E) Superoxide dismutase 1 gene

**2.** Which of the following disorders is consistently observed in a subset of families with amyotrophic lateral sclerosis?

(A) Seizure
(B) Frontotemporal dementia
(C) Sensory neuropathy
(D) Bladder dysfunction
(E) Autonomic dysfunction

**3.** Kearns–Sayre syndrome has

(A) an autosomal dominant transmission
(B) an autosomal recessive transmission
(C) X-linked transmission
(D) mitochondrial transmission
(E) sodium channel protein mutation

**4.** Mutation in the gene coding for calpain 3 causes

(A) oculopharyngeal muscular dystrophy
(B) paramyotonia congenita
(C) limb girdle muscular dystrophy 2A
(D) progressive external ophthalmoplegia
(E) Charcot–Marie–Tooth type 1A disease

**5.** Mutation in the gene coding for transthyretin causes

(A) familial amyloid polyneuropathy
(B) hereditary neuropathy with liability to pressure palsies
(C) Charcot–Marie–Tooth type 4C disease
(D) lipid storage myopathy
(E) hyperkalemic periodic paralysis

**6.** In Charcot–Marie–Tooth type 1B disease, the genetic defect is located in the gene coding for

(A) connexin 32
(B) lamin-A/C
(C) peripheral myelin protein 22
(D) emerin
(E) myelin protein 0

**7.** Arylsulfatase A deficiency causes

(A) metachromatic leucodystrophy
(B) acute intermittent porphyria
(C) X- linked spinobulbar muscular dystrophy
(D) hypokalemic periodic paralysis
(E) mitochondrial myopathy

**8.** A 4-year-old boy was brought for a consultation because of fatigue on exertion. He had a history of recurrent apneic episodes triggered by fever or vomiting. Neurological examination disclosed mild asymmetric ptosis. The test for acetylcholine receptor antibodies is negative. Electromyographic (EMG) studies show a decremental response at 10-Hz stimulation but absence such a response at 2 Hz in rested muscle. The most likely diagnosis is

(A) endplate acetylcholine esterase deficiency
(B) slow-channel congenital myasthenic syndrome
(C) congenital myasthenic syndrome with episodic apnea
(D) botulism
(E) Lambert–Eaton myasthenic syndrome

**9.** A 3-year-old boy was brought in by his mother because of moderate generalized weakness. He had a history of weak fetal movements in utero and was born after 38 weeks' gestation. He was hypotonic from birth with weak suck, lid ptosis, and delayed motor milestones. Neurological examination demonstrates generalized hypotonia, weakness, severe limitation of ocular movement, ptosis, and sluggish pupillary light reflexes. The test for acetylcholine receptor antibodies is negative and the child shows no response to the edrophonium test. EMG studies show repetitive compound muscle action potentials in response to single nerve stimulation. The most likely diagnosis is

(A) endplate acetylcholine esterase deficiency
(B) slow-channel congenital myasthenic syndrome
(C) congenital myasthenic syndrome with episodic apnea
(D) botulism
(E) Lambert–Eaton myasthenic syndrome

**10.** A 16-year-old boy developed diplopia and weakness, exacerbated by effort. Neurological examination demonstrates mild lid ptosis, limitation of vertical and horizontal eye movements, and generalized weakness predominantly in the wrist, finger extensors, and cervical muscles. EMG studies show a repetitive compound muscle action potentials in response to single nerve stimulation with decremental responses on 2-Hz stimulation, which is reversed with neostigmine administration. A younger brother and a maternal uncle have similar symptoms. The most likely diagnosis is

(A) endplate acetylcholine esterase deficiency
(B) slow-channel congenital myasthenic syndrome
(C) congenital myasthenic syndrome with episodic apnea
(D) botulism
(E) Lambert–Eaton myasthenic syndrome

**11.** Which of the following disorders has an X-linked inheritance?

(A) Lesch–Nyhan syndrome
(B) Neurofibromatosis type I
(C) Sturge–Weber syndrome
(D) Tuberous sclerosis
(E) Ataxia–telangiectasia

**12.** Which of the following is a major criterion for the diagnosis of tuberous sclerosis?

(A) Subependymal giant cell astrocytoma
(B) Vestibular schwannoma
(C) Meningioma
(D) Optic glioma
(E) Neurofibroma

**13.** Which of the following is *not* a criterion for neurofibromatosis type I?

(A) Optic glioma
(B) Bilateral auditory nerve schwannoma
(C) Two or more Lisch nodules
(D) Six or more café au lait lesions
(E) A first-degree relative with neurofibromatosis type I

**14.** The primary mechanism leading to cerebral infarction in patients with hereditary hemorrhagic telangiectasia is

(A) cerebral abscess
(B) embolism from pulmonary arteriovenous fistula
(C) cerebral aneurysm
(D) cerebral telangiectasia
(E) cerebral angioma

**15.** Sturge–Weber disease is transmitted as a

(A) sporadic pattern
(B) autosomal dominant pattern
(C) chromosomal deletion
(D) X-linked transmission
(E) mitochondrial transmission

**16.** Which of the following is true of neurofibromatosis type I?

(A) Neurofibromin is the protein encoded by the neurofibromatosis gene.
(B) Merlin is the protein encoded by the neurofibromatosis gene.
(C) It is linked to chromosome X.
(D) Bilateral vestibular schwannomas is one of its diagnostic criteria.
(E) It is associated with a high risk of severe mental retardation.

**17.** Which of the following is true of neurofibromatosis type I?

(A) Neurofibromin is the protein encoded by the neurofibromatosis gene.
(B) Merlin is the protein encoded by the neurofibromatosis gene.
(C) It is linked to chromosome X.
(D) It may occur with moyamoya syndrome.
(E) It is associated with a high risk of severe mental retardation.

**18.** Accumulation of very long chain fatty acids is seen in

(A) X-linked adrenoleukodystrophy
(B) Alexander disease
(C) Canavan disease
(D) cerebrotendinous xanthomatosis
(E) globoid leukodystrophy

**19.** Deficiency of the mitochondrial enzyme sterol 27-hydroxylase is observed in

(A) X-linked adrenoleukodystrophy
(B) Alexander disease
(C) Canavan disease
(D) cerebrotendinous xanthomatosis
(E) globoid leukodystrophy

**20.** The accumulation of glial fibrillary acidic protein exclusively in astrocytes is a hallmark of

(A) X-linked adrenoleukodystrophy
(B) Alexander disease
(C) Canavan disease
(D) cerebrotendinous xanthomatosis
(E) globoid leukodystrophy

**21.** Galactocerebroside deficit is a hallmark of

(A) X-linked adrenoleukodystrophy
(B) Alexander disease
(C) Canavan disease
(D) cerebrotendinous xanthomatosis
(E) globoid leukodystrophy

**22.** Aspartoacylase deficiency is observed in

(A) X-linked adrenoleukodystrophy
(B) Alexander disease
(C) Canavan disease
(D) cerebrotendinous xanthomatosis
(E) globoid leukodystrophy

**23.** Arylsulfatase deficiency is a hallmark of

(A) Canavan disease
(B) cerebrotendinous xanthomatosis
(C) globoid leukodystrophy
(D) metachromatic leukodystrophy
(E) Pelizaeus–Merzbacher disease

**24.** Alteration of the proteolipid protein gene (PLP) is responsible for

(A) Canavan disease
(B) cerebrotendinous xanthomatosis
(C) globoid leukodystrophy
(D) metachromatic leukodystrophy
(E) Pelizaeus–Merzbacher disease

**25.** Which of the following trinucleotide repeat expansion diseases is a type I disorder (i.e., occurs in the frame within the coding region)?

(A) Myotonic dystrophy
(B) Kennedy disease
(C) Fragile-X syndrome
(D) Friedreich ataxia
(E) Progressive myoclonic epilepsy type I

**26.** Which of the following types of frontotemporal dementia is linked to a tau gene mutation on chromosome 17?

(A) Semantic dementia
(B) Corticobasal degeneration
(C) Frontotemporal dementia with motor neuron disease
(D) Pick disease
(E) Dementia with parkinsonism

**27.** Abnormal expansion of the GAA trinucleotide on chromosome 9 is a hallmark of

(A) ataxia with selective vitamin E deficiency
(B) ataxia–telangiectasia
(C) Friedreich ataxia
(D) myotonic dystrophy type 1
(E) Huntington disease

**28.** Mutation in the alpha-tocopherol transfer protein gene on chromosome 8 is observed in

(A) ataxia with selective vitamin E deficiency
(B) ataxia–telangiectasia
(C) Friedreich ataxia
(D) myotonic dystrophy type 1
(E) Huntington disease

**29.** The gene defect in ataxia–telangiectasia is located on chromosome

(A) 11
(B) 8
(C) 17
(D) 19
(E) X

**30.** Which of the following spinocerebellar atrophies has a benign course and normal life span?

(A) Spinocerebellar atrophy type 3
(B) Spinocerebellar atrophy type 4
(C) Spinocerebellar atrophy type 1
(D) Spinocerebellar atrophy type 6
(E) Spinocerebellar atrophy type 7

**31.** Which of the following progressive ataxias are related to CTG repeats?

(A) Spinocerebellar ataxia type 8
(B) Spinocerebellar ataxia type 7
(C) Dentatorubral-pallidoluysian atrophy (DRLPA)
(D) Spinocerebellar ataxia type 6
(E) Spinocerebellar ataxia type 3

**32.** The abnormal gene coding for Huntingtin is located on

(A) chromosome 12
(B) chromosome X
(C) chromosome 19
(D) chromosome 4
(E) chromosome 14

**33.** The abnormal gene coding for Myotonin is located on

(A) chromosome 12
(B) chromosome X
(C) chromosome 19
(D) chromosome 4
(E) chromosome 14

**34.** The abnormal gene coding for Atrophin is located on

(A) chromosome 12
(B) chromosome X
(C) chromosome 19
(D) chromosome 4
(E) chromosome 14

**35.** The abnormal gene coding for Ataxin 3 is located on

(A) chromosome 12
(B) chromosome X
(C) chromosome 19
(D) chromosome 4
(E) chromosome 14

**36.** The abnormal gene coding for the androgen receptor is located on

(A) chromosome 12
(B) chromosome X
(C) chromosome 19
(D) chromosome 4
(E) chromosome 14

**37.** The genetic phenomenon responsible for the clinical heterogeneity of mitochondrial diseases is

(A) sporadic mutation
(B) chromosomal deletion
(C) anticipation
(D) heteroplasmy
(E) mitotic instability

**38.** Which of the following disorders has a mitochondrial inheritance?

(A) Myotonic dystrophy
(B) Wilson disease
(C) Metachromatic leukodystrophy
(D) Myoclonic epilepsy with ragged-red fibers
(E) Adrenoleukodystrophy

**39.** Which of the following have similar genetic transmission to the transmission of Fabry lipid storage disease?

(A) Metachromatic leukodystrophy
(B) Tuberous sclerosis
(C) Adrenoleukodystrophy
(D) Neurofibromatosis
(E) Wilson disease

**40.** Which of the following have similar genetic transmission to Wilson disease?

(A) Myotonic dystrophy
(B) Metachromatic leukodystrophy
(C) Adrenoleukodystrophy
(D) Neurofibromatosis
(E) Fabry lipid storage disease

**41.** Which of the following have similar genetic transmission to tuberous sclerosis?

(A) Metachromatic leukodystrophy
(B) Adrenoleukodystrophy
(C) Fabry lipid storage disease
(D) Myoclonic epilepsy with ragged-red fibers
(E) Neurofibromatosis

**42.** Which of the following is true about chronic progressive external ophtalmoplegia (CPEO)?

(A) Mitochondrial DNA deletion is the most common mutation in CPEO.
(B) The onset of the disorder is usually after the age of 50 years.
(C) The transmission of the disorder is usually X-linked.
(D) Diplopia is a common manifestation of CPEO.
(E) Muscle biopsy is normal in most patients with CPEO.

**43.** Which of the following manifestations differentiates Kearns–Sayre syndrome from chronic progressive external ophthalmoplegia?

(A) Proximal muscles weakness
(B) Ptosis
(C) Ophthalmoplegia
(D) Cardiomyopathy
(E) Elevated cerebrospinal fluid protein

**44.** A 39-year-old man with a history of non-insulin-dependent diabetes suddenly developed right hemisensory loss. A computed tomography (CT) scan of the head showed bilateral calcification of the basal ganglia. Magnetic resonance imaging (MRI) of the brain confirmed the presence of an acute stroke. Subsequently, genetic testing revealed an A3243G mitochondrial mutation. The patient may develop

(A) optic neuritis
(B) ptosis
(C) lactic acidosis
(D) ophthalmoplegia
(E) cardiomyopathy

**45.** The *NOTCH3* gene mutations causes

(A) mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
(B) myoclonic epilepsy with ragged-red fibers
(C) Fabry disease
(D) cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
(E) familial intracranial aneurysms

**46.** Mutations in the procollagen type IV alpha 1 gene *COL4A1* have been associated with

(A) Fabry disease
(B) mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
(C) cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
(D) autosomal dominant small vessel disease with hemorrhagic stroke
(E) myoclonic epilepsy and ragged-red fibers

**47.** Which of the following is an inherited risk factor for cerebral venous thrombosis?

(A) Mutation in the gene coding for amyloid precursor protein (APP)
(B) Factor V Leiden
(C) Mutations in mitochondrial DNA
(D) Homocystinuria
(E) *NOTCH3* mutations

**48.** Carbamazepine-induced Stevens–Johnson syndrome is more prevalent in patients carrying

(A) mutations in the *NOTCH3* gene
(B) *HLA-B 1502*
(C) *HLA-B 5801*
(D) *HLA-B 0702*
(E) mitochondrial DNA mutations

**49.** Mutations in which of the following genes cause autosomal dominant transmission of Parkinson disease?

(A) *PARKIN*
(B) *LRRK2*
(C) *PINK1*
(D) *DJ-1*
(E) *ATP13A2*

**50.** Mutations in which of the following genes cause Parkinson disease with early dementia, autonomic dysfunction, and premature death?

(A) *PARKIN*
(B) *LRRK2*
(C) *PINK1*
(D) *DJ-1*
(E) Alpha-synuclein

**51.** Mutations in which of the following genes frequently cause early onset of Parkinson disease with slow progression and excellent response to levodopa?

(A) *PARKIN A*
(B) *LRRK2*
(C) Alpha-synuclein
(D) *DJ-1*
(E) *ATP13A2*

**52.** Which of the following characteristics differentiate Parkinsons disease patients carrying *PINK1* mutations from those who are carrying *PARKIN* mutations?

(A) Autosomal dominant transmission
(B) Autosomal recessive transmission
(C) Early-onset Parkinson disease
(D) Higher rate of psychiatric symptoms
(E) Higher rate of autonomic dysfunction

**53.** Mutations in the *DJ-1* gene cause

(A) autosomal dominant Parkinson disease
(B) dementia
(C) severe autonomic dysfunction
(D) early-onset Parkinson disease
(E) intractable seizure

**54.** Mutations in which of the following genes frequently cause subacute juvenile-onset levodopa-responsive Parkinson disease?

(A) *PARKIN*
(B) *LRRK2*
(C) Alpha-synuclein
(D) *DJ-1*
(E) *ATP13A2*

**55.** Which of the following disorders causes ataxia with DNA repair defect?

(A) Friedreich ataxia
(B) Refsum disease
(C) Wilson disease
(D) Metachromatic leukodystrophy
(E) Ataxia–telangiectasia

**56.** A 52-year-old man developed progressive ataxia and cognitive deficits. His neurological examination showed a combination of kinetic tremor, gait ataxia, autonomic dysfunction, and polyneuropathy. The most likely diagnosis is

(A) CAG triplet repeat disorder
(B) CGG triplet repeat disorder
(C) pentanucleotide repeat expansion (ATTCT) disorder
(D) Parkinson disease with α-synuclein mutation
(E) Parkinson disease with *PARKIN* mutation

**57.** The association of cerebellar ataxia and pigmentary retinopathy is suggestive of

(A) spinocerebellar ataxia type 7
(B) spinocerebellar ataxia type 10
(C) spinocerebellar ataxia type 1
(D) herediary episodic ataxia
(E) Leigh syndrome

**58.** Beside cerebellar ataxia, spinocerebellar ataxia type 10,17 and DRPLA have in common the occurrence of

(A) ophthalmoaresis
(B) seizure
(C) pigmentary retinopathy
(D) peripheral neuropathy
(E) parkinsonism

**59.** Myokymia can occur in

(A) DRPLA
(B) spinocerebellar ataxia type 10
(C) spinocerebellar ataxia type 5
(D) Friedreich ataxia
(E) ataxia–telangiectasia

**60.** Linkage studies have mapped frontotemporal dementia with parkinsonism to chromosome

(A) 9
(B) X
(C) 3
(D) 17
(E) 1

**61.** Which of the following types of episodic ataxia (EA) causes the longest-lasting attacks?

(A) Episodic ataxia type 1
(B) Episodic ataxia type 2
(C) Episodic ataxia type 3
(D) Episodic ataxia type 4
(E) Episodic ataxia type 7

**62.** Familial hemiplegic migraine type 1 is caused by mutations in which of the following genes?

(A) *CACN1A*
(B) *ATP1A2*
(C) *SCNA1*
(D) *CACNB4*
(E) *KCNA1*

# Answers and Explanations

1. **(E)** The greatest contribution toward an understanding of amyotrophic lateral sclerosis (ALS) thus far has come from the discovery of mutations in the superoxide dismutase 1 (*SOD1*) gene on chromosome 21q22.11, which account for 10% to 20% of autosomal dominant ALS cases. Tremendous efforts have been made to understand not only the multiple likely pathogenic mechanisms of *SOD1* in eliciting disease but also the genetic profile of the reported mutations in this gene. A number of conclusions can be drawn from this research: (1) *SOD1* mutations result in a toxic gain-of-function pathology. Evidence for this arose largely from mouse studies in which the knockout of the *SOD1* gene failed to yield a phenotype; conversely, transgenic mice that overexpressed mutant *SOD1* did develop a motor neuron phenotype. (2) Loss of the normal function of *SOD1* is not the cause of ALS. Mutations in the *SOD1* gene have a broad range of effects on the enzymatic activity of *SOD1*; however, among the mutated SOD1 proteins reported, some noticeably retained full enzymatic activity. The rest of the mutations were shown to influence, among other things, the stability of *SOD1*, its ability to dimerize, its hydrophobicity, and its ability to chelate copper ions. Different *SOD1* mutations may also influence various aspects of the disease, such as its onset or duration, but they nonetheless do not cause ALS. (3) Mutations can occur at almost any position in the *SOD1* gene. One of the most remarkable aspects of this gene is that more than 110 mutations have been reported in nearly 50% of the 153 amino acids in the SOD1 protein. The distribution of these mutations is quite uniform: the largest interval without a reported mutation is only nine consecutive amino acids. (4) With some noteworthy exceptions, mutations are primarily dominant. *(Amato, 53; Valdmanis, 144–152)*

2. **(B)** Frontotemporal dementia (FTD) is the only reported disease which is consistently observed in a subset of ALS families. Estimates of FTD prevalence in ALS cases range between 5% and 15%. *(Valdmanis, 144–152)*

3. **(D)** Single large mitochondrial DNA deletions (ranging from 1.3 to 8.8 kb) can be demonstrated in most patients with Kearns–Sayre syndrome. One is more likely to find mitochondrial DNA mutations in muscle tissue than in peripheral white blood cells, with the percentage of affected mitochondrial genomes in muscle biopsies ranging from 20% to 90%. *(Amato, 636–637).*

4. **(C)** Limb girdle muscular dystrophy 2A is caused by a mutation in the calpain-3 gene. Calpain-3 is a muscle-specific, calcium-dependent, nonlysosomal, proteolytic enzyme. The mutation leads to an absence or reduction in the activity of this enzyme, which can lead to accumulation of toxic substances in muscle cells. *(Amato, 543)*

5. **(A)** Familial amyloid polyneuropathy is an autosomal dominant disorder in which there is extracellular deposition of amyloid in peripheral nerves and other organs. A painful sensory neuropathy with early involvement of autonomic nerves and cardiomyopathy is typically present. Age of onset can vary from 18 to 83 years. Small fibers (for pain and temperature) are more affected than large fibers (for vibration and proprioception); anhidrosis, gastrointestinal disturbances (diarrhea alternating with constipation),

impotence, orthostatic intolerance, visual changes, and arrhythmias are additional features. Mutations in transthyretin (FAP 1 and 2), apolipoprotein A1 (FAP 3), or gelosin (FAP 4) are responsible. Transthyretin is most often implicated in peripheral neuropathy. Nearly 100 different mutations have been identified in the *TTR* gene, the most common being the Val30Met mutation. Liver transplantation halts disease progression. *(Chaudhry, chapter 379)*

6. **(E)** Myelin protein 0 (MPZ) is a major peripheral nervous system protein responsible for myelin compaction and the adherence of myelin wraps to each other. It is also involved in the signal transduction cascade responsible for interaction between the Schwann cell and axon, as well as regulation of myelin-specific gene expression. Mutations in the *MPZ* gene are associated with the autosomal dominant form of Charcot–Marie–Tooth disease type 1 (CMT1B), which is characterized by progressive slowing of nerve conduction and hypertrophy of Schwann cells. Mutations in *MPZ* can also produce the more severe polyneuropathies, Dejerine–Sottas syndrome (DSS) and congenital hypomyelinating neuropathy, as well as several types of axonal CMT2. *MPZ* mutations cause hereditary neuropathy with phenotypic clustering into two major clinical, electrodiagnostic, and pathological entities. The early-onset form causes severe neuropathy in infancy with delayed motor milestones, slow conduction velocities in the demyelinating range, and predominant demyelination on nerve biopsy. It seems that mutations that significantly disturb the tertiary structure of MPZ are responsible for this phenotype. The late-onset form presents in adulthood with neuropathy that is slowly progressive, with axonal features to a greater extent than demyelinating features on electrodiagnostic and nerve biopsy studies. Mutations that subtly affect the MPZ structure may interfere with Schwann cell–axon interaction and cause this phenotype. *(Souayah, 177–179)*

7. **(A)** Metachromatic leukodystrophy is an autosomal recessive disorder caused by a mutation in the arylsulfatase A or prosaposin gene. Arylsulfatase and prosaposin are both enzymes required for metabolizing galactosylsulfatide, a glycolipid present in myelin membranes. *(Amato, 193)*

8. **(C)** The case described in this vignette has the characteristic features of congenital myasthenic syndrome with episodic apnea: recurrent apneic episodes triggered by fever or vomiting, and mild ptosis as well as absence of decremental response on 2-Hz stimulation and presence of this response on 10-Hz stimulation. Muscle biopsy confirms the diagnosis by showing endplate acetylcholine receptor deficiency without postsynaptic structural abnormalities. The abnormality involves a presynaptic defect. There is a marked decrease in the number of acetylcholine quanta released by the nerve impulse due to a defect in the synthesis or axonal transport of vesicle precursors from the anterior horn cell to the nerve terminal. *(Conneally, 9–23)*

9. **(A)** Endplate acetylcholine esterase deficiency causes a congenital myasthenic syndrome characterized by delayed pupillary light reflexes, refractoriness to cholinesterase inhibitors, and repetitive compound muscle action potentials. The illness is caused by the absence of acetylcholine esterase in the synaptic space. The neuromuscular transmission is compromised by the reduced size of the nerve terminals, with their encasement by Schwann cells reducing the number of releasable acetylcholine quanta. The cholinergic overactivity may induce the Schwann cells to encase the nerve terminals, thus protecting the endplate from overexposure to acetylcholine. The absence of acetylcholine esterase in the synaptic terminals results in an overexpression of acetylcholine, causing a prolongation of the synaptic potentials beyond the refractory period of the muscle fiber, which triggers repetitive compound muscle fiber action potentials. The progression of the disease is attributed to an endplate myopathy from cholinergic overactivity. The molecular basis of the disease involves a recessive mutation in COLQ, a triple stranded collagenic tail of the acetylcholinesterase enzyme. Typical clinical manifestations of the disease are described in this vignette. The diagnosis is confirmed by muscle biopsy that demonstrates absence of acetylcholine esterase from endplates. *(Conneally, 9–23)*

**10.** **(B)** The case described in this vignette has features that point to slow-channel congenital myasthenic syndrome: selective involvement of wrist and finger extensors, possible dominant inheritance, and repetitive compound muscle action potentials with decremental response on 2-Hz stimulation repaired by neostigmine administration. An endplate myopathy is caused by prolonged opening episodes of acetylcholine receptors during activity and spontaneous opening of acetylcholine receptors at rest. *(Conneally, 9–23)*

**11.** **(A)** Lesch–Nyhan disease has X-linked inheritance and is characterized by self-mutilation of digits and lips. Its neurological features include mental retardation and dystonia. Neurofibromatosis type I is an autosomal dominant disorder characterized by dermatological and neurological features. Cutaneous features include café au lait spots, axillary freckling, neurofibroma, Lisch nodules of the iris, and plexiform neurofibromas. Neurological features include learning disability, cognitive impairment, and neuraxis tumors. Sturge–Weber disease has sporadic inheritance. The neurological features comprise epilepsy, mental retardation, and focal deficits. Epilepsy, mental retardation, autism, and giant cell astrocytoma complicate tuberous sclerosis, a neurocutaneous disease with autosomal dominant transmission. Ataxia–telangiectasia is an autosomal recessive disease characterized by ataxia, intention tremor, abnormal saccades, and decreased deep tendon reflexes. *(Roach, 591–620)*

**12.** **(A)** Tuberous sclerosis complex (TSC) arises from abnormal cellular differentiation, proliferation, and neuronal migration. It affects the brain (cortical and subcortical tubers, subependymal nodules, and giant cell astrocytomas), kidney, skin (hypomelanotic macules, shagreen patches, facial angiofibromas, and periungual fibromas), eye (retinal hamartomas), heart, and to a lesser extent other organs. The Tuberous Sclerosis Complex Consensus Conference divided the criteria for diagnosis into major and minor features. The major features include cortical tuber, subependymal nodule, subependymal giant cell astrocytoma, and skin changes, as mentioned above. *(Sparagana, 115–119)*

**13.** **(B)** The gene for neurofibromatoses type I occurs as a spontaneous mutation in 1 per 10,000 individuals and can affect most organ systems. Initial signs and symptoms vary. In 1987, the National Institutes of Health issued a consensus statement enumerating the clinical diagnostic criteria for neurofibromatosis type I. They include two of the following: (1) six or more cafe au lait macules greater than 5 mm in prepubertal patients and greater than 15 mm in postpubertal patients; (2) two or more neurofibromas of any type or one plexiform neurofibroma; (3) axillary or inguinal freckling; (4) optic nerve glioma; (5) two or more Lisch nodules (iris hamartomas); (6) sphenoid wing dysplasia or cortical thinning of long bones with or without pseudarthrosis; and (7) a first-degree relative (parent, sibling, or child) with NF-1 based on the preceding criteria. *(Karnes, 1071–1076)*

**14.** **(B)** Hereditary hemorrhagic telangiectasia (HHT), also known as Osler–Weber–Rendu disease, is a hereditary autosomal dominant syndrome characterized by easy bleeding and vascular abnormalities. The classic picture is that of a familial pattern of telangiectasias and epistaxis. The characteristic lesion is the telangiectasia: a lesion 1 to 2 mm in diameter consisting of a dilated vessel directly connecting an artery and a vein. Telangiectasias probably develop from dilated postcapillary venules. Telangiectasias usually appear on the skin and mucosal surfaces, especially on the nose.

Larger arteriovenous malformations (AVMs), consisting of thin-walled vascular spaces with single or multiple feeding arteries occur mostly in the lungs, liver, and brain. These may reach a diameter of several centimeters. Vascular malformations may appear in any organ, however. Transforming growth factor beta is known to have a regulatory role in tissue repair and angiogenesis. Mutation on chromosome 9 seems to predispose to a high prevalence of pulmonary AVMs, which are found in 15% to 33% of patients with HHT and are usually fed by the pulmonary artery, draining through the pulmonary veins.

Some 70% of pulmonary AVMs (PAVMs) occur in the lower lung fields and may enlarge with time or during pregnancy. They can result in a substantial right-to-left shunt, with significant

hypoxemia. Serious complications may occur: bleeding can result in potentially life-threatening hemoptysis or hemothorax, and paradoxical emboli, bypassing the pulmonary capillary system via the PAVM, may give rise to ischemic cerebral events. This is the primary mechanism leading to cerebral infarction in patients with HHT (up to one third of patients with PAVMs suffer from ischemic cerebral events). *(Haitjema, 714–719)*

**15.** **(A)** Sturge–Weber syndrome is a neurocutaneous syndrome characterized by port wine facial nevi and associated leptomeningeal and brain angiomas. The syndrome occurs sporadically but may result from a somatic mutation disturbing the angiogenic process. *(Huq, 780–782)*

**16.** **(A)** Neurofibromatosis (NF) is a neurocutaneous condition, of which two types exist. NF type I (NF-I) occurs in about 1 in 3,000 persons and accounts for 96% to 97% of all cases of NF. NF type II (NF-II) accounts for about 3% of cases. Both NF-I and NF-II have autosomal dominant transmission. Almost every organ system can be involved in NF-I; thus, initial signs and symptoms vary. Lisch nodules and optic nerve gliomas are among the diagnostic criteria of NF-I.

The most common benign tumors in patients with NF-I are neurofibromas. They are composed of Schwann cells, fibroblasts, mast cells, and vascular elements. Plexiform neurofibromas are specific to NF-I. Schwannomas are uncommon in patients with NF-I but when they occur, they exist on spinal nerve sheaths. It has recently been suggested that when a single vestibular schwannoma is detected on an imaging study of the head, it is unlikely that the patient has NF-I.

Central nervous system manifestations of NF-I include aqueductal stenosis, hydrocephalus, and seizures. Of patients with NF-I, 25% to 40% may have learning disabilities, and 5% to 10% may have mental retardation. Essential hypertension may occur in patients with NF-I; hypertension may also be due to pheochromocytoma, renal artery stenosis, neurofibromas that compress the kidneys or renal arteries, renal artery dysplasia, Wilms' tumor, or coarctation of the abdominal or thoracic aorta. Dysplasia of the cerebral artery may occur, causing moyamoya syndrome.

The gene for NF-I is located on the long arm of chromosome 17 at 17q11.2. Neurofibromin is the protein encoded by the neurofibromatosis gene and may act as a tumor suppressor. *(Karnes, 1071–1076)*

**17.** **(B)** The diagnostic criteria for NF-II are either (1) bilateral eighth-nerve masses or (2) a first-degree relative with NF-II and either a unilateral auditory nerve mass or two of the following: neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacity. Schwannoma is the most common tumor in NF-II. Such tumors may involve cranial as well as peripheral nerves. Schwannomas of spinal nerve sheath tumors are also common in patients with NF-II, and spinal cord ependymomas may occur. The gene for NF-II is located on chromosome 22 at 22q11. Merlin, the gene product of the chromosome of NF-II, is a tumor suppressor. *(Karnes, 1071–1076)*

**18.** **(A)** X-linked adrenoleukodystrophy (X-ALD) encompasses widely differing clinical phenotypes that reflect two distinct pathological mechanisms: an inflammatory demyelinating process that leads to a rapidly progressing fatal disorder and a slowly progressing, distal axonopathy that leads primarily to adrenomyeloneuropathy in young adults. In all forms of X-ALD, very long chain fatty acids (VLCFAs) accumulate in tissues and body fluids, due to impaired activation of these fatty acids. *(Berger, 305–312)*

**19.** **(D)** Cerebrotendinous xanthomatosis is a lipid storage disorder caused by deficiency of the mitochondrial enzyme sterol 27-hydroxylase, which leads to accumulation of cholesterol and bile alcohols. *(Berger, 305–312)*

**20.** **(B)** Alexander disease is a lethal leukodystrophy with a variable clinical course. The most common, infantile form is associated with megalencephaly, seizures, developmental retardation, and premature death. Juvenile and adult patients, on the other hand, experience ataxia, spasticity, and bulbar signs, with relatively little loss of myelin. Neuroradiological and neuropathological studies

show extensive white matter involvement with frontotemporal predominance. The pathological hallmark of Alexander disease is the accumulation of intracellular inclusions (Rosenthal fibers) exclusively in astrocytes. These consist of aggregated glial fibrillary acidic proteins (GFAPs) and small stress proteins. *(Berger, 305–312)*

**21.** **(E)** Globoid cell leukodystrophy (GLD), also called Krabbe disease, is an inherited neurological disease caused by mutations in the GALC gene, which encodes the lysosomal enzyme galactocerebrosidase, responsible for the degradation of galactosylceramide and galactosylsphingosine. *(Berger, 305–312)*

**22.** **(C)** Canavan disease is an inherited infantile leukodystrophy associated with spongy degeneration of white matter, macrocephaly, severe psychomotor retardation, seizures, and premature death. It is characterized by aspartoacylase deficiency. The enzyme defect leads to the accumulation of N-acetyl aspartate (NAA) in the brain and body fluids. *(Berger, 305–312)*

**23.** **(D)** A genetic deficiency in the lysosomal enzyme arylsulfatase A (ASA) causes the neurometabolic disease metachromatic leukodystrophy (MLD). Three major clinical variants have been characterized: late infantile, juvenile, and adult MLD. ASA deficiency results in impaired degradation of the substrate galactosylsulfatide, which allows for the biochemical diagnosis of MLD on the basis of ASA activity in leukocytes or fibroblasts and galactosylsulfatide excretion in urine. *(Berger, 305–312)*

**24.** **(E)** Pelizaeus–Merzbacher disease (PMD) is an X-linked dysmyelinating disorder caused by alterations in the proteolipid protein gene (PLP), which encodes two major proteins of central nervous system myelin: PLP and its spliced isoform DM20. *(Berger, 305–312)*

**25.** **(B)** Trinucleotide repeat expansion disorders may be arbitrarily divided into two types, based on the location of the mutations within their respective genes. This classification is useful because the location of the mutation may have implications regarding the mechanism of pathogenesis.

Type I disorders are those in which the expansion occurs in-frame (i.e., within the coding region) and results in an expanded stretch of amino acids generated by the abnormal gene. Huntington disease; Kennedy disease; spinocerebellar ataxia types 1, 2, 3, 6, 7, and 17; DRLPA; and oculopharyngeal muscular dystrophy are among type I expansion disorders.

Type II disorders are those in which the expansion occurs outside the coding region: either upstream of the coding sequence, downstream of the coding sequence, or within an intron. Spinocerebellar ataxia type 8, 10, and 12; fragile-X syndrome; Jacobsen syndrome; progressive myoclonic epilepsy type I; Friedreich ataxia; and myotonic dystrophy are type II diseases.

In type I disorders, the mutant gene is transcribed and translated normally but leads to the production of a protein harboring an expanded stretch of a particular amino acid. The trinucleotide expansions in type I disorders tend to be small, with a similar threshold for disease (36 to 40 trinucleotide repeats, with limited exceptions). To date, in each case of type I disease, the mutant protein is endowed with a toxic "gain of function." In general, all type I diseases except spinobulbar muscular atrophy are dominantly inherited, tend to be of late onset, and have manifestations that are limited to the nervous system.

Conversely, in type II disorders, the coding sequence remains unchanged and the protein product is normal, yet mutations in untranslated regions of the gene lead to abnormal transcription or RNA processing, resulting in altered levels of gene expression. The trinucleotide expansions leading to type II disorders tend to be large, with hundreds to over a thousand trinucleotides. These mutations often result in "loss of function" of the relevant gene. Most of type II disorders are multisystem disorders and tend to have younger ages of onset than type I disorders. *(Taylor, 24–25)*

**26.** **(E)** Frontotemporal dementias occur in either familial forms or, more commonly, as sporadic cases. Neuropathologically, they are characterized by a remarkably circumscribed atrophy of the frontal and temporal lobes of the cerebral

cortex, often with additional subcortical changes. An autosomal dominantly inherited familial form of frontotemporal dementia with parkinsonism was linked to chromosome 17q21.2. A major neuropathological characteristic of FTDP-17 is a filamentous pathology made of hyperphosphorylated tau protein. *(Goedert, 74–83)*

**27.** **(C)** Friedreich ataxia is the most common genetic ataxia and is of autosomal recessive inheritance, with progressive gait and limb ataxia as the cardinal features. It is associated with lower limb areflexia, dysarthria, pyramidal weakness, and sensory loss manifesting later in the course of the disease. The abnormal gene of Freidreich ataxia is located on chromosome 9. The abnormal gene contains an expansion of GAA trinucleotides that number between 200 and 900. (Normal chromosomes contain 10 to 21 GAA repeats). *(Hammans, 327–332)*

**28.** **(A)** Secondary vitamin E deficiency (precipitated by a beta-lipoproteinaemia or other fat malabsorptive syndromes) is associated with ataxia. The onset of symptoms occurs between 4 and 18 years of age, with progressive ataxia, areflexia, sensory loss, pyramidal signs, and sometimes cardiomyopathy. Ataxia with selective vitamin E deficiency was linked to chromosome 8q13 in 1993. Subsequently, the mutation was identified in the alpha-tocopherol transfer protein on chromosome 8. *(Hammans, 327–332)*

**29.** **(A)** Ataxia–telangiectasia is an autosomal recessive disease characterized by ataxia, diminished proprioception, areflexia, and dysarthria. The gene defect is located on chromosome 11q. The ataxia–telangiectasia mutated protein has sequence homologies to phosphatidylinositol-3 kinase and may be involved in a checkpoint response protein to DNA damage. *(Hammans, 327–332)*

**30.** **(D)** Spinocerebellar ataxia type 6 typically occurs at a later age than other spinocerebellar ataxias, which occur between the ages of 24 and 63 years. It accounts for 5.9% of autosomal dominant cerebellar ataxia in Japan and 13% in Germany. The disorder is characterized by gait and limb ataxia, dysarthria, nystagmus, slowing of saccades, signs of corticospinal tract disease, hypotonia, and proprioceptive sensory loss. Other less common features include ophthalmoparesis, spasticity, rigidity, sphincter disturbances, pes cavus or hammertoes, dystonia, and parkinsonism. The disease has a benign course and is associated with a normal life span. *(Evidente, 475–490)*

**31.** **(A)** Spinocerebellar ataxias (SCAs) are a group of neurodegenerative diseases characterized by cerebellar dysfunction; other neurological abnormalities may be associated. The expansions of coded CAG trinucleotide repeats was found to cause dominantly inherited SCAs such as SCAs 1, 2, 3, 6, 7, and DRPLA. The abnormal CAG triple repeat expansion gives rise to an elongated polyglutamine tract in the respective proteins, leading to a gain in function that is toxic to neurons. Spinocerebellar ataxia type 8 is associated with an expansion of a CTG repeat. *(Tan, 191–195)*

**32.** **(D)** Huntington disease (HD) is an autosomal dominant disorder with high penetrance. The characteristic findings of progressive chorea and dementia are caused by severe neuronal loss, initially in the neostriatum and later in the cerebral cortex. HD has been linked to chromosome 4p16.3. The abnormal gene was found to contain an unstable CAG repeat in the open reading frame of its first exon. Normal subjects have a median of 19 CAG repeats (range 11 to 34), whereas nearly all patients with HD have more than 40. The increased number of CAG repeats in the HD gene is expressed as an elongated huntingtin protein with 40 to 150 glutamine residues. *(Martin, 1970–1980; Price, 1079–1083)*

**33.** **(C)** Myotonic dystrophy is CTG repeat triplets disease. The abnormal gene is located on chromosome 19 and the gene product is myotonin. *(Martin, 1970–1980; Price, 1079–1083)*

**34.** **(A)** DRPLA is caused by expanded polyglutamine tracts in the coding region of huntingtin. The gene defect is located on chromosome 12 and the gene product is atrophin. *(Martin, 1970–1980; Price et al., 1079–1083)*

**35.** **(E)** Spinocerebellar ataxia 3 (SCA-3) or Machado–Joseph disease is characterized by ataxia and lack of coordination. The gene defect is located on chromosome 14 and the gene product is ataxin-3. *(Martin, 1970–1980; Price, 1079–1083)*

**36.** **(B)** Spinal bulbar muscular atrophy is an X-linked illness caused by expanded CAG repeats in the coding region of the androgen receptor gene. *(Martin, 1970–1980; Price, 1079–1083)*

**37.** **(D)** Mitochondrial disorders can affect virtually every tissue. However, skeletal muscles and the brain are most often affected. Maternal transmission occurs, since the maternal ovum is the source of most of an individual's mitochondria. The clinical findings depend on the proportion of normal to abnormal mitochondria in a given patient. This phenomenon is called heteroplasmy. The rate of heteroplasmy differs, often drastically, among maternal family members, and the proportion of abnormal mitochondria may vary from one organ to another in the same patient. Also, while one might assume that the more mutant DNA a cell has the more abnormalities it will exhibit, in practice the cell develops the disease when the proportion of mutant mitochondrial DNA reaches a threshold. Below this threshold, the cell is normal. This threshold varies among different tissues (some are more sensitive to energy deficiency than others) and different mutations. *(Conneally, 120)*

**38.** **(D)** Mitochondrial DNA codes for 13 proteins involved in oxidative phosphorylation, ribosomal, and transfer RNAs. Mitochondrial DNA is inherited in the cytoplasm surrounding a mother's egg but not inherited from the sperm of the father. Therefore, mitochondrial disorders are transmitted only by mothers and never by fathers. Male and female children can both be affected. The disease has the potential to appear in all children of an affected mother. Each child of an affected mother may vary in the number of mitochondria containing the DNA mutation he or she has inherited. Furthermore, the proportion of mutant mitochondria may vary considerably from cell to cell in any given affected individual. Therefore, mitochondrial disorders often show extreme variability in clinical expression both within and between families. Point mutations in mitochondrial DNA tend to be inherited through females, whereas deletions of mitochondrial DNA tend to be sporadic events in isolated individuals. Mitochondrial disorders include the MERRF syndrome (myoclonic epilepsy and ragged-red fibers), the MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke), Leber hereditary optic atrophy, and Leigh's encephalopathy *(Bird, 1–17)*

**39.** **(C)** In X-linked disorders, heterozygote female carriers are usually clinically normal, although they may occasionally have mild manifestations of the disease. In X-linked recessive disorders, each son of a carrier female is at 50% risk for the disease. Each daughter of a carrier female is at 50% risk for also being a carrier. If an affected male has children, his daughters are at 100% risk for being carriers (they must inherit his X chromosome) and his sons are at no risk to inherit the mutation (because they must inherit only the Y chromosome from their father). Thus, X-linked recessive disease shows almost exclusively affected males in multiple generations with transmission through normal carrier females and never shows male-to-male transmission. Examples of X-linked recessive neurological disorders include adrenoleukodystrophy, Pelizaeus–Merzbacher disease, Duchenne–Becker muscular dystrophy, Kennedy spinobulbar muscular atrophy, fragile-X mental retardation, Emery–Dreifuss muscular dystrophy, and Fabry lipid storage disease. *(Bird, 1–17)*

**40.** **(B)** Autosomal recessive disorders are usually seen in only one generation, typically among siblings; both males and females can be affected. Examples of autosomal recessive neurological disorders are phenylketonuria, infantile spinal muscular atrophy, Tay–Sachs disease, Wilson disease, metachromatic leukodystrophy, ataxia–telangiectasia, Lafora body myoclonic epilepsy, Canavan disease, ceroid lipofuscinoses, Friedreich ataxia, and Niemann–Pick disease. *(Bird, 1–17)*

**41.** **(E)** In autosomal dominant disorders, a mutation occurring in a single gene on any of the 22 autosomes can produce clinical symptoms or

signs. The carrier of a single mutation on one chromosome is called a heterozygote. Each child of an affected person has a 50% risk of inheriting the mutation and potentially developing the disease. Males and females are equally affected, the disease appears over multiple generations, and heterozygote mothers or fathers pass the gene on with equal risk to sons or daughters. Examples of autosomal dominant neurological disorders include neurofibromatosis (NF-I and II), myotonic dystrophy (1 and 2), tuberous sclerosis, juvenile myoclonic epilepsy, Huntington disease, benign neonatal convulsions, and several forms of hereditary ataxias. With autosomal recessive inheritance, the heterozygote carriers of a single mutation are essentially always clinically normal. However, individuals who have inherited a mutation in the same gene from both parents (homozygotes) will show clinical manifestations of the disease. If both parents are carriers of a mutation in the same gene, then each of their children has a 25% risk for being homozygous and having the disease. *(Bird, 1–17)*

**42.** **(A)** Chronic progressive external ophthalmoplegia (CPEO) is a mitochondrial disorder that usually has its onset before the age of 30 years. Affected patients develop slowly progressive, symmetric or asymmetric, usually nonfatigable ptosis in association with external ophthalmoplegia. Diplopia occurs uncommonly. The most common mutation found in patients with CPEO is a mitochondrial DNA deletion, which is found in 70% of patients. Definitive diagnosis is provided by muscle biopsy in most cases of CPEO. It is negative in only approximately 10% of patients with mitochondrial DNA mutations. *(Amato, 636–637)*

**43.** **(D)** Patients with chronic progressive external ophthalmoplegia may develop ptosis, ophthalmoplegia with and without extremity weakness, and elevated cerebrospinal fluid protein, but they lack pigmentary retinopathy, cardiac conduction defects, or other systemic manifestations observed in Kearns–Sayre syndrome. *(Amato, 636–637)*

**44.** **(C)** The patient described in the vignette carries the A3243G mitochondrial mutation seen in mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). It is a maternally inherited syndrome caused by mutations in mitochondrial DNA characterized by stroke before the age of 40 years, encephalopathy characterized by seizures or dementia, and blood lactic acidosis or ragged-red fibers in skeletal muscle biopsy specimens. The mitochondrial mutations that result in MELAS cause defects in respiratory chain enzymes, particularly complex I. Substitution of an adenine for guanine at nucleotide position 3243 (A3243G) in the gene encoding $tRNA^{Leu(UUR)}$ accounts for 80% of the cases. Spontaneous A3243G mutations are rare. Phenotypic expression of the A3243G mutation is variable. Although MELAS is the most common phenotype for mitochondrial A3243G, the mutation can present as chronic progressive external ophthalmoplegia, Kearns–Sayre syndrome, or diabetes mellitus with or without deafness. Other genetic defects that can cause MELAS include a mutation at position 3260 and the C3256T mutation in the $tRNA^{Leu(UUR)}$ gene, as well as large-scale mitochondrial DNA deletions. *(Meschia, 114–132)*

**45.** **(D)** Mutations in *NOTCH3*, a gene encoding a large transmembrane receptor, cause cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). CADASIL mutations are highly stereotyped missense mutations within epidermal growth factor (EGF)-like repeats in the extracellular domain of *NOTCH3*. Mutations lead to loss or gain of a cysteine, thereby creating an odd number of cysteines within a given EGF domain). Most cases are inherited in an autosomal dominant fashion, but a de novo symptomatic mutation (Arg182Cys) has been reported. Stroke, dementia, psychiatric illness, and migraines are common features of CADASIL. In a study of 102 patients from 29 families, 71% presented with recurrent transient ischemic attacks (TIAs) or ischemic stroke (mean age at onset, 46 years). Cognitive deficits were present in 48% of patients. More than 80% of those with dementia also had a gait disorder, urinary incontinence, or both. A total of 39% of patients had a history of migraine, and 87% of these had migraine with aura. The level of disability from the disease varied considerably both within and

among pedigrees. Fewer than half the patients above 60 years of age could walk without assistance. MRI of the brain is an essential screening test for CADASIL and presymptomatic carriers of a CADASIL mutation. Abnormalities in the white matter can be observed on MRI long before patients present with stroke or TIA. *(Meschia, 114–132)*

**46.** **(D)** Mutations in the *COL4A1* gene, which encodes procollagen type IV alpha 1, have been associated with autosomal dominant small vessel disease and hemorrhagic stroke. The gene is also associated with autosomal dominant porencephaly and infantile spasms. Tortuosity of retinal vessels is commonly seen on funduscopic examination. Brain MRI shows lacunar infarcts, microbleeds on gradient imaging, leukoaraiosis, and dilated perivascular spaces. Head trauma due to parturition, sporting injuries, and anticoagulation are risk factors for intracranial hemorrhage in patients who harbor a *COL4A1* gene mutation. *(Meschia, 114–132)*

**47.** **(B)** The factor V Leiden mutation is a single-base substitution (G1691A) in the factor V gene that leads to the sequence change of Arg506Gln. The mutation destroys a cleavage site for the inactivating enzyme known as activated protein C. Factor V Leiden is the most common inherited risk factor for deep venous thrombosis. The factor V Leiden mutation is also a risk factor for cerebral venous thrombosis. The odds for cerebral venous thrombosis rise nearly eightfold with the factor V G1691A mutation. *(Meschia, 114–132)*

**48.** **(B)** Immune-mediated cutaneous hypersensitivity reactions are the most common idiosyncratic reactions to antiepileptic drugs (AEDs) and affect 5% to 15% of patients started on treatment with carbamazepine (CBZ), phenytoin (PHT), phenobarbital, or lamotrigine (LTG). These reactions usually consist of mild erythematous or maculopapular rashes. However, the same AEDs are also associated with a risk of potentially life-threatening Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-related rash with eosinophilia and systemic symptoms (DRESS), with a frequency that ranges between 1 and 10 per 10,000 new users. Observations in identical twins and in families suggest a genetic association. A breakthrough in the area of pharmacogenetics came in 2004 when Chung and colleagues reported a 100% prevalence of the human leukocyte antigen HLA-B*1502 allele among 44 Han Chinese in Taiwan with CBZ-induced SJS, compared with a frequency of this allele of only 3% among 101 CBZ-tolerant patients (odds ratio [OR] 2504, 95% confidence interval [CI] 126–49,522). The allele was present in 9% of healthy controls without a history of CBZ use. *(Chung, 486; Franciotta, 144–149)*

**49.** **(B)** Six of the known genes associated with Parkinson disease (PD) were localized after linkage analysis in large families, and mutations have been identified in the α-synuclein (SNCA), *PARKIN, PINK1, DJ-1, LRRK2,* and *ATP13A2* genes. While mutations in the *SNCA* and *DJ-1* genes are extremely rare, mutations in the *PARKIN, PINK1,* and *LRRK2* genes combined account for about 3% of all patients and are thus more likely to be encountered in clinical practice. Mode of inheritance is considered autosomal dominant for α-synuclein and LRRK2 and autosomal recessive for *PARKIN, PINK1, DJ-1,* and *ATP13A2.* This is in agreement with functional findings suggesting a gain-of-function mechanism for dominant and a loss-of-function mechanism for recessive forms. *(Lohmann, 9–113)*

**50.** **(E)** The *SNCA* (α-synuclein) gene was the first to be unequivocally associated with familial Parkinson disease (PD). *SNCA*-linked cases of PD often result in a complex phenotype with additional features, such as early dementia, autonomic dysfunction, and premature death. Interestingly, the severity of the phenotype appears to depend on gene dosage, and patients with *SNCA* duplications clinically present with classic PD more often than those with triplications. Although the phenotypic spectrum can be remarkably broad, those with triplications are often characterized by fast disease progression, marked dementia, and a reduced life span. *SNCA* is abundantly expressed in neurons, where it is believed to participate in the maturation of presynaptic vesicles and to function as

a negative coregulator of neurotransmitter release. SNCA localizes to the nucleus and presynaptic nerve terminals. Outside the nucleus, SNCA is peripherally attached to vesicles or is freely diffusible in the cytoplasm, with mutants exhibiting increased nuclear targeting in cell culture. *(Lohmann, 9–113)*

**51.** **(A)** Homozygous or compound heterozygous mutations in the recessive Parkinson disease (PD) gene *PARKIN* are unequivocally associated with heritable PD and represent a common cause (10% to 20%) of early-onset PD. Alterations in *PARKIN* are spread over the entire gene and include deletions and duplications of one or more exons in more than 50% of the reported cases. Overall, carriers of the *PARKIN* mutation present with classic PD but with an earlier age of onset, a slower disease progression, and an excellent and sustained response to levodopa. *(Lohmann, 9–113)*

**52.** **(D)** Carriers of the *PINK1* mutation are clinically indistinguishable from carriers of the *PARKIN* mutation with the possible exception of a higher rate of psychiatric symptoms. *(Lohmann, 9–113)*

**53.** **(D)** Four chromosomal loci (*PARK2*, *PARK6*, *PARK7*, and *PARK9*) associated with autosomal recessive, early-onset parkinsonism are known. The *PARK7* locus was mapped to chromosome 1p36 in a large family from a genetically isolated population in the Netherlands; this linkage was confirmed in an Italian family. By positional cloning within the refined *PARK7* critical region, mutations were recently identified in the *DJ-1* gene in the two *PARK7*-linked families. The function of *DJ-1* remains largely unknown. *DJ-1* is ubiquitously expressed and was initially described in association with oncogenesis and male rat infertility. However, the protein has also been shown to confer chaperone-like activity and to function as an intracellular sensor of oxidative stress. The oxidation of DJ-1 seems to play a critical role through translocation of the protein to mitochondria in response to oxidative stress, as demonstrated in mouse and *Drosophila* models. The neuroprotective role of DJ-1 against oxidative stress was also supported by the detection of increased DJ-1 levels in the cerebrospinal fluid of patients with sporadic PD: this was most pronounced in the early stages of the disease. *(Bonifati, 159–160; Lohmann, 9–113)*

**54.** **(E)** Homozygous and compound heterozygous mutations in a predominantly neuronal P-type ATPase gene (*ATP13A2*) have recently been demonstrated in the two identified families with the rare Kufor–Rakeb syndrome (KRS), a form of recessively inherited atypical parkinsonism. KRS is clinically characterized by subacute, juvenile-onset, levodopa-responsive PD, pyramidal signs, dementia, a supranuclear gaze palsy, along with globus pallidus atrophy and later generalized brain atrophy. Another homozygous mutation was detected in a patient with juvenile parkinsonism (onset at the age of 12 years), levodopa-responsive severe akinetic-rigid parkinsonism, levodopa-induced motor fluctuations and dyskinesias, severe visual hallucinations, supranuclear vertical gaze palsy, and diffuse brain atrophy but no pyramidal deficit or dementia. *(Lohmann, 9–113)*

**55.** **(E)** Autosomal recessive cerebellar ataxias (ARCAs) are a heterogeneous group of neurological disorders involving both the central and peripheral nervous system and in some case other systems and organs. Onset is usually before the age of 20 years. ARCAs are divided into four main groups: degenerative ataxias (Friedreich ataxia), congenital ataxias, metabolic ataxias (Wilson disease, metachromatic leukodystrophy), and ataxias with DNA repair defects. Ataxia telangiectasia is the most common recessive ataxia in children under 5 years of age. It is characterized by ataxia and oculocutaneous telangiectases appearing between the age of 2 and 8 years and is associated with immunodeficiency leading to recurrent infections, endocrine and skin abnormalities, radiation sensitivity, and a predisposition for malignancies. Ataxia telangiectasia is due to mutations in the ataxia telangiectasia mutated gene (ATM) involved in DNA repair. *(Manto, 419–429)*

**56.** **(B)** The patient described in this vignette has sign and symptoms suggestive of X-linked cerebellar ataxia. Fragile-X tremor ataxia syndrome (FXTAS) is representative of this group. The

disorder usually starts after age 50 years. Patients exhibit combinations of kinetic tremor, ataxia of gait, parkinsonism, autonomic dysfunction, polyneuropathy, and cognitive deficits. The age of onset of tremor or ataxia inversely correlates with the repeat size (CGG triplet). Brain MRI in FXTAS shows, in particular, hyperintense lesions in the middle cerebellar peduncles on T2-weighted sequence. *(Manto, 419–429)*

**57.** **(A)** Some clinical features have specific value for predicting a gene defect in spinocerebellar ataxia (SCA). Slowing of saccades is seen in SCA2; ophthalmoplegia is seen in SCA1, SCA2,and SCA3; pigmentary retinopathy is seen in SCA7; spasticity is seen in SCA3; dyskinesias associated with a mutation in the fibroblast growth factor 14 (FGF14) gene, cognitive impairment, and behavioral symptoms are seen in SCA17 and DRPLA; seizure is seen in SCA10, SCA17, and DRPLA; and peripheral neuropathy is seen in SCA1, SCA2, SCA3, SCA4, SCA8, SCA18, and SCA25. *(Manto, 419–429)*

**58.** **(B)** Seizures may occur in SCA10, SCA17, and DRPLA. *(Manto, 419–429)*

**59.** **(C)** Myokemia can occur in spinocerebellar ataxia type 5. *(Manto, 419–429)*

**60.** **(D)** Linkage studies originally mapped some families with frontotemporal dementia with parkinsonism (FTDP-17) to chromosome 17q21-22. Subsequent analysis of this region identified mutations in the gene encoding microtubule-associated protein tau (MAPT). FTDP-17 patients exhibited frontotemporal atrophy with neuronal loss, gray and white matter gliosis, and superficial cortical microvacuolation. Reported cases of FTDP-17 all have neuropathological features of intraneuronal hyperphosphorylated tau inclusions, with glial tau inclusions observed in some families. *(Sikkink, 693–698)*

**61.** **(E)** Episodic ataxia 7 (EA7) was described in a single family with episodic vertigo without tinnitus, weakness, dysarthria, and ataxia lasting from hours to days typically triggered by exertion or excitement, with onset before age 20. There is no interictal finding. Neither is there associated tinnitus. Genome scan mapped the locus of EA7 to chromosome 19q13. The responsible gene has not been identified.

Episodic ataxia type 1 (EA1) is an autosomal dominant condition characterized by brief episodes of ataxia with interictal myokymia. Triggered by exertion, stress, or startle, and lasting from seconds to minutes, these attacks of ataxia usually diminish with age and may spontaneously resolve in the teens. EA1 is caused by mutations in *KCNA1,* located on chromosome 12, which encodes Kv1.1, a human homolog of the Shaker voltage-gated potassium channel in *Drosophila*.

EA2 is a dominantly inherited neurological disorder characterized by bouts of vertigo and ataxia with interictal nystagmus and progressive ataxia. Episodes are typically triggered by exercise or stress, and they are often dramatically relieved by treatment with the carbonic anhydrase inhibitor acetazolamide. Flunarizine and 4-aminopyridine have also been reported to be effective in EA2. Migraine headaches occur in about 50% of patients with EA2, and there is overlap in the clinical features of EA2, familial hemiplegic migraine type 1 (FHM1), basilar migraine, and progressive ataxia. EA2 and FHM1 are caused by mutations in the gene *CACNA1A,* which codes for the alpha-1A subunit of the P/Q-type of voltage-gated calcium channel.

EA3 was described in a single large Canadian family with episodic vertigo, nausea, tinnitus, ataxia, and migraine. Interictal myokymia was observed in some; none had nystagmus or baseline ataxia. There is much clinical overlap between EA3 and MAV. The disease locus for EA3 is distinct from EA1 and EA2 and was recently mapped to chromosome 1q42. The responsible gene has not been identified.

EA4, also called familial periodic vestibulocerebellar ataxia, is an autosomal dominant disorder characterized by episodes of vertigo and ataxia beginning in the third to sixth decades of life. Patients may have interictal nystagmus and mild ataxia similar to EA2, or they may be completely normal in between attacks. The attacks typically last hours and are not relieved by acetazolamide. The most consistent symptom is the inability to suppress the vestibuloocular reflex when objects move in the

periphery. The responsible gene has not been identified. *(Jen, 3–7)*

**62.** **(A)** Familial hemiplegic migraine (FHM) diagnosis is based on the presence of one-sided motor weakness during the aura phase and similar attacks in at least one first-degree or second-degree family member. FHM is genetically heterogenous with mutations in *CACNA1A*, a gene coding for the P/Q-type calcium channel alpha subunit (FHM type1), *ATP1A2*, a gene coding for $Na^+/K^+$-adenosine triphosphatase (FHM type 2), and *SCNA1*, a gene coding for sodium channel alpha subunit (FHM type 3). *(Ropper, 288–293)*

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CHAPTER 12

# Neuroophthalmology
## Questions

**1.** Which of the following is true of Balint syndrome?

(A) It results from bilateral extensive frontal damage.
(B) It is characterized by a difficulty initiating slow eye movement.
(C) It is characterized by the presence of simultagnosia.
(D) It is usually associated with preservation of visual field.
(E) Visual guidance pointing is preserved.

**2.** What type of nystagmus is frequently associated with vertigo and tinnitus?

(A) Downbeat nystagmus
(B) Seesaw nystagmus
(C) Spasmus nutans
(D) Upbeat nystagmus
(E) Vestibular nystagmus

**3.** What type of nystagmus is frequently associated with Arnold–Chiari malformation?

(A) Downbeat nystagmus
(B) Seesaw nystagmus
(C) Spasmus nutans
(D) Upbeat nystagmus
(E) Vestibular nystagmus

**4.** Head turning and head nodding, is usually associated with

(A) downbeat nystagmus
(B) seesaw nystagmus
(C) spasmus nutans
(D) upbeat nystagmus
(E) vestibular nystagmus

**5.** Which of the following conditions may cause upbeat nystagmus?

(A) Spasmus nutans
(B) Arnold–Chiari malformation
(C) Phenytoin use
(D) Posterior fossa tumor
(E) Suprasellar mass lesions

**6.** Seesaw nystagmus is frequently associated with

(A) spasmus nutans
(B) Arnold–Chiari malformation
(C) phenytoin use
(D) posterior fossa tumor
(E) suprasellar mass lesions

**7.** The eye movement that brings objects of interest onto the fovea is called

(A) a saccade
(B) smooth pursuit
(C) vergence eye movement
(D) nystagmus quick phase
(E) optokinetic movement

**8.** The optokinetic system is responsible for

(A) bringing objects of interest to the fovea
(B) holding images of the seen world steady on the retina during sustained head rotation
(C) holding the image of a small moving target on the fovea
(D) bringing an object of interest to the fovea
(E) holding images of the seen world steady on the retina during brief head rotations

**9.** Seesaw nystagmus is caused by

(A) frontal stroke
(B) cerebellar tumor
(C) Arnold–Chiari malformation
(D) $B_{12}$ deficiency
(E) congenital aqueductal stenosis

**10.** The most likely cause of convergence–retraction nystagmus in a 10-year-old boy is

(A) congenital aqueductal stenosis
(B) pinealoma
(C) brainstem vascular malformation
(D) multiple sclerosis
(E) head trauma

**11.** Opsoclonus in an infant is most likely seen in a case of

(A) hyperosmolar coma
(B) brainstem encephalitis
(C) neuroblastoma
(D) lung cancer
(E) toxic encephalopathy

**12.** Ocular myoclonus caused by a lesion in the triangle of Guillain and Mollaret involves which of the following anatomical sites?

(A) Interstitial nucleus of Cajal
(B) Red nucleus
(C) Ipsilateral dentate nucleus
(D) Contralateral inferior olive
(E) Midbrain

**13.** The most common cause of nontraumatic oculomotor nerve palsy with pupillary involvement is

(A) diabetes
(B) basilar artery aneurysm
(C) schwannoma
(D) aneurysm at the junction of the posterior communicating artery and the internal carotid artery
(E) cavernous sinus thrombosis

**14.** Argyll–Robertson pupils may be caused by

(A) chronic ethanol abuse
(B) Parkinson disease
(C) hydrocephalus
(D) hypertension
(E) Huntington disease

**15.** Which of the following vitamin deficiencies does not cause optic atrophy?

(A) Vitamin C
(B) Vitamin $B_{12}$
(C) Pyridoxine
(D) Riboflavin
(E) Folic acid

**16.** Which of the following is *not* true of ocular myasthenia?

(A) Ocular involvement occurs in 90% of myasthenic patients in the course of the disease.
(B) Ocular symptoms account for 75% of initial complaints.
(C) Approximately 20% of patients with ocular onset of myasthenia progress to involve other muscle groups within 2 years.
(D) Only one third of patients with ocular myasthenia have positive acetylcholine receptors antibodies.
(E) The major ophthalmological complaints of ocular myasthenia are ptosis and diplopia.

**17.** Which of the following muscles is the most affected in Graves disease?

(A) Superior oblique
(B) Inferior rectus
(C) Medial rectus
(D) Lateral rectus
(E) Superior rectus

**18.** Which of the following is true of ophthalmoplegic migraine?

(A) The onset is in the fourth decade of life.
(B) The abducens nerve is more often affected than the oculomotor nerve.
(C) The ophthalmoplegia resolves when the headache clears.
(D) Pupils and accommodation are frequently involved.
(E) The ophthalmoplegia is contralateral to the headache.

**19.** Retinal artery obstruction by a platelet fibrin embolus is associated with

(A) bacterial endocarditis
(B) bright orange–yellow refractile emboli
(C) a white intra-arterial plug lodged at the bifurcation of the arter
(D) a friable mass
(E) gray–white nonrefractible emboli

**20.** Retinal artery obstruction by a fat emboli is associated with

(A) a long bone
(B) bright orange–yellow refractile emboli
(C) a white intra-arterial plug lodged at the bifurcation of the artery
(D) a friable mass
(E) gray–white nonrefractible emboli

**21.** Choroidal hemangioma is associated with

(A) neurofibromatosis type I
(B) neurofibromatosis type II
(C) tuberous sclerosis
(D) Von Hippel–Lindau disease
(E) Sturge–Weber syndrome

**22.** Bilateral bulbar and conjunctival telangiectasia is associated with

(A) neurofibromatosis type II
(B) tuberous sclerosis
(C) Von Hippel–Lindau disease
(D) Sturge–Weber syndrome
(E) ataxia–telangiectasia

**23.** Posterior subcapsular cataract is associated with

(A) neurofibromatosis type I
(B) neurofibromatosis type II
(C) tuberous sclerosis
(D) Von Hippel–Lindau disease
(E) Sturge–Weber syndrome

**24.** Retinal hemangioblastoma is associated with

(A) neurofibromatosis type I
(B) neurofibromatosis type II
(C) tuberous sclerosis
(D) Von Hippel–Lindau disease
(E) Sturge–Weber syndrome

**25.** Retinal astrocytic hamartomas are associated with

(A) neurofibromatosis type I
(B) neurofibromatosis type II
(C) tuberous sclerosis
(D) Von Hippel–Lindau disease
(E) Sturge–Weber syndrome

**26.** Racemose angioma is associated with

(A) tuberous sclerosis
(B) Von Hippel-Lindau disease
(C) Sturge–Weber syndrome
(D) ataxia–telangiectasia
(E) Wyburn–Mason syndrome

**27.** Lisch nodules are associated with

(A) neurofibromatosis type I
(B) neurofibromatosis type II
(C) tuberous sclerosis
(D) Von Hippel–Lindau disease
(E) Sturge–Weber syndrome

**28.** What is the most likely finding in the funduscopic examination of the early stage of Leber disease?

(A) Optic nerve atrophy
(B) Papilledema
(C) Hyperemic optic nerve with telangiectatic capillaries
(D) Optic disk vasculitis
(E) Optic nerve drusen

**29.** A 25-year-old man with a 3-year history of diabetes underwent a routine ophthalmological examination. His visual acuity was normal. On funduscopic examination, the ophthalmologist noted the following in both eyes: glistening hyaline bodies and the absence of disk hyperemia, exudates, or hemorrhage. The disk borders were irregular and the cup was absent. The retinal vessels had a central origin and were trifurcated. Spontaneous venous pulsations were present. This funduscopic report is consistent with

(A) papilledema from increased intracranial pressure
(B) drusen
(C) optic neuritis
(D) early diabetic retinopathy
(E) anterior ischemic optic neuropathy

**30.** Downbeat nystagmus is a feature of

(A) episodic ataxia type II
(B) pituitary tumors
(C) progressive supranuclear palsy
(D) healthy subjects
(E) optic neuritis

**31.** Pendular seesaw nystagmus is a feature of

(A) episodic ataxia type II
(B) pituitary tumors
(C) progressive supranuclear palsy
(D) healthy subjects
(E) optic neuritis

**32.** Square wave jerks are a feature of

(A) episodic ataxia type II
(B) pituitary tumors
(C) optic neuritis
(D) healthy subjects
(E) drug intoxication

**33.** A 57-year-old woman developed a sudden painless loss of vision in the right eye. Her funduscopic examination is illustrated in Figure 12-1. The most likely diagnosis is

(A) diabetic neuropathy
(B) acute optic neuritis

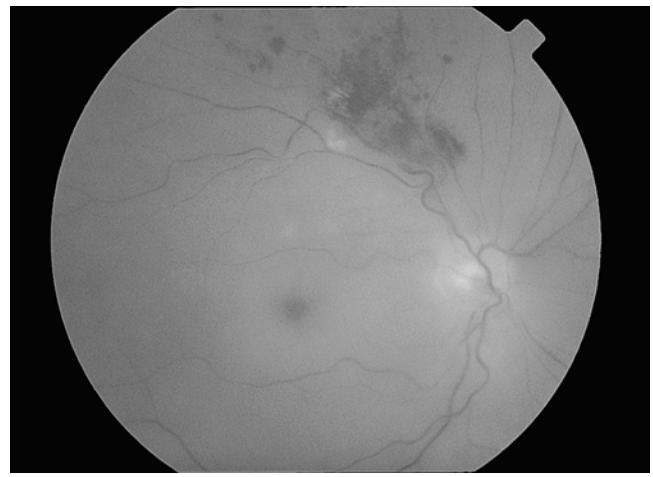

**FIG. 12-1.** See color insert. (Reproduced with permission from Savino PJ, Danesh-Meyer HV. *Neuroopthalmology.* New York: McGraw-Hill; 2003.)

(C) central retinal artery occlusion
(D) retinal vein detachment
(E) central retinal vein occlusion

**34.** Figure 12-2 illustrates the fundoscopic findings in a 34-year-old man who developed right visual loss of sudden onset. The most likely cause of his visual loss is

(A) platelet fibrin emboli
(B) cholesterol emboli
(C) calcium emboli
(D) septic emboli
(E) myxomatous emboli

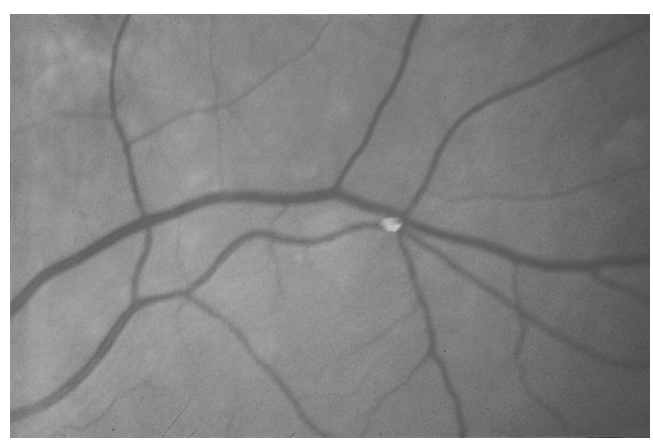

**FIG. 12-2.** See color insert. (Reproduced with permission from Savino PJ, Danesh-Meyer HV. *Neuroopthalmology.* New York: McGraw-Hill; 2003.)

**35.** Which of the following is *true* about optic neuritis?

(A) Typically, it occurs after the age of 60 years.
(B) Visual acuity is preserved until late in disease progression.
(C) It reduces color vision.
(D) Magnetic resonance imaging (MRI) of the head is usually normal.
(E) Oral corticosteroids are effective in hastening recovery from the acute phase and improving the long-term prognosis.

**36.** Which of the following is *false* about anterior ischemic neuropathy?

(A) It is characterized by bilateral painful visual loss.
(B) Migraine is a risk factor in young patients.
(C) Spontaneous improvement of visual loss may occur.
(D) Funduscopic examination may show flame-shaped hemorrhages near the optic disk margin.
(E) A small optic disk is a predisposing factor for developing the nonarteritic form of ischemic optic neuropathy.

**37.** Disturbance of depth perception is produced by a lesion located in the

(A) optic chiasm
(B) optic tract
(C) optic radiation
(D) optic nerve
(E) lateral geniculate body

**38.** Which of the following is inconsistent with the diagnosis of cortical blindness?

(A) Loss of vision in both eyes
(B) Preservation of extraocular movements
(C) Retinal integrity
(D) Absence of pupillary constriction to light
(E) Preserved pupillary constriction to convergence

**39.** A 50-year-old man developed a subacute mild headache. Neurological examination demonstrated right lid ptosis, right miosis, and right anhydrosis. Cocaine and hydroxyamphetamine drops failed to dilate the affected pupil. The right pupil dilated on 2% epinephrine drops and became larger than the left. Among the following diseases, which is consistent with the above findings?

(A) Right hypothalamic infarction
(B) Right lateral medullary infarction
(C) Malignant mass in the apex of the right lung
(D) Right brachial plexus trauma
(E) Right internal carotid artery dissection

**40.** Which of the following supports the diagnosis of a dilated pupil from Adie syndrome rather than pharmacologically induced mydriasis?

(A) Oculomotor nerve palsy
(B) Ptosis
(C) Segmental contraction of the pupils on slit-lamp examination
(D) Ophthalmoplegia
(E) Diplopia

# Answers and Explanations

1. **(C)** Balint syndrome is an acquired oculomotor apraxia caused by an extensive bilateral parietooccipital lesion. There is a difficulty in initiating reflexive visually guided saccades and pursuit in all directions with intact vestibular eye movements. Other signs of Balint syndrome include simultagnosia (inability to perceive more than one object at a time), optic ataxia (inaccurate visual guided pointing), and ocular motor apraxia (difficulty in initiating voluntary saccades). These symptoms are frequently associated with dementia and visual field defects. *(Kline, 68)*

2. **(E)** Vestibular nystagmus is characterized by a mixed direction, horizontal–torsional primary position nystagmus. It is of maximal amplitude when the gaze is directed toward the fast component. The nystagmus is suppressed by visual fixation and increased when fixation is removed. The fast phase usually beats away from the damaged end organ. The nystagmus is usually associated with tinnitus, vertigo, and deafness. *(Kline, 82–85)*

3. **(A)** Downbeat nystagmus is characterized by the occurrence of a fast phase down while the eyes are in primary position. It is usually associated with lesions at the craniocervical junction, such as Arnold–Chiari malformation, and is often accentuated during lateral downgaze. *(Kline, 82–85)*

4. **(C)** The triad of head turning, head nodding, and nystagmus is highly suggestive of spasmus nutans. Symptoms begin in the first 18 months of life and resolve within the first decade of life. The nystagmus is horizontal or vertical, pendular, low in amplitude, and of high frequency. *(Kline, 82–85)*

5. **(D)** Upbeat nystagmus has an up phase while the eyes are in primary position of gaze. Reported causes include cerebellar degeneration, multiple sclerosis, brainstem stroke, posterior fossa tumor, and Wernicke encephalopathy. *(Kline, 82–85)*

6. **(E)** Seesaw nystagmus is a nystagmus with one eye elevated and intorted and the other depressed and extorted, frequently associated with suprasellar mass lesions. *(Kline, 82–85)*

7. **(A)** Saccades are fast eye movements responsible for bringing objects of interest onto the fovea. Saccades are stimulated by voluntary changes in direction. They are also stimulated by sudden peripheral visual, auditory, or sensory stimuli. *(Kline, 47–48)*

8. **(B)** The optokinetic system is stimulated by sustained head rotation. It is responsible for holding images of the seen world steady on the retina during sustained head rotation. The vestibular system responds only to acceleration. With sustained head rotation at a constant velocity, the vestibular response fades and the optokinetic system supplements visually driven compensatory slow-phase eye movements. *(Kline, 47–48)*

9. **(C)** Seesaw nystagmus has been associated with suprasellar mass lesions, midbrain stroke, multiple sclerosis, head trauma, Arnold–Chiari malformation, and congenital causes. *(Kline, 83–84)*

10. **(B)** Convergence–retraction nystagmus is a jerk convergence–retraction movement due to

contraction of the extraocular muscles, especially on attempted convergence or upward gaze. Its etiology may depend on age. Congenital aqueductal stenosis is the most likely cause in a newborn. At the age of 10 years, pinealoma is the most likely cause. Head trauma and brainstem vascular malformations may cause convergence–retraction nystagmus in the 20- and 30-year age groups, respectively. Multiple sclerosis (at the age of 40) and basilar artery stroke (at the age of 50) are the most likely causes of convergence–retraction nystagmus. *(Kline, 84)*

**11. (C)** Opsoclonus is a rapid, involuntary, multivectorial, and unpredictable conjugate fast eye movement that stops during sleep. Neuroblastoma is the most likely cause of opsoclonus in infants, as a paraneoplastic phenomenon. Autoimmune brainstem encephalitis responsive to adrenocorticotropic hormone (ACTH) is also seen in infants. In adults, opsoclonus may occur as a paraneoplastic syndrome caused by lung, breast, or ovarian cancer. *(Kline, 87–88)*

**12. (B)** The triangle of Guillain and Mollaret is formed by the red nucleus, ipsilateral inferior olive, and contralateral dentate nucleus. *(Kline, 88)*

**13. (D)** In its course toward the cavernous sinus, the oculomotor nerve travels lateral to the posterior communicating artery. The pupillomotor fibers are situated in the periphery of the nerve and are affected early in case of compression of the nerve by an aneurysm at the junction of the posterior communicating and internal carotid arteries. This is the most common cause of isolated third nerve palsy with pupillary involvement. In cases of ischemic lesions, as in diabetes, the pathology is confined to the core of the nerve and spares the peripheral pupillomotor fibers. *(Brazis, 168; Kline, 108)*

**14. (A)** Argyll–Robertson pupils are miotic and irregular; they are characterized by absence of the pupillary light response and brisk pupillary constriction to near stimuli, normal function of the anterior visual pathway, and poor dilatation in the dark. The lesion is most likely located in the region of the sylvian aqueduct in the rostral midbrain, interfering with the light reflex fibers and supranuclear inhibitory fibers as they approach the Edinger–Westphal nuclei. More ventrally located fibers for near response are spared. The classic cause of Argyll–Robertson pupils is neurosyphilis. Other reported causes include diabetes mellitus, multiple sclerosis, sarcoidosis, and chronic alcoholism. *(Kline, 141–142)*

**15. (A)** Deficiency optic neuropathy is characterized by a progressive bilateral visual loss with central or centrocecal scotoma and optic atrophy. Deficiencies in the following vitamins may be responsible for optic atrophy: vitamin $B_{12}$ or cobalamin, vitamin B6 or pyridoxine, vitamin B1 or thiamine, niacin, vitamin B2 or riboflavin, and folic acid. *(Kline, 166)*

**16. (C)** Myasthenia involves skeletal but not visceral neuromuscular transmission. Therefore, the major ophthalmological complaints are ptosis and diplopia. Ocular involvement occurs in 90% of individuals with myasthenia and accounts for the initial complaint in 75% of cases. Approximately 36% of patients with ocular onset progress to involve other muscle groups within 2 years. Acetylcholine receptor antibodies, if present, are diagnostic of myasthenia, but they are present in only one third of patients with ocular myasthenia. *(Kline, 473; Kupersmith, 243–248)*

**17. (B)** A restrictive myopathy of ocular muscles may occur in Graves disease, leading to ophthalmoparesis and diplopia. The inferior rectus is the most frequently involved muscle. Its fibrotic shortening leads to elevator palsy. Abduction weakness may occur in case of involvement of the medial rectus, mimicking an abducens nerve palsy. Superior and lateral rectus muscles and superior obliques are less frequently involved. *(Kline, 176; Kupersmith, 243–248)*

**18. (D)** The onset of ophthalmoplegic migraine is usually before the age of 10 years. There is always a history of typical migraine. The ophthalmoplegia is ipsilateral to the headache. The oculomotor nerve is affected 10 to 1 over the abducens nerve. The pupils and accommodation are frequently involved. The ophthalmoplegia occurs at the height of the headache, persisting after the headache clears. It may last days to weeks. *(Kline, 207)*

**19.** **(C)** Platelet fibrin emboli are white intra-arterial plugs that lodge at bifurcations; they arise from ulcerative atheromas that may be located in the internal carotid artery. Cholesterol emboli are bright orange–yellow and refractile. The source may be carotid or aortic atheroma. Calcium emboli are gray–white and nonrefractile. They originate from the cardiac valves or the aortic wall and are usually lodged in retinal arterioles near or on the optic disk. Septic emboli may originate from infected cardiac valves, especially aortic or mitral valves. The heart is the source of myxomatous emboli. *(Kline, 212–214)*

**20.** **(A)** Long bones are the sources of fat emboli. *(Kline, 212–214)*

**21.** **(E)** Ocular manifestations of Sturge–Weber syndrome include glaucoma, which is found in 60% of patients before the age of 2, and choroidal hemangioma, which is seen in 40% of patients with Sturge–Weber syndrome. It is located ipsilaterally to the facial angioma (also referred to as port-wine stain), which is one of the criteria for the diagnosis of the disease. *(Kline, 249–255)*

**22.** **(E)** Ataxia–telangiectasia is inherited as an autosomal recessive trait. Its gene is located on chromosome 11 (11q22–23). The gene encodes a protein called ATM, which is important for cell cycle control and DNA repair. Ocular manifestations of the disease include bilateral bulbar conjunctivitis, telangiectasia, and ocular motility disturbances. These include, at the beginning, ocular apraxia, which may progress to impairment of smooth pursuit and eventually to complete supranuclear ophthalmoplegia. *(Kline, 249–255)*

**23.** **(B)** Neurofibromatosis type II is characterized by bilateral acoustic neurons. It occurs in 1 of 50,000 persons and is inherited as an autosomal dominant trait. The gene is located on chromosome 22 (22q12), a tumor suppressor gene that suppresses a protein called schawannomin. Cutaneous lesions and peripheral neurofibromas are rare. Ocular lesions include posterior subcapsular cataracts, epiretinal membranes, and retinal hamartomas. *(Kline, 249–255)*

**24.** **(D)** Von Hippel–Lindau disease occurs in 1 of 36,000 persons. It is inherited as an autosomal dominant disease with incomplete penetrance. The gene is located on chromosome 3 (3q26) and has a tumor-suppressing function. Ocular manifestations include retinal hemangioblastomas, which are found in both eyes in 50% of patients; 60% of patients have multiple lesions in one eye. *(Kline, 249–255)*

**25.** **(C)** Tuberous sclerosis (TSC) is an autosomal dominant disease with an incidence ranging from 1 of 6,000 to 1 of 10,000 persons. Spontaneous mutations may occur in up to 66% of cases. The condition is caused by defects, or mutations, on two genes, *TSC1* and *TSC2*; both are believed to be tumor suppressor genes. Only one of the genes needs to be affected for TSC to be present. The *TSC1* gene is on chromosome 9 and produces a protein called hamartin. The *TSC2* gene is on chromosome 16 and produces the protein tuberin. Some 75% of TSC patients have ocular lesions including retinal astrocytic hamartomas. Multiple lesions are found in one eye; 25% of patients have bilateral lesions. *(Kline, 249–255)*

**26.** **(E)** Wyburn–Mason syndrome is also known as retinocephalic vascular malformation. Ocular manifestations include arteriovenous malformation of the retinal, orbital, and optic nerves. Arteriovenous malformation of the retina, also known as racemose angioma, is usually unilateral and most often located in the posterior pole. Arteriovenous malformations are also found in the central nervous system and are symptomatic in 50% of patients. *(Kline, 249–255)*

**27.** **(A)** Neurofibromatosis type I occurs in approximately 1 of 3,000 persons. It may be inherited as an autosomal dominant trait (the gene is located on chromosome 17q12-22) and produces neurofibromin, a protein that regulates a tumor suppressor gene named oncoprotein *ras*. The mutated gene leaves the *ras* unopposed to stimulate cell growth. Clinical manifestations may involve cutaneous, ocular, neurological, and visceral organs. Lisch nodules are ocular melanocytic hamartomas, brown or yellow in color. Dome-shaped lesions protrude from the iris

surface. They are uncommon prior to age 6 but increase in number with age. Other ocular lesions include neurofibromas of the eyelids and orbits and optic nerve gliomas. *(Kline, 249–255)*

**28. (C)** Leber hereditary optic neuropathy is a maternally inherited disease linked to abnormalities in mitochondrial DNA. In the early stage of the disease, funduscopic examination may show hyperemia of the optic disk, dilatation, and tortuosity of vessels. A classic triad is seen in many cases of Leber hereditary optic neuropathy, including circumpapillary telangiectatic microangiopathy, swelling of the nerve fiber layer around the disk (pseudoedema), and absence of leakage from the disk or papillary region on fluorescein angiography. This last distinguishes Leber hereditary optic neuropathy from a truly swollen disk. *(Miller, 304–308)*

**29. (B)** This vignette raises the differential diagnosis of an abnormal funduscopic examination in a 25-year-old diabetic male. Although papilledema from increased intracranial pressure is a medical emergency that should not be missed, other less ominous causes of abnormal disk appearance should be considered, such as congenital anomalies, inflammatory processes, ischemia, and diabetic retinopathy. Increased intracranial pressure is characterized clinically by nausea, morning headache, transitory visual obscuration, and ataxia. Visual examination may show an enlarged blind spot and visual field constriction. Color vision and visual acuity are preserved early in the disease. Funduscopy may show the absence of retinal venous pulsations, disk hyperemia, preserved cup, cotton-wool spots, exudates, and blurring of vessels in the peripapillary area. In this patient, the absence of any physical sign suggesting increased intracranial pressure, the preservation of the retinal venous pulsations, and the absence of hyperemia argue against the diagnosis of papilledema. Optic neuritis may complicate the course of multiple sclerosis rather than diabetes. The patient may report retroorbital pain on eye movement. Visual examination may demonstrate loss of central acuity and color discrimination, while funduscopic examination may show unilateral disk swelling. The disk's appearance may be normal with retrobulbar involvement. The patient in this vignette is asymptomatic and has normal visual acuity. Optic neuritis is unlikely to be the diagnosis.

Ischemic optic neuropathy is the most common cause of acute painless monocular visual loss in the elderly population. It may be seen in patients after the age of 50 years. Diabetes and hypertension are predisposing factors. Funduscopic examination may demonstrate segmental disk edema. Ischemic optic neuropathy is unlikely to be the diagnosis in this patient, as he has normal visual acuity. In diabetic retinopathy, funduscopic examination may show microaneurysms, hemorrhages that may occur within the compact middle layers of the retina, hard exudates, and retinal edema. Diabetic retinopathy is due to microangiopathy affecting the retinal precapillary arterioles, capillaries, and venules. The funduscopic findings in this patient are not suggestive of diabetic retinopathy. The patient in this vignette is asymptomatic, has normal visual acuity and bilaterally irregular disk borders with absent cup on funduscopic examination. These findings are highly suggestive of drusen. This is a congenital elevation of the optic disk not associated with cotton-wool spots, peripapillary swelling, or hemorrhage. Retinal venous pulsations are preserved. Retinal vessels may appear to originate from the center of the disk. There are no exudates, neovascularization, or hyperemia. *(Laskowitz, 323–353)*

**30. (A)** Downbeat nystagmus is a vertical jerk nystagmus. It is exacerbated by looking down and laterally. It is poorly suppressed by visual fixation. Downbeat nystagmus is encountered when lesions affect the vestibular pathways or in cases of drug intoxication. Downbeat nystagmus is also a feature of episodic ataxia type II, a calcium channelopathy. *(Serra, 615–618)*

**31. (B)** Pendular seesaw nystagmus consists of elevation and intorsion of one eye and synchronous depression and extorsion of the other eye in the first half cycle, followed by change in direction during the next half cycle. It is encountered in diseases affecting the crossing axons of the optic chiasm, such as pituitary tumors. *(Serra, 615–618)*

**32. (D)** Square-wave jerks are small conjugate saccades that briefly take the eye away from the fixation position and then return it there. It is a prominent finding in progressive supranuclear palsy and also occurs in healthy subjects. *(Serra, 615–618)*

**33. (C)** Figure 12-1 illustrates central retinal artery occlusion with a cherry-red spot. Nerve fiber layer hemorrhages are seen superior to the disk.

In patients 55 years of age or older with central retinal artery occlusion, giant cell arteritis must be considered. Carotid and cardiac sources of emboli must be sought in central and in branch retinal artery occlusion in particular, even if no retinal emboli are identified, so that appropriate treatment can be given to reduce the risk of stroke. Migraine, oral contraceptives, systemic vasculitis, congenital or acquired thrombophilia, and hyperhomocysteinemia should be considered in young patients. Internal carotid artery dissection should be considered when there is neck pain or a recent history of neck trauma. Diabetes, hyperlipidemia, and systemic hypertension should be considered in all patients. Central retinal artery occlusion presents as sudden profound monocular visual loss. Visual acuity is usually reduced to counting fingers or worse, and the visual field is restricted to an island of vision in the temporal field. Ophthalmoscopy reveals pallid swelling of the retina, most obvious in the posterior segment, with a cherry-red spot at the fovea. The retinal arteries are attenuated, and "box-car" segmentation of blood in the veins may be seen. Occasionally, emboli are seen in the central retinal artery or its branches. The retinal swelling subsides over a period of 4 to 6 weeks, leaving a relatively normal retinal appearance but a pale optic disk and attenuated arterioles. *(Savino, 29; Riordan-Eva, chapter 7)*

**34. (B)** Figure 12-2 shows a bright plaque that appears larger than the artery in which it resides. The plaque is seen at a retinal arteriole bifurcation. This glistening appearance suggests a cholesterol embolus of carotid artery origin. *(Savino, 30)*

**35. (C)** Optic neuritis is an inflammatory disorder of the optic nerve. Its incidence is higher among adults below 46 years of age, where it is the most common cause of acute optic neuropathy. Most cases are idiopathic or associated with multiple sclerosis. Its clinical features may include perioocular pain, particularly with eye movement, and progressive visual loss over several days. Visual acuity, color vision, and visual fields are reduced early in disease onset. Funduscopy may show a normal optic nerve or optic disk edema. In 50% to 70% of cases, MRI of the head may show white matter abnormalities identical to those seen in multiple sclerosis. Low doses of oral prednisone have no demonstrable efficacy in the recovery of visual function in acute monosymptomatic optic neuritis. Although high-dose oral or parenteral methylprednisolone has been shown to have an effect in hastening recovery from the acute phase of optic neuritis, it does not confer long-term benefit on visual function. *(Kaufman, 2039–2044)*

**36. (A)** Anterior ischemic optic neuropathy (AION) results from an ischemic lesion of the laminar and prelaminar portions of the optic nerve. The disease occurs in patients over 50 years of age. Diabetes mellitus, hypertension, and giant cell arteritis are predisposing factors. Migraine and systemic vasculitis particularly increase the risk of AION in young patients. Congenital small optic disk with absent or small central cup is thought to be the major predisposing factor for developing nonarteritic AION.

Clinically, AION is characterized by a sudden monocular and painless loss of vision. In about 40% of cases of the nonarteritic form, the loss of vision may improve spontaneously over weeks or months. Funduscopic examination may show either hyperemic or pallid disk swelling with flame-shaped hemorrhages near the margins of the disk. *(Miller, 138–140)*

**37. (A)** In addition to the bitemporal field defects, patients with lesions of the optic chiasm may develop a disturbance of depth perception. Clinically, the patient complains of difficulties with near tasks such as using precise tools. In such tasks the required convergence causes crossing of the two blind temporal hemifields. This produces a completely blind triangular area of field with its apex at fixation. The image of an object beyond fixation falls on blind nasal retinas

and thus disappears; binocular vision, however, is preserved. *(Miller, 323–327)*

**38. (D)** Pupillary constriction to light and to convergence is preserved in cortical blindness. Retinal structures are preserved except if the blindness is caused by prenatal or perinatal injury. *(Miller, 358–362)*

**39. (E)** The patient described in this vignette has Horner syndrome. This syndrome can be confirmed and further characterized by pharmacological tests. The cocaine test is most commonly used to confirm the diagnosis. Cocaine blocks the reuptake of norepinephrine into the sympathetic nerve endings. In the normal eye, it causes dilatation of the pupil. This dilatation occurs if only there is continuous release of norepinephrine from the sympathetic nerves. In case of sympathetic denervation, cocaine fails to dilate the affected pupil.

Hydroxyamphetamine can be used to differentiate between postganglionic and preganglionic Horner syndrome. Hydroxyamphetamine acts by releasing norepinephrine from adrenergic stores in nerve endings. In case of damage to the postsganglionic neuron (third-order neuron), norepinephrine stores are depleted; thus hydroxyamphetamine fails to dilate the denervated pupil.

In this vignette, the affected pupil failed to dilate after exposure to cocaine and hydroxyamphetamine. Postganglionic sympathetic neuron dysfunction is the most likely cause. Evidence of denervation supersensitivity to adrenergic substances of the postganglionic neuron is supported by full dilation of the right pupil after exposure to a 2% solution of epinephrine, a weak direct-acting topical adrenergic drug. Postganglionic Horner syndrome may occur in diseases of the internal carotid artery, such as internal carotid artery dissection or atherosclerosis, and in cavernous sinus infection or tumors.

Lesions of the hypothalamus and lateral medulla cause damage to the first-order neuron of the sympathetic pathway. Tumors of the lung apex and brachial plexus damage may cause a preganglionic (second-order) neuron lesion. *(Miller, 434–774)*

**40. (C)** Holmes–Adie tonic pupil syndrome is caused by a generalized peripheral or autonomic neuropathy that also affects the ciliary ganglion or the short ciliary nerves. Clinically, the patient has a unilaterally dilated pupil or bilaterally dilated pupils, which may be confused with pharmacologically induced mydriasis.

The distinction between these two entities can be made by slit-lamp examination. Patients with Holmes–Adie tonic pupils have segmental contraction of the iris sphincter. In pharmacological anticholinergic blockade, the sphincter is entirely paralyzed and there is no segmental contraction with light stimulation. *(Miller, 450–455)*

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CHAPTER 13

# Neurooncology
## Questions

**1.** What is the most likely diagnosis of a well-circumscribed lobulated mass displacing the brain that, on microscopic examination, exhibits perivascular pseudorosettes?

(A) Oligodendroglioma
(B) Pilocytic astrocytoma
(C) Fibrillary astrocytoma
(D) Germ cell tumor
(E) Ependymoma

**2.** Ependymomas have

(A) a greater incidence among males than among females
(B) a predominant supratentorial location in the adult population
(C) thoracic predominance when located in the spinal cord
(D) an association with neurofibromatosis type II when there is multifocal spinal cord involvement
(E) a peak incidence at the age of 23 years

**3.** Myxopapillary ependymomas occur most frequently in the

(A) fourth ventricle
(B) third ventricle
(C) cervical spinal cord
(D) conus–cauda–filum terminal
(E) lumbar spinal cord

**4.** The most frequent location of choroid plexus papillomas in children is

(A) the lateral ventricle
(B) the third ventricle
(C) the suprasellar region
(D) the cerebellopontine angle
(E) the ventricles, with multifocal involvement

**5.** The most common location of germ cell tumors in the central nervous system is the

(A) basal ganglia
(B) thalamus
(C) pineal region
(D) cerebellum
(E) brainstem

**6.** Hormonal assays indicate that most meningiomas express receptors to

(A) androgen
(B) glucocorticoid
(C) estrogen
(D) progesterone
(E) somatostatin

**7.** The most frequent location of intracranial meningiomas is the

(A) olfactory groove
(B) parasagittal/falcine area
(C) sphenoidal ridge
(D) optic sheath
(E) choroid plexus

**8.** Psammoma bodies are seen in

(A) glioblastoma
(B) pituitary adenoma
(C) ependymoma
(D) medulloblastoma
(E) meningioma

**9.** What is the most common location of intracranial schwannomas?

(A) Facial nerve
(B) Abducens nerve
(C) Trigeminal nerve
(D) Oculomotor nerve
(E) Optic nerve

**10.** The presence of a biphasic architectural pattern composed of Antoni A and B areas is a hallmark of

(A) meningiomas
(B) gliomas
(C) ependymomas
(D) oligodendrogliomas
(E) schwannomas

**11.** Neurofibromas are composed of

(A) Schwann cells
(B) astrocytes
(C) oligodendrocytes
(D) melanocytes
(E) neuronal cells

**12.** The most frequent pituitary secreting adenoma is the

(A) prolactinoma
(B) growth hormone adenoma
(C) TSH-secreting adenoma
(D) ACTH-secreting adenoma
(E) FSH/LH-secreting adenoma

**13.** What is the dominant type of hormone-secreting cell seen in the normal anterior lobe of the pituitary gland?

(A) Prolactin-secreting cell
(B) Adrenocorticotrophin-secreting cell
(C) Thyrotrophin-secreting cell
(D) Growth hormone–secreting cell
(E) Luteinizing stimulating hormone–secreting cells.

**14.** An astrocytoma of intermediate differentiation with the presence of nuclear atypia and mitotic activity but without necrosis or endothelial proliferation is best classified as a

(A) pilocytic astrocytoma (WHO grade I)
(B) fibrillary astrocytoma (WHO grade II)
(C) anaplastic astrocytoma (WHO grade III)
(D) glioblastoma multiforme (WHO grade IV)
(E) pleomorphic xanthoastrocytoma (WHO grade II)

**15.** Which of the following immunohistochemical reactions helps to differentiate glioblastoma from metastatic melanoma?

(A) Glial fibrillary acidic protein
(B) S-100 protein
(C) HMB 45
(D) Vimentin
(E) Keratin

**16.** Which of the following often does not appear as a cystic lesion with an enhancing mural nodule on gadolinium-enhanced magnetic resonance imaging (MRI)?

(A) Oligodendroglioma
(B) Ependymoma
(C) Pilocytic astrocytoma
(D) Hemangioblastoma
(E) Ganglion cell tumor

**17.** Which of the following neoplasms is typically located near the foramen of Monro as an intraventricular mass?

(A) Lymphoma
(B) Medulloblastoma
(C) Oligodendroglioma
(D) Dysembrioplastic neuroepithelial tumor
(E) Central neurocytoma

**18.** Tuberous sclerosis is associated with molecular abnormalities involving the

(A) *p53* suppressor on 17p 13.1
(B) *CDKN2* suppressor
(C) N-*myc* oncogene
(D) neurofibromin
(E) tubulin

**19.** Anaplastic astrocytoma is associated with molecular abnormalities involving

(A) the *p53* suppressor on 17p 13.1
(B) the *CDKN2* suppressor
(C) the N-*myc* oncogene
(D) neurofibromin
(E) tubulin

**20.** Neuroblastoma is associated with molecular abnormalities involving

(A) the *p53* suppressor on 17p 13.1
(B) the *CDKN2* suppressor
(C) the N-*myc* oncogene
(D) neurofibromin
(E) tubulin

**21.** WHO grade II astrocytoma is associated with molecular abnormalities involving

(A) the *p53* suppressor on 17p 13.1
(B) the *CDKN2* suppressor
(C) the N-*myc* oncogene
(D) neurofibromin
(E) tubulin

**22.** von Recklinghausen neurofibromatosis is associated with molecular abnormalities involving

(A) the *p53* suppressor on 17p 13.1
(B) the *CDKN2* suppressor
(C) the N-*myc* oncogene
(D) neurofibromin
(E) tubulin

**23.** The presence of cellular pleomorphism, nuclear atypia, and marked mitotic activity with the absence of necrosis and endovascular proliferation is highly suggestive of

(A) WHO grade I astrocytoma
(B) WHO grade II astrocytoma
(C) WHO grade III astrocytoma
(D) glioblastoma multiforme
(E) gemistocytic astrocytoma

**24.** The most consistent chromosomal abnormality in glioblastoma multiforme is a

(A) gain of chromosome 7
(B) gain of chromosome 17p
(C) loss of chromosome 1p
(D) loss of chromosome 11p
(E) loss of chromosome 9q

**25.** Mutations in the PTEN gene (phosphatase and tensin homologue gene located on chromosome 10) occur most commonly in cases of

(A) oligodendroglioma
(B) medulloblastoma
(C) pilocytic astrocytoma
(D) anaplastic astrocytoma
(E) de novo glioblastoma

**26.** Which of the following molecular features is shared between well-differentiated oligodendrogliomas and anaplastic oligodendrogliomas?

(A) Loss of heterozygosity on chromosome 15
(B) Deletion of the CDKN2A gene
(C) Loss of heterozygosity on chromosome 4
(D) Loss of heterozygosity on chromosome 1p
(E) Mutation of the PTEN gene

**27.** What is the most common endocrine abnormality seen in suprasellar germ cell tumors?

(A) Precocious puberty
(B) Diabetes insipidus
(C) Impotence
(D) Acromegaly
(E) Amenorrhea

**28.** The most efficacious single agent in the chemotherapeutic treatment of malignant gliomas is

(A) a nitrosourea derivative (BCNU, CCNU)
(B) procarbazine
(C) temozolomide
(D) vincristine
(E) carboplatin

**29.** Which of the following statements is true about primary central nervous system lymphoma in immunocompetent patients?

(A) It is more common before age 40.
(B) Glucocorticoids should be administrated before stereotactic biopsy.
(C) The survival rate significantly improves with tumor resection.
(D) The B lymphocyte phenotype is found in more than 80% of cases.
(E) It is resistant to radiation therapy.

**30.** The most frequent brain tumor in the pediatric population is a

(A) craniopharyngioma
(B) brainstem glioma
(C) medulloblastoma
(D) germ cell tumor
(E) ependymoma

**31.** Which of the following statements is true of medulloblastoma?

(A) It typically arises from the vermis and the roof of the fourth ventricle.
(B) Its peak incidence is at the age of 20 years.
(C) Hydrocephalus is usually seen late in the course of the disease.
(D) High tyrosine protein kinase C receptors expression may be an indicator of poor prognosis.
(E) Radiotherapy has a modest benefit in the management of medulloblastoma.

**32.** Which of the following criteria suggests a higher risk of disease recurrence in the case of medulloblastoma?

(A) Posterior fossa location of the tumor
(B) Patient's age above 4 and below 21 years at the time of the diagnosis
(C) Decreased tyrosine kinase C receptor activity
(D) Total resection of nondisseminated tumor
(E) None of the above

**33.** Cerebrospinal fluid alpha fetoprotein may be elevated in

(A) choroid plexus tumors
(B) ependymomas
(C) medulloblastomas
(D) germ cell tumors
(E) craniopharyngiomas

**34.** The most frequent origin of brain metastasis is

(A) breast cancer
(B) lung cancer
(C) skin cancer
(D) kidney cancer
(E) an unknown primary site

**35.** The most frequent origin of metastasis causing epidural spinal cord compression is

(A) the prostate
(B) the lung
(C) lymphoma
(D) the GI tract
(E) the breast

**36.** Which of the following structures of the brain is the most sensitive to radiation damage in a 4-year-old girl who is undergoing a whole-brain radiation for leukemia treatment?

(A) Hippocampus
(B) Thalamus
(C) Frontal cortex
(D) Occipital cortex
(E) Vermis

**37.** The most frequent malignancy associated with paraneoplastic sensory neuronopathy is

(A) breast cancer
(B) small cell lung cancer
(C) ovarian cancer
(D) lymphoma
(E) colon cancer

# Answers and Explanations

1. **(E)** Ependymomas arise throughout the neuraxis, often in an intraventricular location. In the adult population, 64.1% of ependymomas are in the spinal cord, 11.8% are supratentorial, and 24.1% are infratentorial. Among the pediatric population, ependymomas are the third most common intracranial tumors after pilocytic astrocytomas and primitive neurectodermal tumors. About 30% of them appear before the age of 3 years and about 50% before the age of 5 years. Nearly 90% of pediatric ependymomas are intracranial and only 10% are intraspinal. Approximately, two thirds of intracranial ependymomas in children occur in the infratentorial compartment. Classic ependymomas grow as demarcated soft, gray masses that arise in the ventricular system. In the posterior fossa, they may fill the fourth ventricle and pass through its exit foramina. On microscopic examination, ependymomas are generally composed of uniform cells with indistinct cytoplasmic borders and round or oval nuclei. The nuclear/cytoplasmic ratio varies; it is usually high, but infrequent nodules of densely packed cells may be scattered throughout paucicellular areas. The pseudorosette is a perivascular anuclear zone of radial fibrillary processes that taper toward a vessel and is a hallmark of ependymomas. Less commonly, ependymomas show the characteristic epithelial features of true ependymal pseudorosettes. *(Parisi, 6–8; McGuire, 725–729)*

2. **(D)** Most ependymomas occur in childhood, with a peak incidence between 1 and 5 years. Males and females are nearly equally affected. In the adult population, infratentorial ependymomas are more common that supratentorial ependymomas. Ependymomas represent 60% of intramedullary gliomas of the spinal cord, most arising in the filum terminale (as myxopapillary variants) and occurring primarily in adults. Multifocal spinal cord ependymomas are associated with neurofibromatosis type II. *(Parisi, 6–8; McGuire, 725–729)*

3. **(D)** Myxopapillary ependymomas appear as well-defined, sausage-shaped lesions located in the cauda equina and tending to distend it. Hemorrhagic rupture of these tumors may result in seeding of the subarachnoid space. *(Parisi, 6–8)*

4. **(A)** The site of predilection for the development of choroid plexus papillomas is the lateral ventricle in children and the fourth ventricle in adults. *(Parisi, 9–10)*

5. **(C)** Central nervous system germ cell tumors are most common in children and adolescents, with a peak incidence between the ages of 10 and 12 years. They are more common in males than females, with an overall male-to-female ratio of 2.5 to 1. The most common locations of germ cell tumors are the pineal and suprasellar regions. Occasionally, these tumors may occur in the basal ganglia, thalamus, and other sites in the central nervous system. *(Jones, 2)*

6. **(D)** Meningiomas may become clinically evident during pregnancy or the luteal phase of the menstrual cycle, suggesting that their growth may be hormonally related. Hormone assays indicate that most meningiomas express receptors to progesterone rather than to estrogen or both hormones. *(Parisi, 1)*

7. **(B)** Approximately 90% of meningiomas are intracranial, while 9% are intraspinal. The most

frequent intracranial location is the skull base (planum spheroidale, sphenoid wing, petrous ridge, etc.), and at sites of dural reflection (falx, tentorium, etc.). Other less frequent locations include the tuberculum sella, olfactory groove, foramen magnum, optic nerve sheath, and choroid plexus. *(Parisi, 11; Whittle, 1535–1543)*

**8.** **(E)** Psammoma bodies are concentrically laminated calcifications seen in meningiomas. *(Parisi, 2)*

**9.** **(C)** Schwannomas account for approximately 8% of all primary intracranial neoplasms. The most common intracranial schwannomas develop from the vestibular nerve and occupy the posterior cranial fossa. The second most common develop from the trigeminal nerve and account for less than 8% of intracranial schwannomas. Trigeminal schwannomas are encapsulated masses that are predominantly solitary. They are more common in females between the ages of 35 and 60 years. Facial nerve schwannomas are less frequent than trigeminal schwannomas, followed by glossopharyngeal, vagus, and spinal accessory nerve schwannomas. Schwannomas involving the oculomotor, trochlear, abducens, and hypoglossal nerves are rare. Intraparenchymal schwannomas are very rare. Since the olfactory and optic nerves do not have a Schwann cell layer, they do not develop schwanommas. *(Parisi, 6–7)*

**10.** **(E)** The microscopic hallmark of schwannomas is a biphasic histological pattern composed of distinct compact (Antoni A) areas intermixed with loose microcytic (Antoni B) areas. The Antoni A regions are cellular but lack the mitotic figures of a malignant nerve-sheath tumor. The identification of an encapsulated Schwann cell tumor implies a benign nature. The Antoni B areas are hypocellular and lack a patterned arrangement. Cells are loosely arranged in a myxoid matrix accompanied by thin strands of collagen. Occasional mast cells may be identified in the Antoni B area. *(Parisi, 7)*

**11.** **(A)** Schwann cells, perineural cells, and fibroblasts are all present in neurofibromas. *(Parisi, 9)*

**12.** **(C)** Pituitary adenomas represent the third most common primary intracranial neoplasm encountered in neurosurgical practice, with a reported annual incidence ranging from 1 to 14.7 per 100,000 persons. They may account for approximately 10% to 15% of primary brain tumors. Prolactinomas have the highest incidence among pituitary-secreting tumors. They account for 40% to 60% of functioning adenomas and are the most common subtype of pituitary tumor diagnosed in adolescents. Men are generally diagnosed in their fourth and fifth decades, whereas women are generally diagnosed earlier. GH-secreting adenomas represent nearly 30% of all functioning tumors, followed by ACTH adenomas, which account for 15% to 25% of all functioning adenomas. TSH- and LH/FSH-secreting tumors are the least frequent functioning pituitary adenomas. An immunocytochemical study of 100 subclinical pituitary adenomas discovered at autopsy found that 50% were null cell adenomas (non-hormone-secreting adenomas) and 45% were prolactinomas. *(Freda, 3859–3866; Lafferty, 4317–4323; McComb, 488)*

**13.** **(D)** The normal adenohypophysis pituitary gland comprises growth hormone–secreting cells (somatotroph cells), prolactin-secreting cells (lactotroph cells), ACTH-secreting cells (corticotroph cells), LH/FSH-secreting cells (gonadotroph cells), and TSH-secreting cells. The total composition of secreting cells in the pituitary gland is as follows:

- 50% growth hormone–secreting cells
- 10% to 30% prolactin-secreting cells
- 10% to 20% ACTH-secreting cells
- 10% LH/FSH-secreting cells
- 5% TSH-secreting cells (Scheithauer, 2)

**14.** **(C)** The World Health Organization has assigned four grades to the spectrum of astrocytic tumors: grade I (pilocytic astrocytoma), grade II (diffuse astrocytoma), grade III (anaplastic astrocytoma), and grade IV (glioblastoma multiforme). The pilocytic astrocytoma is one of the most benign forms of astrocytic tumor. The 10-year survival in supratentorial cases is generally over 90% in most studies after gross total resection and 74% after subtotal resection. Most but not all pilocytic astrocytomas occur in children or young

adults. They are most abundant in the cerebellum, where they represent the majority of childhood astrocytomas. They are also found in the region of the third ventricle, thalamus, hypothalamus, and neurohypophysis, where they can be difficult to treat owing to their location near clinically sensitive brain structures.

"Pilocytic" means "hair cell," referring to one of the major microscopic features of this tumor, namely, parallel bundles of elongated, fibrillar cytoplasmic processes resembling mats of hair. These hair-like processes contain large amounts of glial fibrils that stain well with either Mallory PTAH (phosphotungstic acid and hematoxylin stain) or immunoperoxidase for GFAP (glial fibrillary acidic protein).

Diffuse (low-grade) grade II astrocytomas are well-differentiated, diffusely infiltrative neoplasms composed of fibrillary astrocytes with nuclear atypia but no mitoses. Anaplastic astrocytomas are grade III astrocytomas. They are characterized by an intermediate differentiation, increased cellular density, increased nuclear pleomorphism, and moderately increased nuclear hyperchromatism plus mitoses. The lack of endothelial proliferation and foci of coagulation necrosis in anaplastic astrocytic gliomas distinguishes them from glioblastomas, but individual cells with pyknotic nuclei may be interspersed in anaplastic astrocytomas.

Glioblastoma multiforme (glioblastoma) is classified as a grade IV astrocytoma. It is a glioma that may be uniformly undifferentiated or may contain focal areas of differentiation, including oligodendroglioma, and rarely ependymoma-like elements. Endothelial proliferation (increased density of cells in vascular walls), necrosis, nuclear atypia, and mitotic activity are the most important characteristic of grade IV astrocytoma. The pleomorphic xanthoastrocytoma is a bizarre supratentorial astrocytoma of young individuals that often involves both leptomeninges and cerebral cortex. It is occasionally hemorrhagic. Its fibrillary, pleomorphic, hyaline, and lipid-laden multinucleated giant cells are clues to its diagnosis. Protein granular degeneration may be prominent, similar to that seen in pilocytic astrocytomas. Intracellular lipid content varies from abundant to absent between individual tumors. Astrocytomas are characterized by cells strongly positive for glial fibrillary acidic protein (GFAP), often with histiocytic features. *(Scheithauer, 1–2)*

**15. (C)** HMB 45 staining is useful because it is specific for melanoma. Both melanoma and glioblastoma can react with S-100 proteins and vimentin. Glioblastomas may or may not react with GFAP and keratin. Glioblastomas lack reactivity to HMB 45, whereas metastatic melanoma reacts specifically with this immunohistochemical stain, which is helpful in differentiating between these two tumors. *(Scheithauer, 15)*

**16. (A)** The following tumors may appear cystic with an enhancing mural nodule: pleomorphic xanthoastrocytoma, pilocytic astrocytoma, ganglion cell tumors, hemangioblastoma, and ependymoma. *(Burger, 295)*

**17. (E)** Central neurocytomas are rare large intraventricular globular masses, commonly straddling the midline in the region of the septum pellucidum. They can obstruct the flow of cerebrospinal fluid, resulting in increased intracranial pressure and hydrocephalus. Other intraventricular masses arising near the foramen of Monro include colloid cysts, subependymomas, and subependymal giant cell astrocytomas. *(Burger, 296)*

**18. (E)** Mutations of two different genes (TSC1 at 9q34 and TSC2 at 16p13.3) result in the tuberous sclerosis complex (TSC). It is inherited as an autosomal dominant trait with a high rate of spontaneous mutations in the TSC genes (65% to 75% of cases arise from new mutations). Tubulin is the gene product of TSC2. Although the phenotypic expression of TSC is highly variable, it is not determined by the specific gene mutation. In fact, even affected members of the same family often develop very different manifestations. *(Davis, 846–847; Rasheed, 162–167; Sparagana, 115–119; Tai, 255–262)*

**19. (B)** The most common genetic abnormality observed in anaplastic astrocytomas and glioblastomas is a defect in the cell-cycle regulatory pathway, such as inactivation of the CDKN2A

and B genes. *(Davis, 846–847; Rasheed, 162–167; Sparagana, 115–119; Tai, 255–262)*

**20.** **(C)** The N-*myc* gene plays an essential role in organogenesis. Gene overexpression due to genomic amplification has been observed in many human tumors such as the common childhood tumor neuroblastoma. *(Davis, 846–847; Rasheed, 162–167; Sparagana, 115–119; Tai, 255–262)*

**21.** **(A)** Mutation in the *p53* tumor-suppressor gene may be seen in WHO grade II astrocytoma. The gene is located on chromosome 17p13.1. It encodes nuclear phosphoprotein, a transcription factor that enables passage through the cell cycle.

**22.** **(D)** Neurofibromin belongs to the family of GTPase-activating proteins (GAPs), which turn off the growth-promoting function of the Ras family of proteins by stimulating the hydrolysis of GTP bound to Ras. Without enough neurofibromin, Ras remains unchecked, resulting in cellular overgrowth and tumors. Mutation of the neurofibromin gene causes neurofibromatosis 1 (NF-1), also known as von Recklinghausen disease. This is an autosomal dominant condition caused by mutations of the NF-1 gene, which is located on chromosome 17q11.2. *(Davis, 846–847; Rasheed, 162–167; Sparagana, 115–119; Tai, 255–262)*

**23.** **(C)** WHO grade III astrocytoma (also called anaplastic astrocytoma) diffusely infiltrates the surrounding brain parenchyma and has an intrinsic tendency for malignant progression to glioblastoma. Histological examination shows greater cellular and nuclear atypia than seen in grade II astrocytoma, but there is absence of the necrosis and microvascular glomeruli or festoons seen in glioblastoma. Glioblastoma multiforme is the most common primary malignant tumor in adults and is characterized by the presence of endothelial proliferation (increased density of cells in vascular walls), necrosis, nuclear atypia, and mitotic activity. Grade II astrocytomas are slow-growing, diffusely infiltrating, well-differentiated astrocytomas. Histologically, they are composed of well-differentiated astrocytes exhibiting moderate cellular density and nuclear atypia. Gemistocytic astrocytoma is a variant of astrocytoma with a tendency toward rapid progression to glioblastoma. Pilocytic astrocytomas (WHO grade I) are typically circumscribed, slow-growing, cystic neoplasms. Histologically, they are characterized by a biphasic pattern of compact bipolar cells and loose-textured multipolar cells, the presence of Rosenthal fibers, microcysts, and eosinophilic granular bodies. *(Hildebrand, 11)*

**24.** **(A)** The most consistent chromosomal changes in glioblastoma multiforme are gains of chromosome 7; losses of chromosomes 9p, 10, and 17p; and genetic amplification represented by the presence of double-minute chromosomes (small extrachromosomal segments of amplified DNA sequences containing oncogenic alleles). *(Hildebrand, 12)*

**25.** **(E)** The PTEN gene (phosphatase and tensin homologue deleted from chromosome 10) encodes a protein that dephosphorylates phospatidylinositol-3,4,5-triphosphate (PIP3), thus inactivating a cellular growth pathway. Growth factor receptors activate phospatidylinositide-3-kinase (PI3K), which phosphorylates phospatidylinositol-4,5-diphosphate (PIP2) to PIP3, thus activating protein kinase B (PKB). Activated PKB stimulates cell growth and blocks apoptosis. PTEN shuts off this pathway, suppressing oncogenesis. Analyses of LOH (loss of heterozygosity) have consistently shown losses of all or part of chromosome 10 in more than 80% of glioblastoma cases as well as a common deletion region in distal 10q. PTEN mutations and overexpression of (epidermal growth factor receptors (EGFRs) are more common in primary de novo tumors rather than secondary progressing glioblastoma multiforme tumors. *(Rasheed, 162–167; Weiss, 543–548)*

**26.** **(D)** Anaplastic oligodendrogliomas share many molecular features with well-differentiated oligodendrogliomas, including loss of heterozygosity for 19q, 1p, or both. In contrast to well-differentiated oligodendrogliomas, anaplastic oligodendrogliomas can exhibit allelic loss of 9p, homozygous deletion of the CDKN2A gene, and losses involving chromosomes 4, 14, 15, and 18. Patients with anaplastic oligodendrogliomas

with 1p deletions, especially if coupled with 19q loss, have a better response to chemotherapy and an improved prognosis. *(Hildebrand, 15)*

**27. (B)** Diabetes insipidus is the most likely endocrine manifestation of germ cell tumors in the suprasellar areas. Precocious puberty is the most frequent endocrine disorder seen in hamartoma and hypothalamic glioma. Impotence, amenorrhea, galactorrhea, and acromegaly are seen in pituitary tumors. *(Hildebrand, 31)*

**28. (A)** Nitrosourea derivatives (BCNU, CCNU) remain for many neurooncologists the most effective single agents, with a 20% to 30% partial or complete response rate and 20% to 30% rate of stabilization. *(Hildebrand, 48)*

**29. (D)** For unknown reasons, the incidence of primary central nervous system lymphoma (PCNSL) in immunocompetent patients has increased fivefold during the last decades. Most CNS lymphomas occur in patients over the age of 50 years, with a median onset of 58 years. There is a slight preponderance of men among immunocompetent patients. PCNSL has a poor prognosis if untreated, with a median survival of 3 to 4 months. The predominant locations of PCNSL are the corpus callosum, frontal lobes, and deep periventricular structures of the brain. Most PCNSLs are non-Hodgkin lymphomas, with approximately 80% being non-Hodgkin B-cell lymphoma. The clinical features of the disease may include deterioration of cognitive function, headache, and seizures. When lymphoma is suspected, a biopsy should be performed before starting treatment, particularly with glucocorticosteroids. In about 50% of patients, the tumor responds to steroid administration and occasionally may transiently disappear completely, compromising the pathological diagnosis and delaying treatment. PCNSLs can initially be highly sensitive to the combination of radiation therapy and glucocorticosteroids, which increases the median of survival from a few to 12 to 18 months. High-dose of methotrexate can extend 5-year survival rates to about 20%, but when combined with radiation therapy, it is associated with significantly delayed neurotoxicity, especially in individuals over 60 years of age. However, tumor resection does not significantly improve survival. *(DeAngelis, 687–691; Hildebrand, 54–56)*

**30. (C)** Medulloblastoma is the most common malignant brain tumor of childhood, with a peak incidence around the first decade of life and a male-to-female preponderance of about 2 to 1. It is a member of the primitive neuroectodermal tumor family of CNS neoplasms and is considered a grade IV lesion by the World Health Organization. *(Reddy, 681–685)*

**31. (A)** Medulloblastomas are invasive embryonal tumors of the cerebellum with a tendency to metastasize in the CNS. They represent 10% to 20% of brain tumors and 30% of tumors localized in the posterior fossa. The peak incidence of medulloblastoma is in the first decade of life, with an annual incidence of 0.5 per 100,000 children. In the brain, medulloblastoma typically arises in the vermis of the cerebellum or roof of the fourth ventricle, causing ataxia and signs of hydrocephalus early on. At the time of diagnosis, over 80% of children have hydrocephalus. Tyrosine protein kinase C receptor (TrkC) is expressed on mature granular cells. It is also the receptor for neurotropin-3, which is one of the regulators of cerebellar granular cell development. TrkC expression in medulloblastoma correlates with a favorable clinical outcome. The management of patients with medulloblastoma includes surgical resection followed by craniospinal radiation. With this treatment, patients with average-risk disease (patients who have localized tumor totally or nearly totally resected by surgery) have approximately a 60% 5-year progression-free survival. The addition of chemotherapy to the management of high-risk patients with medulloblastoma (patients with disseminated disease or partially resected tumor) may improve the outcome. *(Reddy, 681–685; Hildebrand, 61)*

**32. (C)** Factors associated with poor outcome in medulloblastoma include nonposterior fossa location, disseminated tumor, nondisseminated incompletely resected tumor with residual tumor greater than 1.5 cm in its greatest dimension, decreased tyrosine protein kinase C receptor

activity, and age less than 3 years at the time of diagnosis. *(Hildebrand, 61)*

**33.** **(D)** Alpha fetoprotein and β-HcG are elevated in the cerebrospinal fluid of the majority of patients with mixed germ cell tumors, while only β-HcG is elevated in patients with choriocarcinomas. *(Hildebrand, 72)*

**34.** **(B)** Brain metastases are seen in approximately 15% to 20% of cancers. The most frequent primary tumor associated with brain metastasis is non–small cell lung cancer, which represents about 50% of brain metastases. Breast cancer is the second most frequent cause of brain metastases and represents about 19% of all brain metastases. Skin/melanoma brain metastases represent about 10.5% of total brain metastasis, whereas GI metastases account for about 10% of all brain metastases. Unknown primary site metastases represent 11% of brain metastases. *(Kleihues, 252; Hildebrand, 76)*

**35.** **(E)** The most frequent origin of metastasis causing epidural spinal cord compression is the breast (it represents 22% of epidural metastasis). Other origins include lung, prostate, and malignant lymphoma with about 15%, 10%, and 10% of epidural spinal cord compression cases, respectively. *(Kleihues, 252)*

**36.** **(A)** The radiation tolerance of normal brain and spinal cord depends mostly on the rate of turnover of mature functioning cells. Neurons, because they do not replicate, are resistant to radiotherapy but dependent for their functioning on the slow renewal of glial cells and the endothelial cells of blood vessels, which continue to proliferate throughout life. In addition, the hippocampus, where neurogenesis continues to occur postnatally, has been shown to be especially sensitive to radiation damage. *(Monje, 2003; Taphoorn, 93–115)*

**37.** **(B)** Paraneoplastic sensory neuronopathy (PSN) is characterized by progressive numbness and often painful dysesthesias involving the limbs, trunk, and, less frequently, the cranial nerves, causing facial numbness or sensorineural hearing loss. The symptom presentation is frequently asymmetric, associated with decreased or abolished reflexes and relative preservation of strength. All types of sensation can be affected, but loss of proprioception is often predominant. As a result, patients develop sensory ataxia and pseudoathetoid movements of the extremities (predominantly the hands). PSN results from inflammatory involvement of the dorsal root ganglia, usually accompanied by dorsal nerve root inflammation. PSN is frequently associated with paraneoplastic encephalomyelitis, particularly in patients with small cell lung cancer. *(Bataller, 69–92)*

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CHAPTER 14

# Movement Disorders
## Questions

**1.** The combination of generalized seizures with ataxia and dementia is *not* seen in which one of the following conditions?

(A) Huntington disease
(B) Neuronal ceroid lipofuscinosis
(C) Lafora disease
(D) $G_{M2}$ gangliosidosis
(E) Mitochondrial encephalomyelopathy

**2.** Alien limb occurs significantly in case of

(A) Huntington disease
(B) corticobasal degeneration
(C) Parkinson disease (PD)
(D) Wilson disease
(E) carbon monoxide intoxication

**3.** Which of the following is true of the dorsal prefrontal circuit?

(A) It originates in the frontal convexity and projects to the nucleus accumbens.
(B) It involves the ventral posterolateral nucleus of the thalamus.
(C) Lesion of the circuit results in deficits in executive function and motor programming.
(D) The Mini-Mental State Examination is typically impaired when there is a lesion of the prefrontal cortex.
(E) The prefrontal circuit is particularly spared in Huntington disease.

**4.** Lesion of the lateral orbitofrontal circuit results in

(A) contralateral hemiplegia
(B) depression
(C) reduced executive function
(D) apathy
(E) disinhibition

**5.** Lesion of the anterior cingulate circuit results in

(A) apathy
(B) euphoria
(C) agitation
(D) hallucination
(E) loss of executive function

**6.** Which of the following movement disorders carries the highest risk of depression with suicide?

(A) Huntington disease
(B) PD
(C) Progressive supranuclear palsy
(D) Wilson disease
(E) Gille de la Tourette syndrome

**7.** The main movement disorder associated with apraxia is

(A) PD
(B) Huntington disease
(C) Creutzfeldt–Jacob disease
(D) corticobasal degeneration
(E) Wilson disease

**8.** Which of the following is characteristic of dementia in PD?

(A) Aphasia
(B) Agnosia
(C) Psychomotor slowing
(D) Amnesia
(E) Apraxia

**9.** Cerebral blood flow studies showed that when untreated PD patients are asked to perform a paced movement with a joystick, there is a decrease of blood flow in the

(A) sensorimotor cortex
(B) lateral premotor cortex
(C) lateral parietal cortex
(D) contralateral anterior cingulated
(E) ipsilateral lentiform nucleus

**10.** Age-related mitochondrial deletion is most frequently seen in the

(A) putamen
(B) globus pallidus
(C) hippocampus
(D) cerebellum
(E) cerebral cortex

**11.** Inherited dystonia is caused by a defect of the oxidative phosphorylation complex involving

(A) complex I (NADH)
(B) complex II (succinate)
(C) complex III (ubiquinone)
(D) complex IV (cytochrome oxidase)
(E) complex V (adenosine triphosphate)

**12.** The neurotoxin 1 methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) may cause PD. It acts by

(A) inhibiting monoamine oxidase B in basal ganglia neurons
(B) increasing ATP generation
(C) blocking complex I of the oxidative phosphorylation complex
(D) blocking complex II of the oxidative phosphorylation complex
(E) blocking complex V of the oxidative phosphorylation complex

**13.** Proximal limb kinetic apraxia is caused by a lesion in the

(A) primary motor cortex
(B) supplementary motor cortex
(C) lateral premotor cortex
(D) cingulate motor area
(E) parietal cortex

**14.** The motor component of the basal gangliothalamocortical circuits is processed by the

(A) caudate
(B) globus pallidus internal segment
(C) nucleus accumbens
(D) globus pallidus external segment
(E) putamen

**15.** Which of the following is true of cognitive impairment and Parkinson disease?

(A) Dementia is observed in less than 10% of patients with Parkinson disease, usually at an advanced stage of the disease.
(B) Mild cognitive impairment is rarely observed in the early stage of Parkinson disease. and is usually reported in severe cases.
(C) The risk of developing dementia in Parkinson disease patients is similar to the risk in the general population.
(D) Attentional impairment is a major cognitive feature of dementia in Parkinson disease.
(E) Impairment of ability to copy a figure showing intersecting pentagons may be observed in Parkinson disease dementia; however, it does not predict a rapid decline in cognitive function.

**16.** An inverse relationship has been observed between the occurrence of Parkinson disease and

(A) cigarette smoking
(B) exposure to pesticides
(C) exposure to lead
(D) exposure to manganese
(E) hypertension

**17.** Mutations in which of the following genes cause autosomal recessive forms of parkinsonism?

(A) *PARK1*
(B) *PARK2*
(C) *PARK3*

(D) *PARK4*
(E) *PARK5*

**18.** Which of the following is true about parkinsonism caused by mutations in the gene for parkin?

(A) It causes an autosomal dominant parkinsonism.
(B) The mutation is located on chromosome 4q21.
(C) The age of onset of parkinsonism is usually around 60 years.
(D) Point mutations of the parkin gene lead to a milder form of parkinsonism than gene deletion.
(E) Rapid disease progression.

**19.** Which of the following neurotransmitters is common to the direct and indirect pathways of the striatum?

(A) GABA
(B) Substance P
(C) Enkephalin
(D) Glutamate
(E) Glycine

**20.** The subthalamic nucleus projects to the internal part of the globus pallidus and substantia nigra using which of the following neurotransmitters?

(A) Glutamate A
(B) Glycine
(C) GABA
(D) Acetylcholine
(E) Substance P

**21.** A 65-year-old man died of progressive dementia complicating a parkinsonian syndrome that was poorly responsive to levodopa. Pathological examination showed a shrinking globus pallidus associated with atrophy of the subthalamic nucleus and pallor of the substantia nigra with enlargement of the aqueduct of Sylvius. The most likely diagnosis is

(A) Huntington disease
(B) progressive supranuclear palsy
(C) multisystem atrophy
(D) PD
(E) corticobasal degeneration

**22.** Which of the following is associated with an increased risk of PD?

(A) Vitamin E
(B) Manganese
(C) Caffeine
(D) Cigarette smoking
(E) Alcohol

**23.** Which of the following is true about 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP)?

(A) MPTP-induced parkinsonism has more resting tremor than idiopathic PD.
(B) MPTP is oxidized inside the neuron into MPP+.
(C) MPTP inhibits mitochondrial respiration in astrocytes.
(D) MPP+ inhibits mitochondrial complex I, which results in failure of ATP synthesis.
(E) MPTP has a cocaine-like mechanism of action.

**24.** Which of the following is most disabling in PD?

(A) Tremor
(B) Akinesia
(C) Rigidity
(D) Postural instability
(E) Depression

**25.** Which of the following dopamine receptors stimulate adenylate cyclase?

(A) D1 receptors
(B) D2 receptors
(C) D3 receptors
(D) D4 receptors
(E) None of the above

**26.** Which of the following dopamine receptors are D2-like receptors?

(A) D2 and D3 receptors
(B) D1 and D2 receptors
(C) D2 and D5 receptors
(D) D1, D2, and D5 receptors
(E) D1, D2, D3, and D5 receptors

**27.** Clozapine is a selective

(A) D4 receptor agonist
(B) D4 receptor antagonist
(C) D2 receptor agonist
(D) D2 receptor antagonist
(E) D5 receptor agonist

**28.** The medulla contains

(A) no dopamine receptors
(B) D1 receptors
(C) D2 receptors
(D) D3 receptors
(E) D4 receptors

**29.** A 73-year-old man diagnosed with early-stage PD who is given L-dopa three times a day may show a sustained motor response because of

(A) hypersensitivity to L-dopa
(B) presynaptic storage of exogenous dopamine
(C) half-life of L-dopa (8 hours)
(D) postsynaptic storage of L-dopa
(E) none of the above

**30.** Entacapone is

(A) an anticholinergic drug
(B) an MAOB inhibitor
(C) an anti-NMDA receptor
(D) a dopamine agonist
(E) a catechol-O-methyl transferase (COMT) inhibitor

**31.** Pergolide is

(A) an anticholinergic drug
(B) an MAOB inhibitor
(C) an anti-NMDA receptor
(D) a dopamine agonist
(E) a COMT inhibitor

**32.** Selegiline is

(A) an anticholinergic drug
(B) an MAOB inhibitor
(C) an anti-NMDA receptor
(D) a dopamine agonist
(E) a COMT inhibitor

**33.** Pramipexole is

(A) an anticholinergic drug
(B) an MAOB inhibitor
(C) an anti-NMDA receptor
(D) a dopamine agonist
(E) a COMT inhibitor

**34.** Remacemide is

(A) an anticholinergic drug
(B) an MAOB inhibitor
(C) an anti-NMDA receptor
(D) a dopamine agonist
(E) a COMT inhibitor

**35.** Riluzole is

(A) an anticholinergic drug
(B) an MAOB inhibitor drug
(C) an anti-NMDA receptor
(D) a dopamine agonist
(E) an inhibitor of glutamic acid release

**36.** The most common neurobehavioral abnormality observed in PD is

(A) depression
(B) personality change
(C) panic attacks
(D) illusion
(E) hallucination

**37.** Which of the following differentiate supranuclear palsy from PD?

(A) Staring gaze
(B) Absence of tremor

(C) Flexed posture
(D) Hypersensitivity to dopamine
(E) Gait disturbance late in the progression of the disease

**38.** The earliest sign of progressive supranuclear palsy is

(A) dysarthria
(B) visual symptoms
(C) gait difficulties
(D) dysphagia
(E) dementia

**39.** Which of the following is *not* in favor of the diagnosis of supranuclear palsy?

(A) Absence of tremor
(B) Vertical gaze palsy
(C) Preserved horizontal oculocephalic reflex
(D) Early cerebellar sign
(E) Neck rigidity greater than limb rigidity

**40.** Which of the following is observed in Parkinson disease but not in progressive supranuclear palsy?

(A) Cerebral cortical and midbrain atrophy on magnetic resonance imaging (MRI) of the head
(B) Neurofibrillary tangles
(C) Symmetric axial rigidity with postural instability
(D) Positive L-dopa response in early stage of the disease
(E) Down-gaze palsy

**41.** Which of the following cerebral cortical layers are the most affected in case of progressive supranuclear palsy?

(A) Layers I and II
(B) Layers III and V
(C) Layers IV and VI
(D) Layers III and IV
(E) Layers V and VI

**42.** MPTP may cause parkinsonism by causing damage to the

(A) caudate
(B) putamen
(C) globus pallidus
(D) substantia nigra
(E) none of the above

**43.** Manganese may cause parkinsonism by causing damage to the

(A) caudate
(B) putamen
(C) globus pallidus
(D) substantia nigra
(E) none of the above

**44.** Cyanide may cause parkinsonism by causing damage to the

(A) caudate
(B) putamen
(C) globus pallidus
(D) substantia nigra
(E) none of the above

**45.** Methanol may cause parkinsonism by causing damage to the

(A) caudate
(B) putamen
(C) globus pallidus
(D) substantia nigra
(E) none of the above

**46.** Carbon monoxide may cause parkinsonism by causing damage to the

(A) caudate
(B) putamen
(C) globus pallidus
(D) substantia nigra
(E) none of the above

**47.** On MRI of the head, a bilateral decrease of signal intensity on T-2 weighted images of the globus pallidus in a 20-year-old man with a history of Parkinson syndrome is highly suggestive of

(A) Hallervorden–Spatz disease
(B) neuroacanthocytosis
(C) Rett syndrome
(D) MPTP intoxication
(E) diffuse Lewy body disease

**48.** Tremor is most commonly caused by which of the following drugs?

(A) Phenytoin
(B) Phenobarbital
(C) Valproic acid
(D) Carbamazepine
(E) Lamotrigine

**49.** Which of the following is true of the huntingtin protein?

(A) It is formed by consecutive proline residues encoded by a CCG repeat.
(B) Its gene is located on the long arm of chromosome 4.
(C) It is expressed in neuronal and nonneuronal cells.
(D) The pattern of huntingtin expression is parallel to areas of Huntington pathology.
(E) Huntingtin is a nuclear protein; its location is altered in cases of Huntington disease.

**50.** Which of the following is true of the clinical features of Huntington disease?

(A) The severity of chorea correlates with disease progression.
(B) Chorea is the most disabling symptom.
(C) Executive function is selectively lost.
(D) Apraxia is the earliest sign of cognitive impairment.
(E) Optokinetic nystagmus is typically conserved.

**51.** The unpleasant sensation of internal restlessness that is partially relieved by volitional movement in a patient on chronic neuroleptic treatment is called

(A) dystonia
(B) akathisia
(C) choreic movement
(D) tics
(E) myoclonus

**52.** What is the initial treatment of choice for a 15-year-old teenager who is complaining of motor tics related to Tourette syndrome?

(A) Clonidine
(B) Haloperidol
(C) Fluoxetine
(D) Botulinum toxin
(E) Clonazepam

**53.** Which of the following is true of the disturbance of eye movements in cases of cerebellar lesion?

(A) Saccadic dysmetria results from a lesion of the dorsal vermis.
(B) Gaze-evoked nystagmus is seen in case of a lesion of the fastigial nucleus.
(C) A lesion of the nodulus results in impaired smooth tracking.
(D) A lesion of the flocculus results in impairment of the duration of the vestibular response.
(E) A paraflocculer lesion causes saccadic dysmetria.

**54.** Which of the following molecular abnormalities is related to stiff-man syndrome?

(A) Abnormal CAG repeat
(B) Abnormal CCG repeat
(C) Glutamic acid decarboxylase antibodies
(D) Abnormal Cooper metabolism
(E) Alpha-synuclein abnormality

**55.** Which of the following gene mutations is seen in PD?

(A) Huntingtin gene
(B) Alpha-synuclein
(C) Adhalin gene
(D) Dystrophin gene
(E) Synaptophysin gene

# Answers and Explanations

1. **(A)** Progressive myoclonic epilepsy (PME) is a slowly progressive autosomal recessive disorder occurring in late childhood or early adulthood. Generalized seizures, ataxia, and dementia are prominent features. Linkage analysis has shown that the gene responsible is located on the long arm of chromosome 21q22.3. The common causes of PME are neuronal ceroid lipofuscinosis, mitochondrial encephalomyelopathy, sialidosis, Lafora disease, Baltic myoclonus, $G_{M2}$ gangliosidosis, and dentatorubropallidoluysian atrophy. *(Evidente, 475–490)*

2. **(B)** Alien limb is defined as the lack of recognition of movement in the affected limb, or a feeling that one limb is foreign associated with observable involuntary motor activity. The upper extremity is the most frequently affected limb. Signs include the failure to perceive ownership of one's limb in the absence of visual cues, an impression that the seen limb is foreign, personification of the affected limb, and autonomous motor activity deemed by the patient as beyond voluntary control. Alien limb syndrome is a well-established part of corticobasal degeneration. It is reported to complicate the course of the disease in nearly 50% of cases. Vascular etiology is most commonly reported in ischemic or hemorrhagic lesions of the anterior cerebral artery. Surgical lesions such as corpus callosotomy and thalamotomy have been associated with alien limb. Other causes of alien limb include Alzheimer disease and Creutzfeldt–Jacob disease. *(Hanna, 135–145)*

3. **(C)** The dorsal lateral prefrontal circuit originates in the frontal lobe convexity and projects to the dorsolateral head of the caudate and subsequently to the dorsomedial globus pallidus and rostral substantia nigra. These structures project to ventral anterior and medial dorsal thalamic nuclei, which connect back to the dorsolateral prefrontal cortex. Lesion of this circuit results in deficits in executive function and motor programming. The patient exhibits difficulties in maintaining or shifting set, generating organizational strategies, and retrieving memory. The dorsolateral prefrontal circuit is assessed by the Wisconsin Card Sort test. The circuit is disturbed in Huntington disease, as the degenerative process involves the caudate nucleus. *(Watts, 15)*

4. **(E)** The lateral orbitofrontal circuit of the frontal subcortical pathways originates in the inferolateral prefrontal cortex and projects to the ventromedial caudate nucleus, which then projects to the dorsomedial globus pallidus and substantia nigra. The return pathway is via the ventral anterior and dorsothalamic nuclei, which project back to the orbitofrontal cortex. Lesion of the orbitofrontal circuit causes personality changes with irritability and disinhibition (similar to personality changes seen in idiopathic calcification of the basal ganglia and neuroacanthocytosis). *(Watts, 16)*

5. **(A)** The anterior cingulate circuit of the subcortical frontal lobe pathway originates in the anterior cingulate gyrus and projects to the ventral striatum, which includes the nucleus accumbens, olfactory tubercles, and parts of the caudate and putamen. The ventral striatum then sends afferents to the globus pallidus and substantia nigra, which in turn project to the paramedian part of the medial dorsal thalamus. The thalamus projects back to the cingulate gyrus. Lesion of the anterior cingulate circuit causes

apathy, reduced drive and initiative, and decreased motivation. Akinetic mutism and profound apathy may result from bilateral lesions of the anterior cingulate circuit. *(Watts, 16)*

6. **(A)** Depression may complicate the course of a number of movement disorders. Among all of these, Huntington disease carries the highest risk of depression and suicide. Depression may affect half of the patients, with 30% meeting the criteria of major depression. Suicide is four to six times more common among Huntington disease patients than other depressed patients. In one study including Huntington disease patients and their relatives, the rate of death caused by suicide reached 7.3%. Depression may complicate the course of PD patients in approximately 40% of cases. Depression is seen in 20% to 30% of patients with the diagnosis of Wilson disease. Depression is less frequently seen in progressive supranuclear palsy and Gilles de la Tourette disorders. *(Di Maio, 293–295; Poewe, S2–S6; Watts, 17)*

7. **(D)** Apraxia is the inability to perform motor acts despite intact comprehension, cooperation, and motor and sensory skills. Corticobasal degeneration is the main movement disorder associated with apraxia (reported in 71% of cases in one series). The disorder is attributed to neuronal loss and achromasia in the frontoparietal cortex. *(Watts, 23)*

8. **(C)** Studies of the frequency of dementia in patients with Parkinson disease (PD) have found rates ranging from 8% to 81%. The addition of mental impairment to the motor symptoms of PD increases functional impairment and the need for health care in patients with PD. The dementia in PD is of the subcortical type. It is characterized by a psychomotor slowing (also called bradyphrenia), memory retrieval deficits, abnormal cognition with impaired ability to manipulate knowledge, and disturbed executive function. Aphasia, apraxia, agnosia, and amnesia are absent. *(Watts, 23)*

9. **(D)** When normal subjects perform paced movements with a joystick in freely selected directions with the right hand, there is an increase of the cerebral blood flow in the contralateral lentiform nucleus and sensorimotor cortex and bilateral increase of the blood flow of the anterior cingulate, supplementary motor cortex, lateral premotor cortex, and dorsolateral prefrontal cortex. When an untreated PD patient performs the same task, there is normal activation of sensorimotor cortex, lateral premotor cortex, and lateral parietal association areas. There is, however, decreased activation of the contralateral lentiform nucleus, anterior cingulate, supplementary motor area, and dorsolateral prefrontal area. *(Watts, 33)*

10. **(A)** The susceptibility of the central nervous system to somatic mitochondrial mutations is high and occurs with age in specific brain regions. The caudate and putamen are the locations of the highest accumulation of mitochondrial DNA mutations, whereas the cerebellum and myelinated axons have the lowest level of mitochondrial DNA mutations. *(Watts, 54)*

11. **(A)** Complex I–specific activity as determined by the nicotinamide adenine dinucleotide ubiquinone assay is reduced in brains of patients with inherited dystonia compared with controls. *(Watts, 58)*

12. **(C)** 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces parkinsonism by causing selective degeneration of nigral neurons. 1-Methyl-4-phenylpyridinium ion (MPP+), the oxidative metabolite of MPTP, is actively taken up into dopaminergic neurons through the dopamine transporters and concentrated within dopaminergic neurons. In nigral neurons, MPP+ inhibits complex I of the mitochondrial electron transport chain and the A-ketoglutarate dehydrogenase complex (KGDHC) of the Krebs cycle. This has been considered the major mechanism of neuronal death in MPTP-induced PD, although other mechanisms such as apoptosis have also been postulated. *(Mizuno, 893–902)*

13. **(C)** The control of proximal limb musculature and interlimb coordination is related to the lateral premotor area of the cortex. This is suggested by the heavy projections from this region to the medial pontomedullary reticular formation, where spinal projections constitute the bulk of the ventromedial descending brainstem system associated with control of the proximal

musculature. Lesion of the lateral premotor cortex causes a proximal limb kinetic apraxia that contrasts sharply with the bimanual distal apraxia of the supplementary motor cortex. Such patients may have difficulties making coordinated rotary movements of both shoulders whereas independent movement of either shoulder is performed with ease within the limits of any associated weakness. *(Watts, 76)*

**14.** **(E)** Motor circuitry is initiated in cortical regions that transmit parallel glutaminergic projections to the striatum. The motor component of the basal gangliothalamocortical circuits is processed by the putamen, whereas the caudate and nucleus accumbens mediate cognitive, emotive, and limbic processes. *(Hallett, 177–183; Watts, 100)*

**15.** **(D)** Point-prevalence of dementia is approximately 30%, with a sixfold increased risk for developing dementia in PD compared with non-PD. Two recent longitudinal studies of 12 and 20 years' duration have highlighted the inevitability, over time, of dementia in patients with PD, with over 80% developing dementia. The time from onset of PD to dementia varies considerably, however; it is therefore of key importance to identify the factors associated with time to dementia so as to optimize management and planning of care. Currently, only general features such as the severity of parkinsonism—in particular gait and postural disturbances, mild cognitive impairment (MCI), and age—have been found to be associated with a shorter time to dementia. In addition, the concept of MCI–PD disease has recently attracted increasing interest. Already at disease onset, 25% to 30% of patients have some cognitive impairment. Although consensus criteria for MCI–PD are not yet available, evidence in support of the concept has come both from longitudinal studies showing shorter time to dementia and more cortical atrophy and metabolic changes in those with MCI compared with those with cognitively intact PD and healthy individuals. A rapid decline in cognitive function in PD patients has been associated with impairment in neuropsychological tasks with a more posterior cortical basis, including semantic fluency and ability to copy an intersecting pentagons figure, as well as a gait and postural motor changes, The functional impact of cognitive impairment has been demonstrated with semantic fluency and psychomotor skills as well as attention being related to functional outcome. *(Aarsland, 676–682)*

**16.** **(A)** Although an inverse association between cigarette smoking and PD has been reported in many studies, the origin of this association remains debated. Two studies explored this relation in detail. As part of the Cancer Prevention Study II Nutrition Cohort (n = 143,325, with 9 years of follow-up and 413 incident cases), one study investigated the temporal relationship between cigarette smoking and PD and showed that participants with older age at quitting smoking and fewer years since quitting smoking had lower PD risk. However, a 30% to 60% decreased risk of PD was apparent for smoking as early as 15 to 24 years before symptom onset, but not for smoking 25 years or more before onset. This finding suggests that risk reduction is unlikely to result from changes in smoking behavior in the preclinical phase of the disease. A similar pattern was observed in a pooled analysis of eight case-control and three cohort studies that also confirmed an inverse association between PD and cigarette smoking, with stronger relations in current compared with former smokers, in cohort than in case-control studies, and in younger- than older-onset cases. An inverse association was also found for smoking cigars or pipes and for chewing tobacco in male participants. The inverse association between PD and cigarette smoking was confirmed in a cohort study from Singapore. *(Elbaz, 454–460; Thacker 764–768; Ritz, A990–A997)*

**17.** **(B)** Recessive forms of parkinsonism are known to be caused by mutations in parkin (*PARK2*), *PINK1* (*PARK6*), and *DJ-1* (*PARK7*), and represent an important cause of early-onset PD (onset usually before 40 years of age). In addition to the typical triad of akinesia, rigidity, and resting tremor, the clinical phenotype of early-onset recessive parkinsonism often includes dystonia at onset, hyperreflexia, and relatively slow disease progression. *(Gasser, 363–369)*

**18.** **(D)** Mutations in the *PARKIN* gene are by far the most common among the recessive forms of parkinsonism. More than 40 mutations have been

identified, and a recent review suggests both mutational hot spots and founder effects as a source of recurrent mutations in *PARKIN* regardless of the mutation type. There is only a weak correlation between clinical manifestation and type of mutation, but the relatively large case series available now indicate that patients with point mutations that presumably lead only to a partial loss of *PARKIN* function tend to be more mildly affected than patients with deletions. The age of onset of parkinsonism is between 20 and 40 years. The gene mutations are located on chromosome 6q25. The clinical phenotype of early-onset recessive parkinsonism seen with *PARKIN* gene mutations often includes dystonia at onset, hyperreflexia, and relatively slow disease progression. *(Gasser, 363–369)*

**19.** **(A)** The spiny neurons of the putamen are the principal input–output cells of the striatum. These cells project to the internal segment of the globus pallidus via two separate pathways: direct and indirect. The direct pathway involves a subpopulation of spiny cells using GABA and substance P as neurotransmitters and projecting directly to the internal segment of the globus pallidus and the substantia nigra pars reticulata, which are the output nuclei of the basal ganglia. The indirect pathway involves another subpopulation of spiny cells that use GABA and enkephalin as neurotransmitters and project to the external segment of the globus pallidus, which sends GABAergic projections to the subthalamus. *(Watts, 99–100)*

**20.** **(A)** The subthalamic nucleus projects to the internal part of the globus pallidus and substantia nigra, using glutamate as a neurotransmitter. This model of neurotransmission suggests that there is an equilibrium between the direct pathway, tending to reduce the basal ganglia output, and the indirect pathway, tending to increase the output from the internal segment of the globus pallidus and substantia nigra. *(Watts, 99–100)*

**21.** **(B)** The pathological features mentioned in this question are highly suggestive of progressive supranuclear palsy (PSP). Typical PSP patients present with early postural instability, supranuclear vertical gaze palsy, parkinsonism (bradykinesia and axial more than limb rigidity), resistance to levodopa therapy, pseudobulbar palsy, and subcortical dementia. Subsequent to the onset of postural instability, dysarthria and bradykinesia are the most common problems. An absent, poor, or waning response to levodopa is a characteristic feature defining the atypical parkinsonian disorders. Often although not always, patients with these disorders may exhibit axial more than limb muscle involvement.

Several features should make us suspect that a patient may suffer from PSP. Early instability and falls, particularly during the first year of symptom onset, should suggest the diagnosis of PSP. However, these features may also rarely develop in patients with corticobasal degeneration (CBD), when asymmetric symptoms develop in the lower extremities. Instability and falls may also develop early in multiple system atrophy (MSA), although these symptoms are usually present when patients already exhibit autonomic disturbances.

Marked slowing of vertical saccades usually precedes the development of vertical supranuclear gaze palsy and should readily point toward the diagnosis of PSP. The saccades in CBD may have increased latency but normal speed and are similarly affected in the vertical and horizontal planes, whereas in MSA the saccades have normal speed and latency. Patients with PSP may present prominent early or severe speech and swallowing difficulties and may exhibit oversized mouthfuls or overstuffing the mouth when eating, but these features may also be present in CBD.

Neuropathologically, PSP is characterized by abundant neurofibrillary tangles and/or neuropil threads in particular areas of the basal ganglia and brainstem; neuronal loss and gliosis are variable. Neurofibrillary tangles, neuronal loss, and gliosis in PSP affect the striatum, pallidum, subthalamic nucleus, substantia nigra, oculomotor complex, periaqueductal gray, superior colliculi, basis pontis, dentate nucleus, and prefrontal cortex. *(Litvan, 41–48)*

**22.** **(B)** The only definite risk factor for PD is age. However, epidemiological studies have suggested an increased risk of PD in males, those with a family history of the disease, exposure to iron,

farming, rural residence, steel alloy industries, and herbicide and pesticide exposure. Manganese was found to increase the incidence PD. Smoking cigarettes is consistently associated with a decreased risk for PD. However, whether this association is truly caused by cigarette smoking or instead reflects a personality characteristic or another behavior associated with smoking is not known. Caffeine was recently reported to decrease the risk of PD. Other factors associated with decreased risk of PD include vitamin E, tocopherol, and alcohol consumption. *(Ross, 2674–2679; Tanner, 427–430)*

**23.** **(D)** MPTP-induced parkinsonism is very much like idiopathic PD except for the resting tremor, which is less frequent with MPTP intoxication. In the brain, MPTP is taken up into astrocytes, where it is oxidized to MPP+ by monoamine oxidase B. MPP+ is then actively taken up into nigrostriatal neurons through dopamine transporters and concentrated in dopaminergic neurons. MPP+ inhibits mitochondrial respiration in the dopaminergic neurons, which causes the selective death of that type of cell. MPP+ inhibits mitochondrial complex I and NADH-linked state 3 respiration, causing a loss of oxidative phosphorylation mechanism and fall in the ATP level. *(Watts, 162)*

**24.** **(D)** Among the cardinal signs of PD, postural instability is usually the last sign to appear, the most disabling, and the least treatable. Postural instability results from the combination of changes in postural adjustment, loss of postural reflexes, rigidity, and akinesia. *(Watts, 187)*

**25.** **(A)** D1receptors are able to stimulate adenylate cyclase. *(Watts, 202)*

**26.** **(A)** Dopamine receptors are divided into five subtypes based on their action on adenylate cyclase: D1-like receptors include D1 and D5 and are able to stimulate adenylate cyclase. D2-like receptors include D2, D3, and D4 and are able to inhibit adenylate cyclase. D1 receptors are encoded by a gene located on chromosome 5; D2 and D4 receptor genes are located on chromosome 11; D3 receptors are coded by a gene located on chromosome 3; and D5 receptors are encoded by a gene located on chromosome 4. *(Watts, 202)*

**27.** **(B)** D2 receptors have bromocriptine as an agonist and haloperidol as an antagonist. Clozapine is a selective D4 receptor antagonist. *(Watts, 202)*

**28.** **(E)** D1 and D2 receptors are located mainly in the striatum and substantia nigra in the postsynaptic areas, although D2 and D3 receptors also have presynaptic locations. The olfactory tubercle contains both D1 and D2 receptors; the medulla contains D4 receptors. *(Watts, 202)*

**29.** **(B)** Despite the short half-life of L-dopa (60 minutes), patients in early stages of the disease may experience a sustained motor response with the administration of L-dopa three or four times per day. This sustained response is speculated to be caused by storage of exogenous dopamine in presynaptic terminals in survival dopaminergic striatal cells. *(Watts, 204)*

**30.** **(E)** Tolcapone and entacapone are catechol-O-methyl transferase (COMT) inhibitors that may be used as an adjuvant therapy to dopamine for the management of PD. Both drugs are used for treatment of motor fluctuations in patients treated with levodopa for long periods. COMT is an enzyme that convert levodopa into an inactive metabolite, 3-O-methyldopa. Coadministration of entacapone delays clearance of levodopa from plasma and prolongs the action of individual doses of levodopa. *(Jankovic, 785–790)*

**31.** **(D)** Dopamine agonists exert their pharmacological effect by directly activating dopamine receptors, bypassing the presynaptic synthesis of dopamine. Several new dopamine agonists—cabergoline, pramipexole, and ropinirole—have been added to the previously known potent antiparkinsonian drugs bromocriptine and pergolide. *(Jankovic, 785–790)*

**32.** **(B)** Neuroprotective therapies can be defined as medical or surgical interventions that favorably alter the underlying etiology or pathogenesis and thus delay the onset or slow or even halt the progression of the neurodegenerative process such as PD. Selegiline was found to prevent

parkinsonism induced by the oxidated form of MPTP, which has stimulated interest in an antioxidative therapy to retard the progression of PD. Selegiline acts as a "suicide substrate" for monoamine oxidase (MAO) type B, irreversibly inhibiting this enzyme. Selegiline has a levodopa-sparing effect, and it smoothes out levodopa-related motor fluctuations, possibly by prolonging dopamine-induced responses in midbrain dopaminergic neurons. *(Jankovic, 785–790)*

**33.** **(D)** Pramipexole is a nonergot dopamine agonist with specificity of D2 dopamine receptor but also has been shown to bind to D3 and D4 receptors and may stimulate dopamine activity on nerves of striatum and substantia nigra. *(Jankovic, 785–790)*

**34.** **(C)** Remacemide, an anticonvulsant with anti-NMDA effects, has been shown to enhance the effects of levodopa in parkinsonian rats and monkeys. It may have a neuroprotective effect in PD and Huntington disease. The rationale behind using remacemide as a neuroprotective agent is that in PD, there is an increased activity in the subthalamic nucleus and internal segment of the globus pallidus. The subthalamic nucleus provides an excitatory glutaminergic input to the internal part of the globus pallidus. Glutamate inhibition would be expected to improve parkinsonism. *(Jankovic, 785–790)*

**35.** **(E)** Riluzole, a drug approved for the treatment of amyotrophic lateral sclerosis, acts primarily by inhibiting glutamic acid release and noncompetitively blocking NMDA receptors, and as such it may exert antiexcitotoxic effects similar to those of NMDA antagonists. *(Jankovic, 785–790)*

**36.** **(A)** Depression is the most frequent neurobehavioral abnormality seen in PD, with a prevalence of 25% to 40%. Depression may appear before the emergence of the first motor signs and does not correlate with the severity of the disease. Psychotic signs such as illusions or hallucinations are among the most disabling complications of L-dopa treatment in PD. They are seen in 8% to 15% of patients with PD, especially elderly patients who show signs of impaired cognition and have longer duration on L-dopa treatment. Other neurobehavioral abnormalities seen in PD include sleep alterations, personality change, anxiety, and panic attacks. *(Watts, 257–259)*

**37.** **(B)** Progressive supranuclear palsy is characterized by gait disturbance with multiple falls, erect posture with retrocollis, contracted facial muscles, bradykinesia, predominantly proximal rigidity, vertical supranuclear gaze abnormalities, and spastic dysarthria. Progressive supranuclear palsy can be differentiated from PD by the presence of contracted rather than flaccid face, undirected rather than staring gaze, erect rather than flexed posture, spastic dysarthria, and absence of rest tremor. *(Watts, 279)*

**38.** **(C)** Early instability and falls, supranuclear vertical gaze palsy, and poor response to levodopa are features highly suggestive of the diagnosis of PSP. Other features of PSP include subcortical dementia and pseudobulbar palsy. Marked slowing of vertical saccades is seen earlier than the development of vertical supranuclear palsy in PSP. Instability and falls may also develop in corticobasal degeneration as well as in early multiple system atrophy (MSA), although these symptoms are usually present when patients already exhibit autonomic disturbances. The saccades in CBD may have increased latency but normal speed, and are similarly affected in the vertical and horizontal planes, whereas in MSA the saccades have normal speed and latency. *(Litvan, 41–48)*

**39.** **(D)** The presence of early or prominent cerebellar signs, unexplained polyneuropathy, and prominent noniatrogenic dysautonomia other than isolated postural instability contradict the diagnosis of PSP. *(Watts, 280)*

**40.** **(D)** MRI of the head does not show specific abnormalities in most patients with the diagnosis of PSP. However, it may show more prominent cerebral cortical atrophy than in PD. In moderate to advanced stages, there may be a thinning of the anteroposterior diameter of the midbrain tectum and tegmentum with atrophy of the colliculi and disproportionate enlargement of the sylvian fissures and posterior third ventricle. Cerebellar atrophy is seen in multisystem atrophy. The presence of neurofibrillary tangles is necessary for the

neuropathological diagnosis of PSP. Most of these neurofibrillary tangles are rounded in shape, whereas in Alzheimer disease most of them have a flame-shaped form. Clinically, patients with PSP have a symmetric neurological deficit, prominent axial rigidity, postural instability, and severe vertical gaze restriction. In PD, the neurological symptoms are not symmetric, axial rigidity and postural instability are less prominent than in PSP, and there is a good response to L-dopa early in the course of the disease. *(Watts, 281–283)*

**41.** **(E)** The cerebral cortex is one of the major areas of primary involvement in PSP. Motor strip 4 and the oculomotor association areas are the most important sites of pathology. Area 17, the primary visual cortex, is the least affected. The large pyramidal and small neurons of layers V and VI are the most affected layers of the cerebral cortex in PSP; layers III and V are the most affected in Alzheimer disease. *(Watts, 283)*

**42.** **(D)** MPTP induces parkinsonism by selective damage to the substantia nigra. MPTP is converted by glial cells to MPDP+, which is then converted to MPP+ and enters dopaminergic neurons through a dopamine uptake system. MPP+ induces mitochondrial damage, causing cell death. *(Watts, 315–332)*

**43.** **(C)** Overexposure to manganese may cause Parkinson syndrome by inducing selective neuronal loss in the globus pallidus, probably by increasing autooxidation of dopamine by a higher valence ion, causing an increase in the generation of free radicals. *(Watts, 315–332)*

**44.** **(C)** Pathological changes after acute cyanide intoxication have demonstrated selective destruction of the basal ganglia, especially the globus pallidus. Cyanide radicals inactivate cytochrome oxidase and other oxidative systems, leading to cell death. *(Watts, 315–332)*

**45.** **(B)** Methanol is metabolized to formic acid, which achieves high concentration in the putamen and causes selective damage there. *(Watts, 315–332)*

**46.** **(C)** Carbon monoxide intoxication may cause Parkinson syndrome, with more damage in the white matter and globus pallidus. Carbon monoxide causes tissue anoxia. The globus pallidus is vulnerable to anoxic injury, probably from intrinsic metabolic susceptibility. *(Watts, 315–332)*

**47.** **(A)** Hallervorden–Spatz syndrome (HSS) is a rare autosomal recessive disease that has been mapped to chromosome 20p12.3–p13. The symptoms usually start in childhood and involve the cognitive, speech, and motor domains. Children demonstrate signs of cognitive and motor regression, the speech becomes dysarthric, and extrapyramidal symptoms appear.

Typical symptoms at onset involve difficulty walking or postural abnormalities. Personality changes and cognitive changes infrequently are the presenting symptoms. Rigidity gradually progresses. Spasticity associated with hyperreflexia is seen in over half of the cases. Dysarthria becomes evident in all cases. Dystonia, chorea, and tremor are also seen. Ophthalmic abnormalities are seen in HSS patients including pigmentary retinopathy and optic atrophy. Movement disorders associated with HSS include rigidity, which can involve half of the body, axial structures, arms, legs, or be generalized. Dystonia is also seen, typically involving the facial musculature and the feet.

Parkinsonism as an initial manifestation is rare, and usually occurs only in adult-onset cases. In rare adult-onset cases, presenting symptoms can be indistinguishable from PD. The cognitive abnormalities are common in HSS. They may precede the motor symptoms of the disease. Seizures can also be seen in this disorder. The disease usually starts between the ages of 7 and 12 years. The disorder typically progresses and leads to death within 20 years.

Definitive diagnosis of HSS can only be made histologically. Presumptive clinical diagnosis is based on the constellation of the clinical signs, supported by the neuroimaging data. Computed tomography (CT) may reveal cerebral atrophy with increased ventricular size. Mineralization of the globus pallidus is also seen. Hyperlucency of the putamen and globus pallidus is seen on CT. MRI is more sensitive. There is decreased T-2 weighted and proton density signal in the globus pallidus, which is caused by iron deposition. In some patients there is a hyperintense area within the area of hypointensity, the "eye of the tiger"

sign. Pathologically, the hallmark of the disease, is rust-brown discoloration of the pars reticulata of the substantia nigra and the internal segment of the globus pallidus. The pigmentation is caused not only by the abnormal iron deposition but also by high concentration of the organic pigments lipofuscin and neuromelanin. *(Colcher, 629–649)*

**48. (C)** Valproic acid is the most common cause of tremor among antiepileptic medications. Chronic treatment with valproic acid may cause a tremor in up to 25% of patients. Occasionally, phenytoin and carbamazepine have been reported to cause tremor. *(Watts, 350)*

**49. (C)** An aberrant expansion of glutamines in the protein huntingtin causes Huntington disease (HD), a neurodegenerative disorder that strikes in middle age. The HD gene is located on the short arm of chromosome 4. It is a CAG repeat located in exon1 of a 67-exon gene, which is transcribed into huntingtin. Huntingtin is expressed in neuronal and nonneuronal tissues, suggesting that its normal function is not confined to cells in the areas of HD. Huntingtin is a cytoplasmic protein that conserves its location in HD.

The pattern of huntingtin expression does not parallel the region of HD neuropathology. Only a small subset of neurons that express huntingtin in neuronal population succumb to the effect of HD. It has been presumed that mutant huntingtin with its extra glutamines is toxic to neurons, possibly because it has a tendency to form aggregates. In HD, there is selective destruction of the medium-sized spiny neurons in the striatum of the brain, which has been attributed either to the accumulation of mutant huntingtin aggregates or to the continued expansion of glutamine repeats. Mutant huntingtin affects cortical neurons, producing brain-derived neurotrophic factor (BDNF), which is necessary for the survival of striatal neurons.

One proposal suggests that partial loss of the beneficial effects of wild-type huntingtin combined with the toxicity of the mutant huntingtin conspire to selectively destroy the striatum of the brain. Huntingtin is a widely expressed protein that resides in the cell cytoplasm and may be important for transport of vesicles in the endosomal and secretory pathways, and for preventing cells from undergoing apoptosis. Mutant huntingtin is proteolytically processed, and the resulting amino-terminal fragments containing the glutamine expansions form aggregates that are deposited in nuclear and cytoplasmic inclusions in the brains of HD patients. *(Trottier, 445–446; Watts, 484–485)*

**50. (C)** Chorea, although of cosmetic concern, is not disabling per se and does not correlate with the severity of disease. Patients may be able to ambulate and accomplish activities of daily living despite suffering from severe chorea. Bradykinesia, rigidity, dystonia, and postural instability are more disabling. Dementia in HD is of the subcortical type. There is prominence of slowed thinking, impairment of sequencing, with the absence of cortical deficit, such as aphasia, agnosia, and apraxia. Diminished executive function includes loss of the ability to plan, sequence, and carry out complex tasks. Eye movement abnormalities occur early in the course of PD. Optokinetic nystagmus is impaired in both vertical and horizontal directions as well as voluntary initiation of ocular saccades. *(Watts, 492–493)*

**51. (B)** Akathisia is an unpleasant sensation of internal restlessness that is partially relieved by volitional movements occurring in a patient who has received chronic neuroleptics. *(Watts, 319)*

**52. (A)** Clonidine, an alpha-adrenergic agonist originally approved for treatment of hypertension, is actually the treatment of choice for children with mild or moderate tics. Clonidine has the potential for decreasing impulsiveness and improving attention span along with decreasing tics. The most common side effects are sedation and orthostatic hypotension. Dizziness can occur at higher doses. Guanfacine is similar to clonidine and is also marketed as an antihypertensive agent. It has shown some promise as a medication capable of both decreasing tics and improving behavior. Clonidine is often the drug of first choice for children with tics or Tourette syndrome who require symptomatic help. This is because the tic problem is often accompanied by attentional or other behavioral difficulties.

The dopamine-blocking agent haloperidol has been found to be effective in treating tics. Although newer neuroleptic agents are available, haloperidol has always been the gold standard by which all new medications have been judged. Experience indicates that haloperidol can reduce tics in approximately 70% of treated persons, but over 50% of treated patients will complain of side effects. Only 25% of patients report significant improvement without side effects. The potential side effects of all neuroleptics are similar to those seen with haloperidol, most commonly fatigue and increased appetite. Others include depression and school or work phobia. A third type of medication used for the control of tics has been clonazepam. Traditionally used as a medication either for control of seizures or anxiety, this has helped individual patients. The dosage is titrated in a weekly basis until a clinical effect is observed or until there are side effects. Other medications that have been reported to improve tics include tetrabenzamine, local injection of botulinum toxin, and calcium channel antagonists. *(Watts, 573)*

**53.** **(A)** Cerebellar control of extraocular movements is performed mainly by the following structures: the dorsal vermis and underlying fastigial nucleus, the flocculus and paraflocculus, and the nodulus. Lesions of the dorsal vermis and fastigial nucleus result in saccadic dysmetria, typically with hypermetric movements and at time with macrosaccadic oscillations. Lesions of the flocculus and paraflocculus cause gaze-evoked nystagmus, rebound nystagmus, downbeat nystagmus, impaired smooth tracking, glissadic postsaccadic drift, and disturbance in adjusting the gain of the vestibuloocular reflex. Lesions of the nodulus lead to an increase in the duration of the vestibular response. *(Watts, 580)*

**54.** **(C)** Stiff-man syndrome is a rare disorder of the CNS, which is characterized clinically by fluctuation and progressive muscle rigidity and spasms. The diagnosis relies also on the presence of continuous motor unit activity, without evidence of neuromyotonia, extrapyramidal or pyramidal dysfunction, or focal lesions of the spinal cord. Rigidity and spasms may dominate in the axial muscles, or in one or more distal limbs. Some 50% to 60% of these patients have autoantibodies in the serum and CSF directed against glutamic acid decarboxylase (GAD), an enzyme present in GABAergic neurons and pancreatic beta-cells, and a high proportion of them have other autoimmune diseases including diabetes mellitus. *(Folli, 618)*

**55.** **(B)** Two distinctive mutation have been identified in the α-synuclein gene (SNCA) located on chromosome 4q have been linked to a familial form of PD. Alpha-synuclein is a highly conserved, abundant 140–amino acid protein of unknown function that is expressed mainly in presynaptic nerve terminals in the brain. *(Lang, 1044–1053)*

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CHAPTER 15

# Neuropathology
## Questions

**1.** Figure 15-1 shows

(A) polymyositis
(B) dermatomyositis
(C) mitochondrial myopathy
(D) inclusion body myositis
(E) a cluster of regenerating muscle fibers

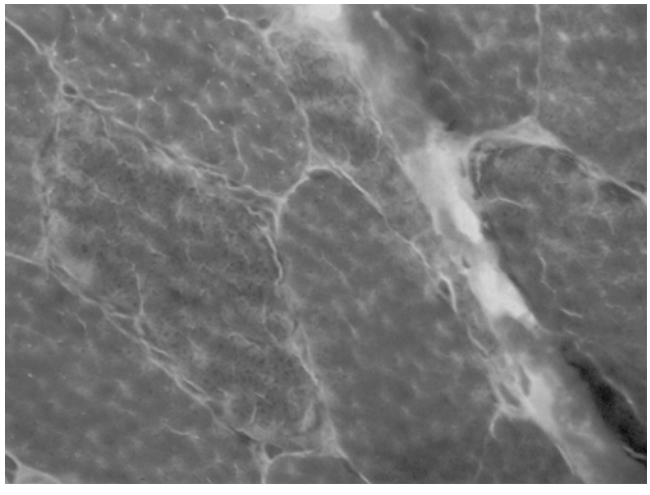


**FIG. 15-1.** See color insert. (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders*. New York: McGraw-Hill; 2008.)

**2.** Figure 15-2 is a myofibrillary adenosine triphosphatase (ATPase)-stained slide. The dark fibers are characterized by

(A) a slow twitch speed
(B) an intermediate resistant to fatigue
(C) strong staining with modified Gomori trichome
(D) high myoglobin content
(E) high glycogen content

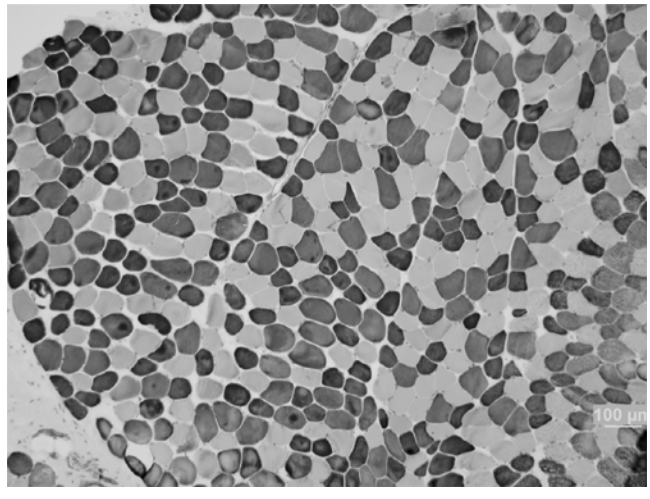
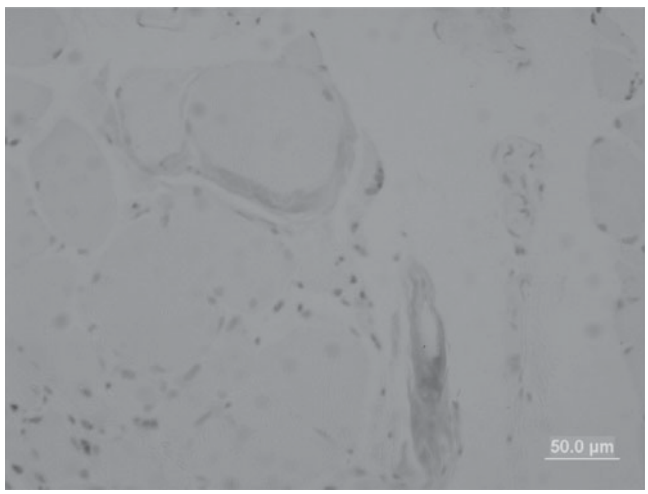


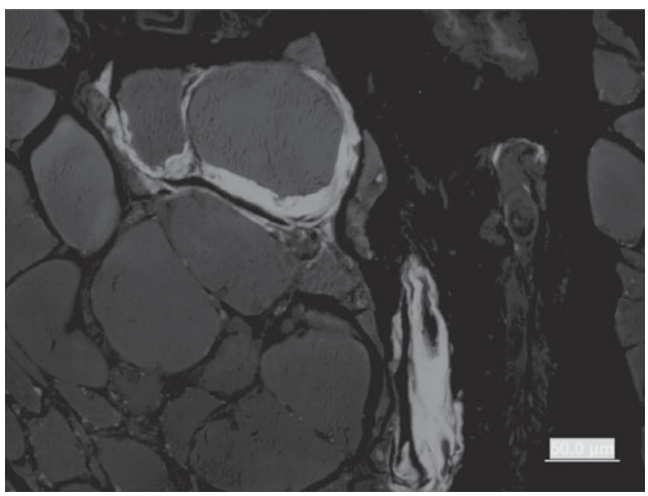
**FIG. 15-2.** See color insert. (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders*. New York: McGraw-Hill; 2008.)

**3.** Figures 15-3 shows

(A) ragged-red fibers
(B) inclusion body myositis
(C) polymyositis
(D) amyloid deposition
(E) glycogen deposition




**A**

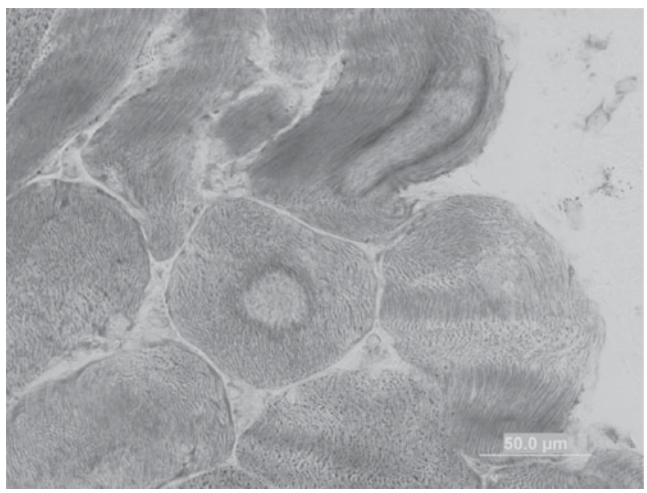



**B**

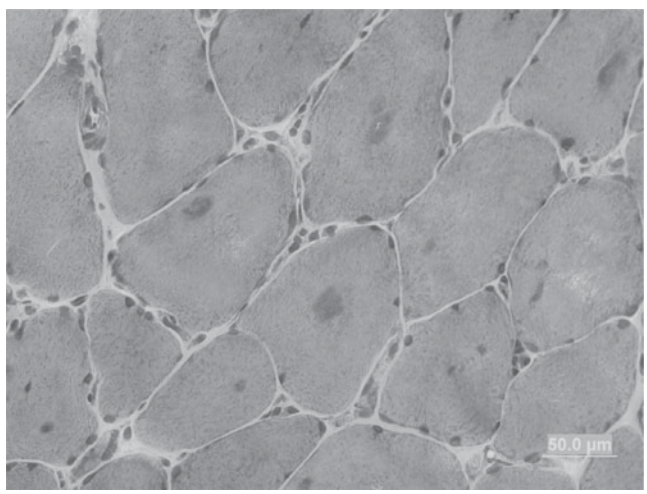
**FIG. 15-3.** See color insert. (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders*. New York: McGraw-Hill; 2008.)

**4.** Figure 15-4 shows

(A) target fibers
(B) amyloid deposition
(C) dermatomyositis
(D) ragged-red fibers
(E) metabolic myopathy




**A**




**B**

**FIG. 15-4.** See color insert. (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders*. New York: McGraw-Hill; 2008.)

**5.** Figure 15-5 shows

(A) nemaline myopathy
(B) Duchenne muscular dystrophy
(C) central core myopathy
(D) ragged-red fibers
(E) inclusion body myositis

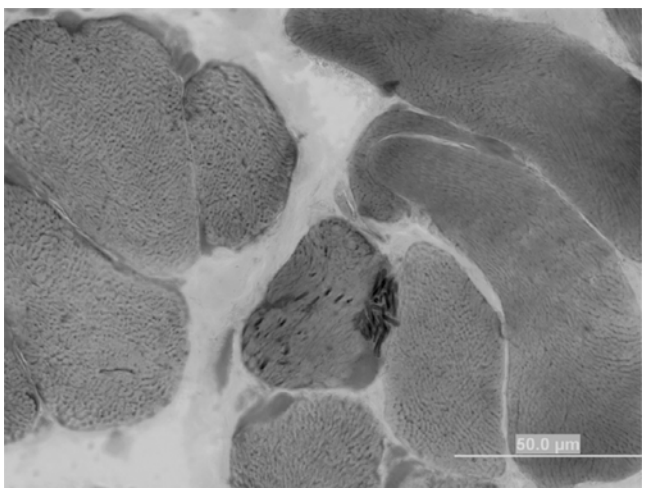


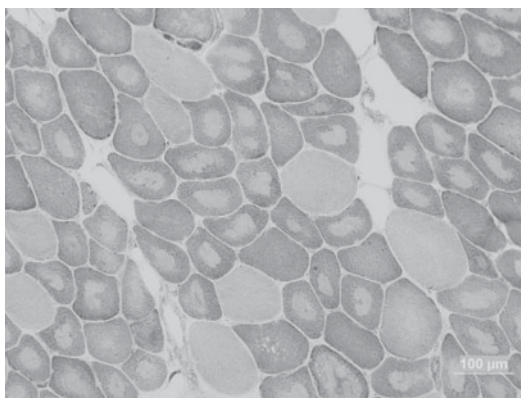

**FIG. 15-5.** See color insert. (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders*. New York: McGraw-Hill; 2008.)

**6.** Figure 15-6 is suggestive of

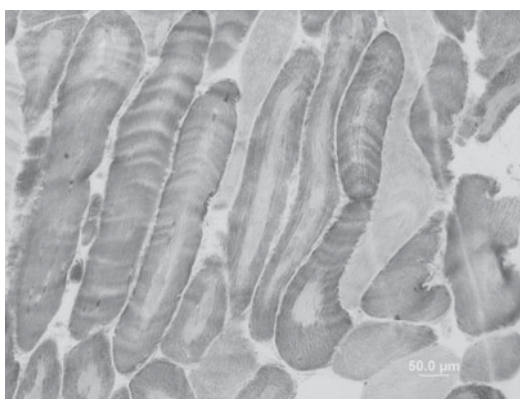
(A) centronuclear myopathy
(B) hyaline body myopathy
(C) central core myopathy
(D) Becker muscular dystrophy
(E) mitochondrial myopathy

**7.** Figure 15-7 is suggestive of

(A) central core myopathy
(B) inclusion body myositis
(C) target fibers
(D) amyloid deposition
(E) mitochondrial myopathy

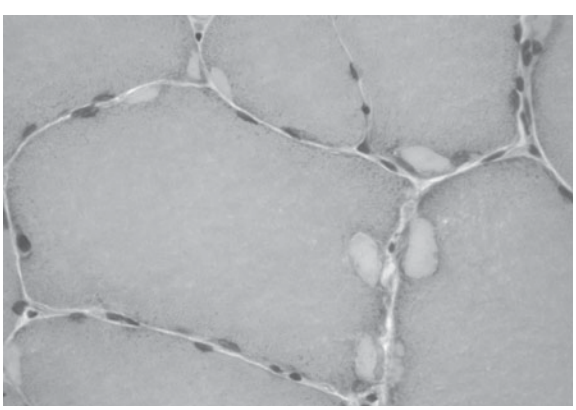



**A**

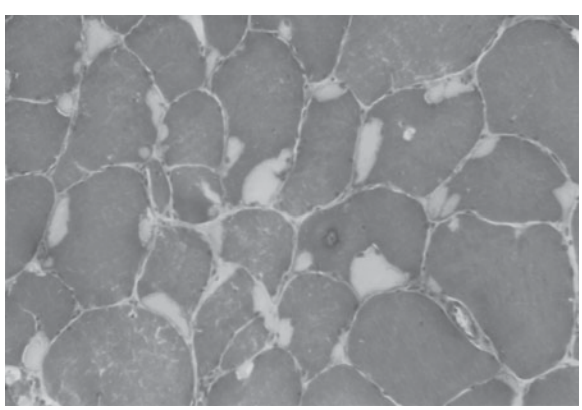



**B**

**FIG. 15-7.** (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders*. New York: McGraw-Hill, 2008.)



**A**



**B**

**FIG. 15-6.** See color insert. (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders*. New York: McGraw-Hill; 2008.)

**8.** Figure 15-8 is suggestive of

(A) nemaline myopathy
(B) inclusion body myositis
(C) target fibers
(D) amyloid deposition
(E) mitochondrial myopathy

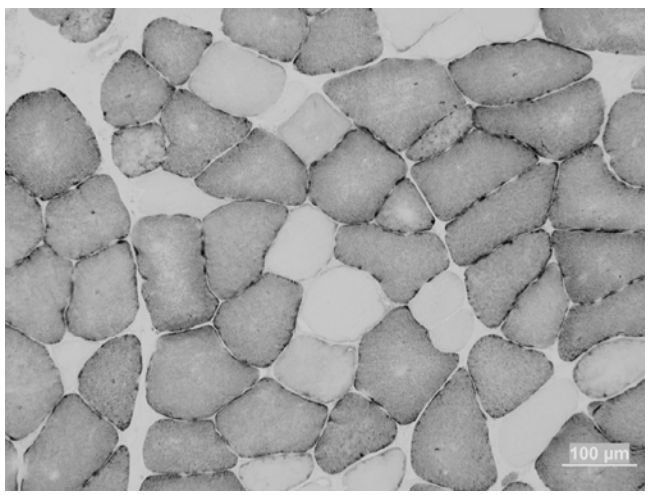



**FIG. 15-8.** (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders*. New York: McGraw-Hill, 2008.)

**9.** Figure 15-9 is suggestive of

(A) mitochondrial myopathy
(B) steroid myopathy
(C) statin myopathy
(D) nemaline myopathy
(E) dermatomyositis

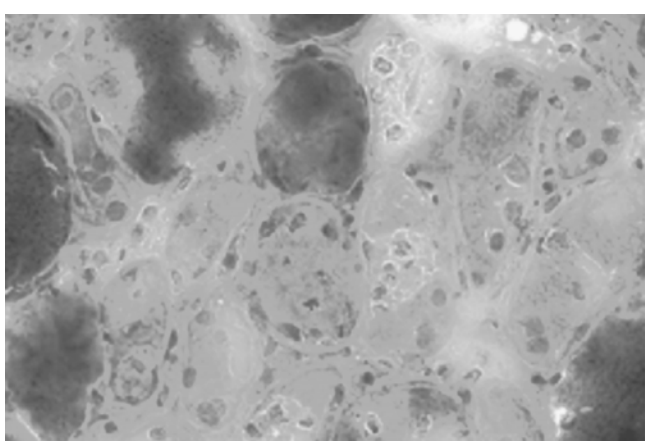


**FIG. 15-9.** See color insert. (Reproduced with permission from Amato AA, Russell JA. *Neuromuscular Disorders*. New York: McGraw-Hill; 2008.)

**10.** Figure 15-10 is suggestive of

(A) astrocytoma grade II
(B) glioblastoma multiforme (GBM)
(C) ependymoma
(D) medulloblastoma
(E) oligodendroglioma

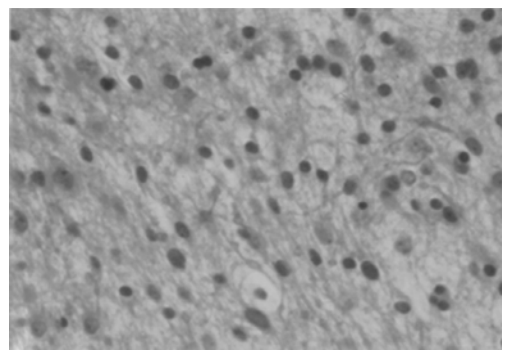


**FIG. 15-10.** See color insert. (Reproduced with permission from Schiff D, O'Neill BP, eds. *Principles of Neurooncology*. New York: McGraw-Hill; 2005.)

**11.** Figure 15-11 is suggestive of

(A) anaplastic astrocytoma grade III
(B) medulloblastoma
(C) ependymoma
(D) meningioma
(E) lymphoma

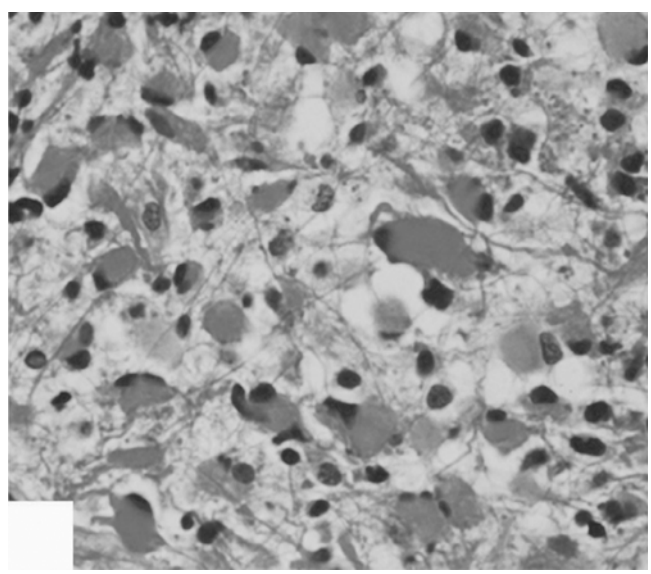


**FIG. 15-11.** See color insert. (Reproduced with permission from Schiff D, O'Neill BP, eds. *Principles of Neurooncology*. New York: McGraw-Hill; 2005.)

**12.** Figure 15-12 is suggestive of

(A) astrocytoma grade II
(B) GBM
(C) ependymoma
(D) choroid plexus papilloma
(E) meningioma

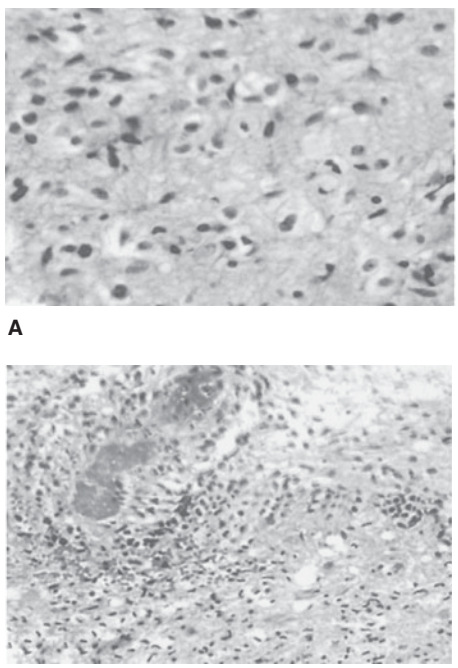



**FIG. 15-12.** See color insert. (Reproduced with permission from Schiff D, O'Neill BP, eds. *Principles of Neurooncology*. New York: McGraw-Hill; 2005.)

**13.** Figure 15-13 is suggestive of

(A) astrocytoma grade IV
(B) pilocytic astrocytoma
(C) ependymoma
(D) oligodendroglioma
(E) meningioma

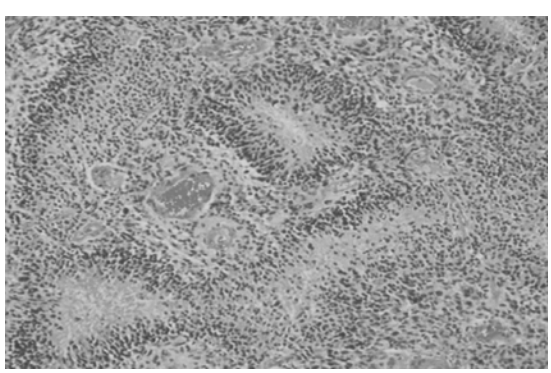


**FIG. 15-13.** See color insert. (Reproduced with permission from Schiff D, O'Neill BP, eds. *Principles of Neurooncology*. New York: McGraw-Hill; 2005.)

**14.** Figure 15-14 is suggestive of

(A) GBM
(B) pilocytic astrocytoma
(C) ependymoma
(D) oligodendroglioma
(E) pleomorphic xanthoastrocytoma

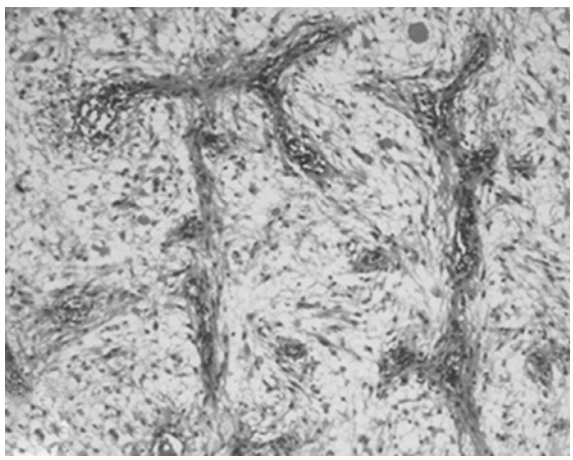


**FIG. 15-14.** See color insert. (Reproduced with permission from Schiff D, O'Neill BP, eds. *Principles of Neurooncology*. New York: McGraw-Hill; 2005.)

**15.** Figure 15-15 is suggestive of

(A) central neuroblastoma
(B) pilocytic astrocytoma
(C) gangliocytoma
(D) oligodendroglioma
(E) pleomorphic xanthoastrocytoma

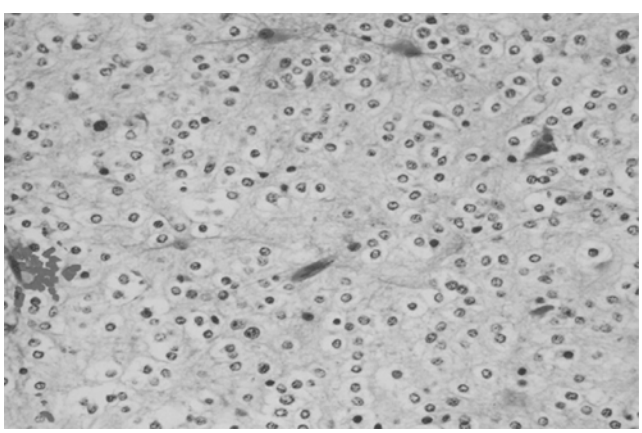


**FIG. 15-15.** See color insert. (Reproduced with permission from Schiff D, O'Neill BP, eds. *Principles of Neurooncology*. New York: McGraw-Hill; 2005.)

**16.** Figure 15-16 is suggestive of

(A) central neuroblastoma
(B) pilocytic astrocytoma
(C) gangliocytoma
(D) oligodendroglioma
(E) pleomorphic xanthoastrocytoma

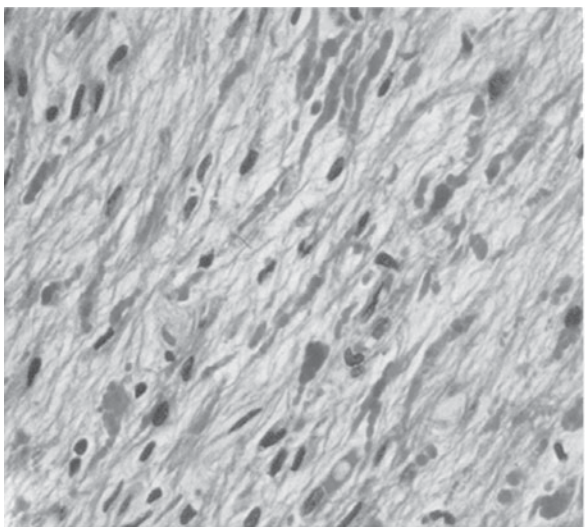


**FIG. 15-16.** See color insert. (Reproduced with permission from Schiff D, O'Neill BP, eds. *Principles of Neurooncology*. New York: McGraw-Hill; 2005.)

**17.** Figure 15-17 is suggestive of

(A) GBM
(B) pilocytic astrocytoma
(C) ependymoma
(D) oligodendroglioma
(E) pleomorphic xanthoastrocytoma

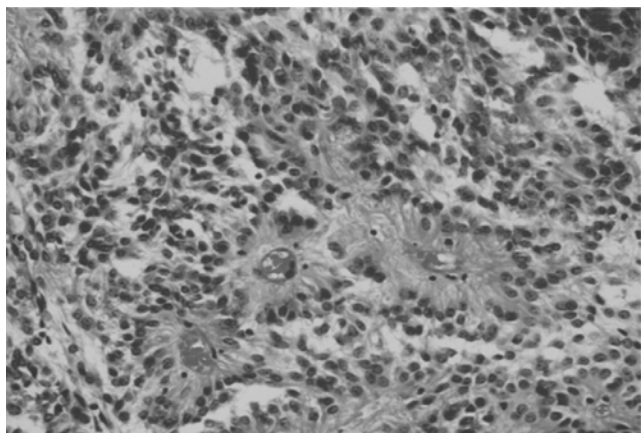
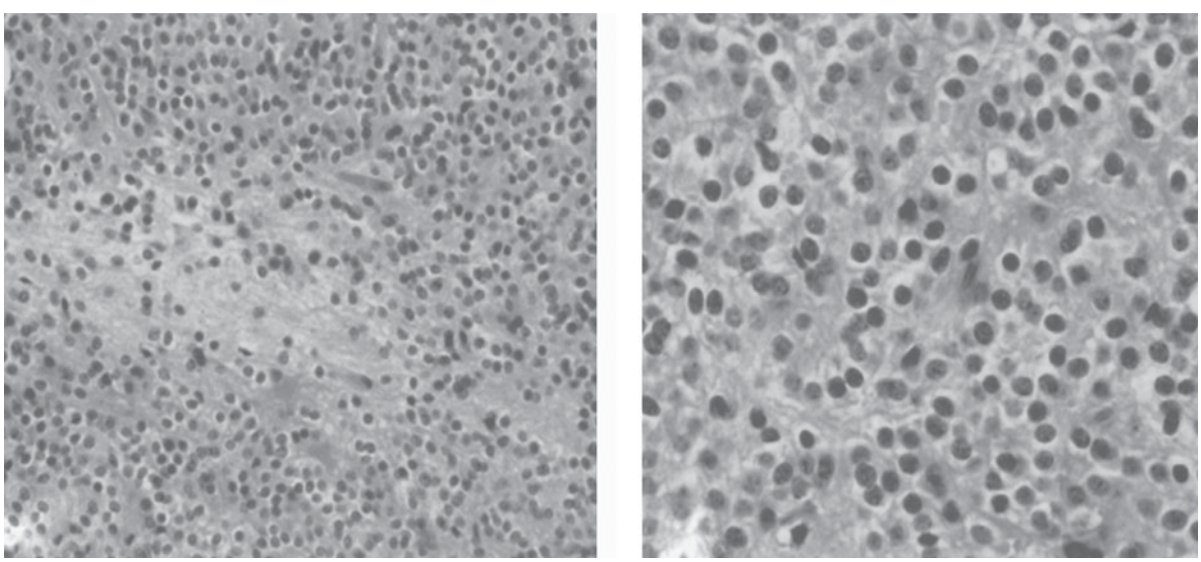


**FIG. 15-17.** See color insert. (Reproduced with permission from Schiff D, O'Neill BP, eds. *Principles of Neurooncology*. New York: McGraw-Hill; 2005.)

**18.** Figure 15-18 is suggestive of

(A) GBM
(B) pilocytic astrocytoma
(C) meningioma
(D) central neurocytoma
(E) pleomorphic xanthoastrocytoma

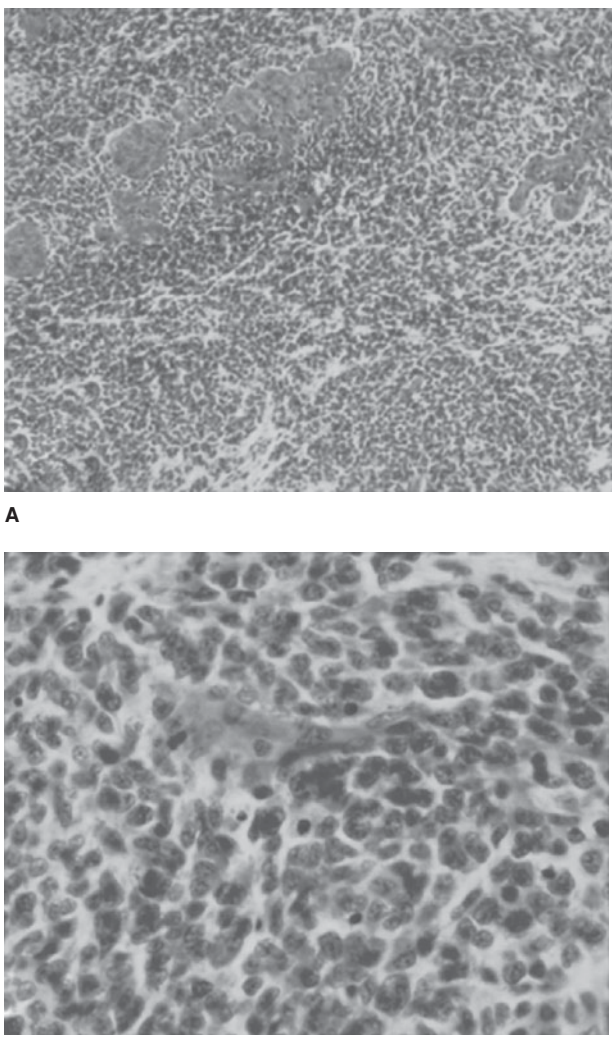


**A** **B**

**FIG. 15-18.** (Reproduced with permission from Schiff D, O'Neill BP, eds. *Principles of Neurooncology*. New York: McGraw-Hill; 2005.)

**19.** Figure 15-19 is suggestive of

(A) GBM
(B) ependymoma
(C) meningioma
(D) medulloblastoma
(E) pleomorphic xanthoastrocytoma



**A**

**B**

**FIG. 15-19.** (Reproduced with permission from Schiff D, O'Neill BP, eds. *Principles of Neurooncology*. New York: McGraw-Hill; 2005.)

**20.** Figure 15-20 is suggestive of

(A) GBM
(B) ependymoma
(C) meningioma
(D) medulloblastoma
(E) pilocytic astrocytoma

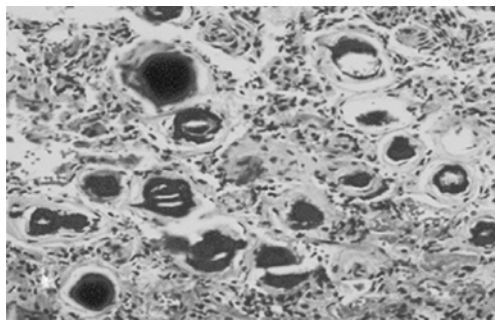


**FIG. 15-20.** See color insert. (Reproduced with permission from Schiff D, O'Neill BP, eds. *Principles of Neurooncology.* New York: McGraw-Hill; 2005.)

**21.** Figure 15-21 is suggestive of

(A) lymphoma
(B) ependymoma
(C) meningioma
(D) medulloblastoma
(E) shwannomas

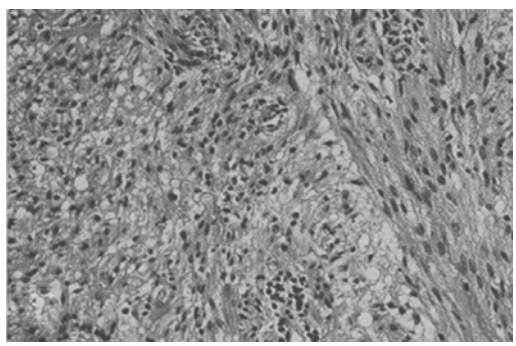


**FIG. 15-21.** See color insert. (Reproduced with permission from Schiff D, O'Neill BP, eds. *Principles of Neurooncology.* New York: McGraw-Hill; 2005.)

**22.** Figure 15-22 is suggestive of

(A) lymphoma
(B) ependymoma
(C) meningioma
(D) neurofibroma
(E) shwannomas

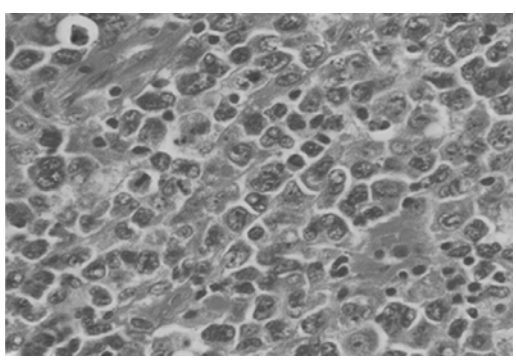


**FIG. 15-22.** See color insert. (Reproduced with permission from Schiff D, O'Neill BP, eds. *Principles of Neurooncology.* New York: McGraw-Hill; 2005.)

**23.** Figure 15-23 is suggestive of

(A) lymphoma
(B) ependymoma
(C) meningioma
(D) neurofibroma
(E) medulloblastoma

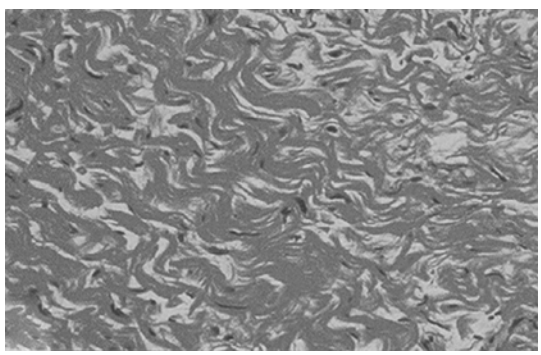


**FIG. 15-23.** See color insert. (Reproduced with permission from Schiff D, O'Neill BP, eds. *Principles of Neurooncology.* New York: McGraw-Hill; 2005.)

**24.** Which of the following is a pathological nuclear inclusion?

(A) Marinesco body
(B) Lipofuscin
(C) Lewy bodies
(D) Cowdry type A
(E) Hirano body

**25.** Neurofibrillary tangles are *not* found in

(A) normal aging
(B) Alzheimer disease
(C) Huntington disease
(D) progressive supranuclear palsy
(E) postencephalitic Parkinson disease

**26.** Bunina bodies are found in

(A) Pick disease
(B) amyotrophic lateral sclerosis (ALS)
(C) multiple system atrophy
(D) Alzheimer disease
(E) normal aging

**27.** Alzheimer type II glia are seen in

(A) Canavan disease
(B) Alzheimer disease
(C) Parkinson disease
(D) Huntington disease
(E) supranuclear palsy

**28.** Brain herniation through a skull defect is called

(A) fungating herniation
(B) subfalcine herniation
(C) tonsillar herniation
(D) central herniation
(E) unclear herniation

**29.** Cowdry A inclusions are pathological hallmarks of

(A) Creutzfeldt–Jacob disease
(B) rabies encephalitis
(C) herpes encephalitis
(D) progressive multifocal leukodystrophy
(E) cytomegalovirus (CMV) encephalitis

**30.** Owl's-eye cells are pathological hallmarks of

(A) Creutzfeldt–Jacob disease
(B) rabies encephalitis
(C) herpes encephalitis
(D) progressive multifocal leukodystrophy
(E) CMV encephalitis

**31.** Negri bodies are hallmarks of

(A) Creutzfeldt–Jacob disease
(B) rabies encephalitis
(C) herpes encephalitis
(D) progressive multifocal leukodystrophy
(E) CMV encephalitis

**32.** Oligodendrocytes with inclusion bodies are hallmarks of

(A) Creutzfeldt–Jacob disease
(B) rabies encephalitis
(C) herpes encephalitis
(D) progressive multifocal leukodystrophy
(E) CMV encephalitis

**33.** Spongiform changes in the cortex are hallmarks of

(A) Creutzfeldt–Jacob disease
(B) rabies encephalitis
(C) herpes encephalitis
(D) progressive multifocal leukodystrophy
(E) CMV encephalitis

**34.** Mumps virus has an affinity for which of the following central nervous system (CNS) cells?

(A) Neurons
(B) Astrocytes
(C) Ependymal cells
(D) Oligodendrocytes
(E) Microglia

**35.** HIV encephalitis is characterized by

(A) microglial nodules with perivascular or parenchymal multinucleated cells
(B) periventricular mixed large and small B cells
(C) hemorrhagic necrotizing lesions in the cortex, basal ganglia, and brainstem with Cowdry type A nuclear inclusions and small cytoplasmic basophilic inclusions
(D) Cowdry type B nuclear inclusions
(E) meningoencephalitis with ventriculitis

**36.** The most common histological characteristic of lacunar strokes is

(A) atherosclerosis
(B) mycotic aneurysm
(C) amyloid deposition
(D) lipohyalinosis
(E) coagulation necrosis

**37.** Cytokeratin is positive in which of the following neoplasms?

(A) Pituitary adenoma
(B) Meningioma
(C) Melanoma
(D) Glioma
(E) Craniopharyngioma

**38.** Alpha fetoprotein immunohistochemical stain is useful to identify

(A) meningioma
(B) Choroid plexus tumor
(C) neurofibroma
(D) endodermal sinus tumor
(E) medullomyoblastoma

**39.** Desmin immunohistochemical stain is useful to identify

(A) meningioma
(B) Choroid plexus tumor
(C) neurofibroma
(D) endodermal sinus tumor
(E) medullomyoblastoma

**40.** Cytokeratin immunohistochemical stain is useful to identify

(A) Choroid plexus tumor
(B) neurofibroma
(C) endodermal sinus tumor
(D) medullomyoblastoma
(E) chordoma

**41.** Epithelial membrane antigen immunohistochemical stain is useful to identify

(A) meningioma
(B) choroid plexus tumor
(C) neurofibroma
(D) endodermal sinus tumor
(E) medullomyoblastoma

**42.** L26 immunohistochemical stain is useful to identify

(A) endodermal sinus tumor
(B) medullomyoblastoma
(C) chordoma
(D) melanoma
(E) B-cell lymphoma

**43.** Transthyretin immunohistochemical stain is useful to identify

(A) meningioma
(B) choroid plexus tumor
(C) neurofibroma
(D) endodermal sinus tumor
(E) medullomyoblastoma

**44.** HMB-45 immunohistochemical stain is useful to identify

(A) endodermal sinus tumor
(B) medullomyoblastoma
(C) chordoma
(D) melanoma
(E) B-cell lymphoma

**45.** Neurofilament immunohistochemical stain is useful to identify

(A) meningioma
(B) choroid plexus tumor
(C) neurofibroma
(D) endodermal sinus tumor
(E) medullomyoblastoma

**46.** Deletion of chromosome 19q occurs in

(A) ependymoma
(B) glioblastoma
(C) oligodendroglioma
(D) schwannoma
(E) meningioma

**47.** The presence of cellular monotony, uniform cell density, and nuclei surrounded by a rim of clear cytoplasm giving a "fried egg" appearance is most suggestive of

(A) oligodendroglioma
(B) ependymoma
(C) meningioma
(D) dysembryoplastic neuroepithelial tumor
(E) pilocytic astrocytoma

**48.** The transverse section of the brain in Figure 15-24 shows

(A) *Nocardia* abscess
(B) mucormycosis
(C) *Plasmodium falciparum* malaria
(D) brain metastasis
(E) cysticercosis

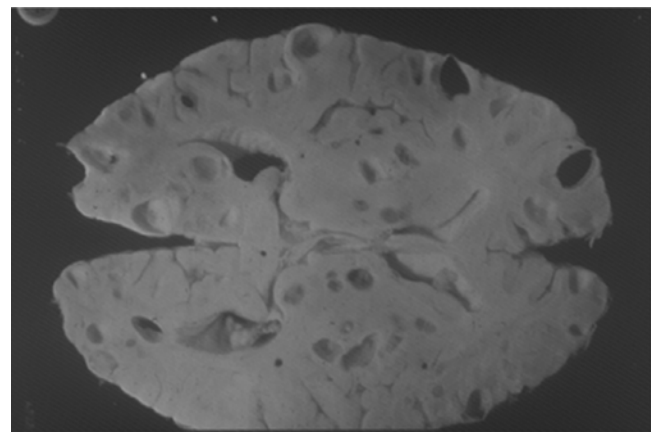


**FIG. 15-24**

**49.** Figure 15-25 shows

(A) cavernous hemangioma
(B) temporal arteritis
(C) arteriovenous malformation
(D) polymyositis
(E) cerebral amyloid angiopathy

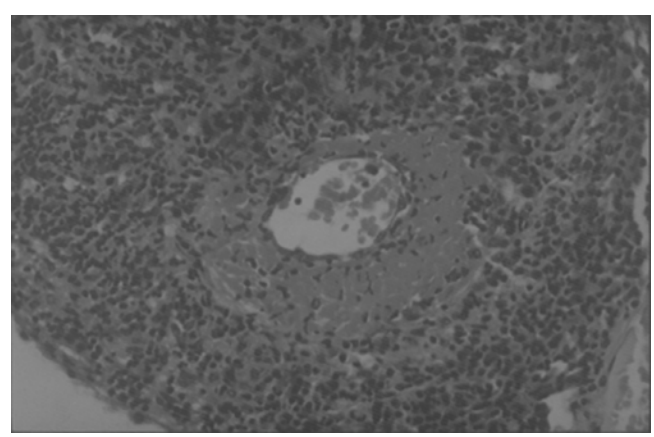


**FIG. 15-25.** See color insert.

**50.** Figure 15-26 shows

(A) acute inflammatory demyelinating neuropathy
(B) vasculitic neuropathy
(C) Charcot–Marie–Tooth neuropathy
(D) leprosy neuropathy
(E) diabetic neuropathy

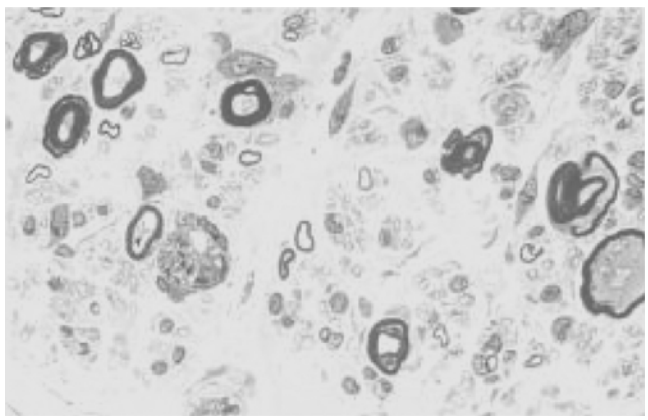


**FIG. 15-26**

**51.** Figure 15-27 shows

(A) acute inflammatory demyelinating neuropathy
(B) vasculitic neuropathy
(C) Charcot–Marie–Tooth neuropathy
(D) leprosy neuropathy
(E) diabetic neuropathy

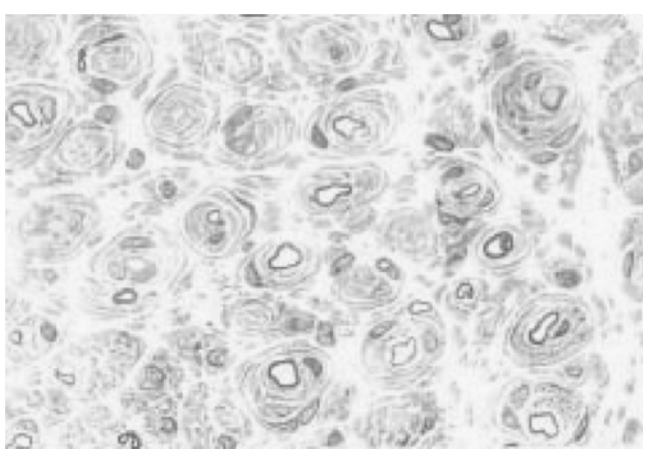


**FIG. 15-27**

**52.** The lesion in Figure 15-28 is an example of

(A) poliomyelitis
(B) Brown–Sequard syndrome
(C) Krabbe disease
(D) vacuolar myelopathy
(E) multiple sclerosis

**FIG. 15-28.** See color insert.

**53.** The lesion in Figure 15-29 is characteristic of

(A) central pontine myelinolysis
(B) multiple sclerosis
(C) progressive multifocal leukoencephalopathy
(D) ischemic stroke
(E) Krabbe disease

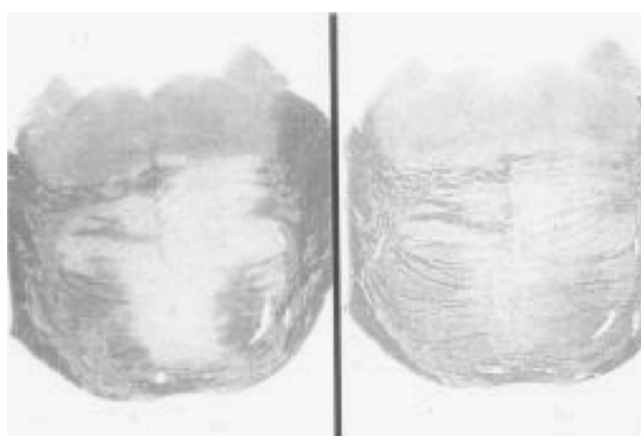


**FIG. 15-29.** See color insert.

**54.** Figure 15-30 shows a

(A) neurofibrillary tangle
(B) neuritic plaque
(C) Lewy body
(D) Bunina body
(E) Hirano body

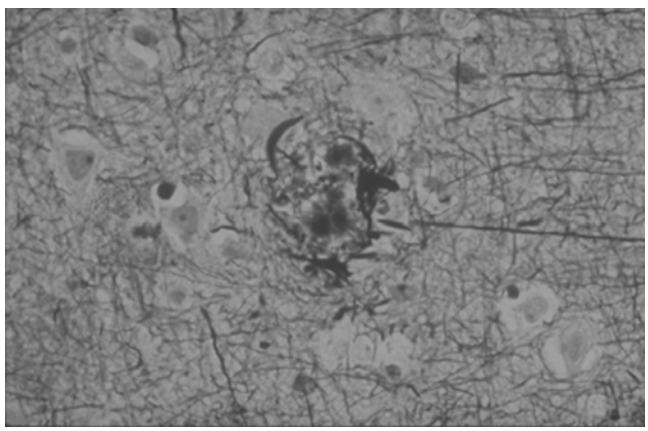


**FIG. 15-30.** See color insert.

**55.** Figure 15-31 shows

(A) Lewy bodies
(B) Bunina bodies
(C) neurofibrillary tangles
(D) Lafora bodies
(E) Cowdry A inclusions

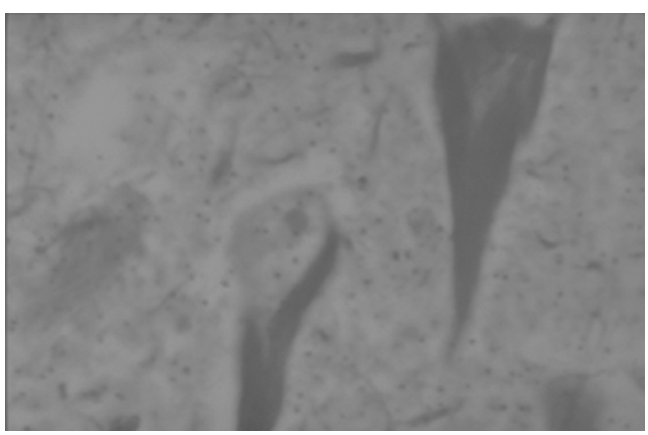


**FIG. 15-31.** See color insert.

**56.** Figure 15-32 shows

(A) Cowdry A inclusions
(B) Marinesco bodies
(C) Bunina bodies
(D) Lafora bodies
(E) Lewy bodies

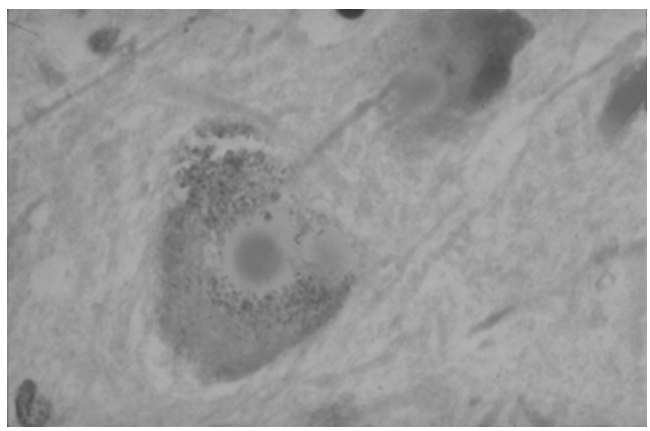


**FIG. 15-32.** See color insert.

**57.** The section of the brain in Figure 15-33 shows a lesion characteristic of

(A) Wernicke encephalopathy
(B) carbon monoxide intoxication
(C) central pontine myelinolysis
(D) Parkinson disease
(E) Huntington disease

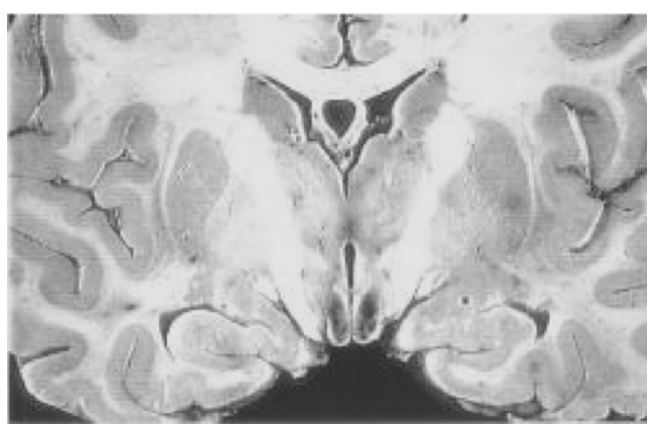


**FIG. 15-33.** See color insert.

**58.** The lesion in the brain section shown in Figure 15-34 is characteristic of

(A) chronic ethanol intoxication
(B) carbon monoxide intoxication
(C) chronic phenytoin toxicity
(D) methanol intoxication
(E) lead intoxication

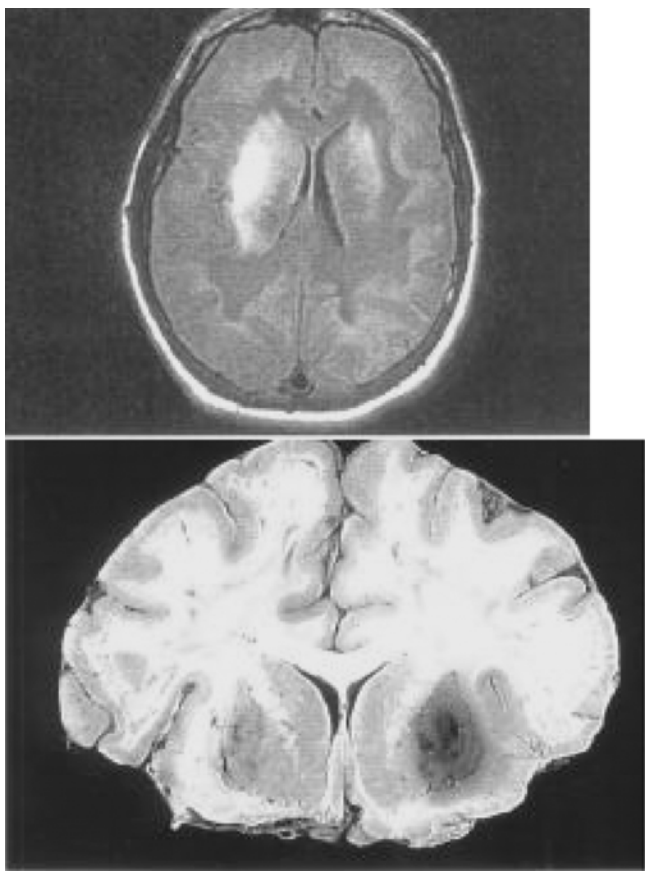


FIG. 15-34

**59.** Figure 15-35 illustrates

(A) heterotopia
(B) agyria
(C) polymicrogyria
(D) porencephaly
(E) holoprosencephaly

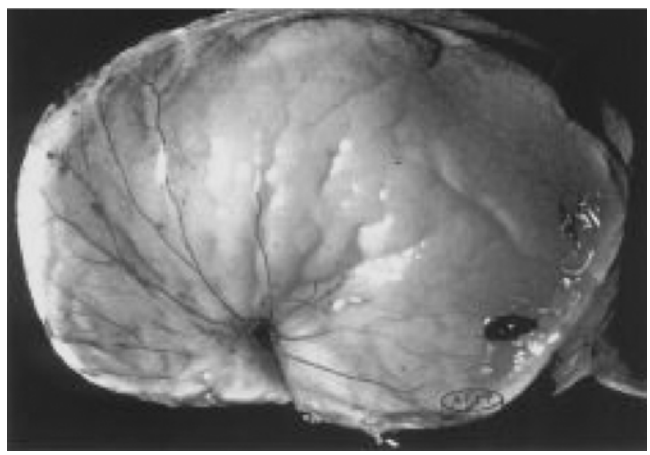


FIG. 15-35

**60.** Figure 15-36 shows

(A) polymicrogyria
(B) pachygyria
(C) heterotopia
(D) porencephaly
(E) agenesis of the corpus callosum

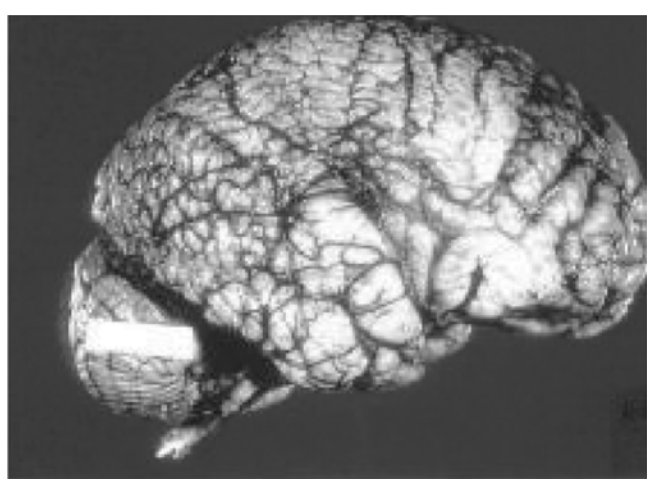


FIG. 15-36

**61.** Figure 15-37 shows

(A) porencephaly
(B) holoprosencephaly
(C) agenesis of the corpus callosum
(D) heterotopia
(E) cortical dysplasia

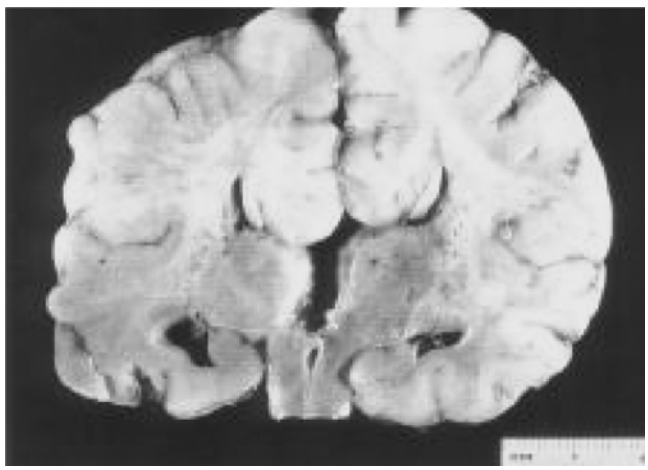


**FIG. 15-37.** See color insert.

**62.** Figure 15-38 is a CT scan of the head and biopsy slide of a 40-year-old man who developed a new onset of seizure. What is the most likely diagnosis?

(A) GBM
(B) Clear cell ependymoma
(C) Fibrillary astrocytoma
(D) Oligodendroglioma
(E) Dysembrylastic neuroepithelial tumor

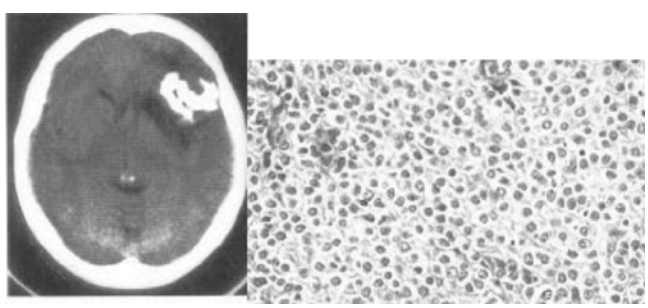


**FIG. 15-38.** See color insert.

**63.** Figure 15-39 shows an

(A) ependymoma
(B) medulloblastoma
(C) fibrillary astrocytoma
(D) subependymoma
(E) colloid cyst of the third ventricle

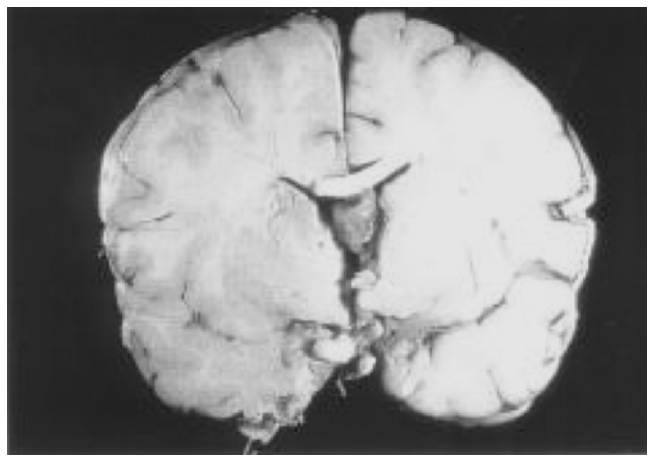


**FIG. 15-39.** See color insert.

**64.** Figure 15-40 illustrates

(A) psammoma bodies
(B) Lewy bodies
(C) neuritic plaques
(D) Cowdry type A inclusions
(E) Hirano bodies

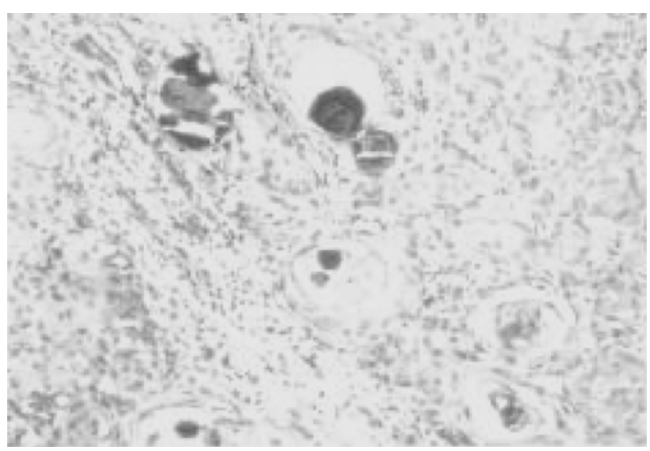


**FIG. 15-40.** See color insert.

**65.** Figure 15-41 illustrates

(A) normal muscle
(B) central core disease
(C) nemaline myopathy
(D) ragged-red fibers
(E) dermatomyositis

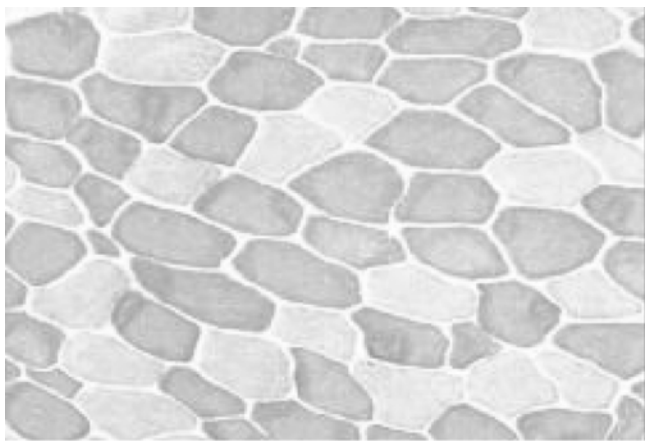


**FIG. 15-41**

**66.** Figure 15-42 illustrates

(A) normal muscle
(B) central core disease
(C) nemaline myopathy
(D) ragged-red fibers
(E) dermatomyositis

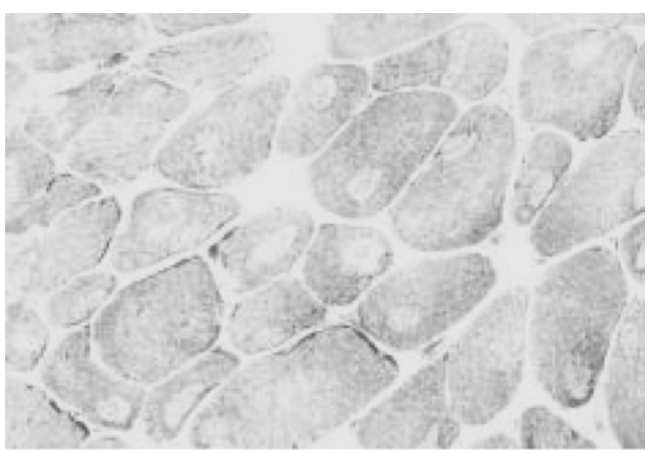


**FIG. 15-42.** See color insert.

**67.** Figure 15-43 illustrates

(A) normal muscle
(B) central core disease
(C) nemaline myopathy
(D) ragged-red fibers
(E) dermatomyositis

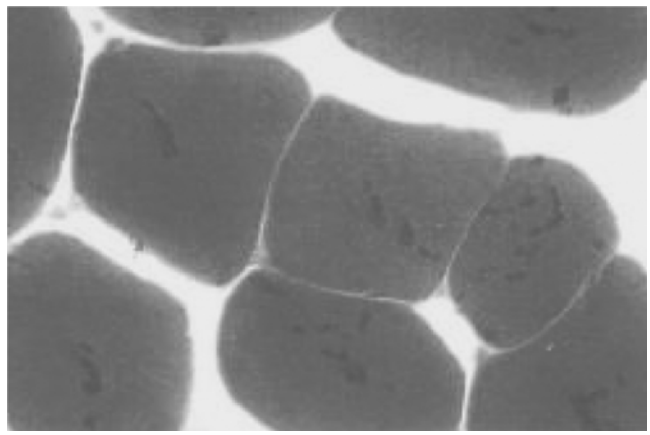


**FIG. 15-43.** See color insert.

**68.** Figure 15-44 illustrates

(A) ragged-red fibers
(B) dermatomyositis
(C) target fibers
(D) infantile spinal muscular atrophy
(E) polymyositis

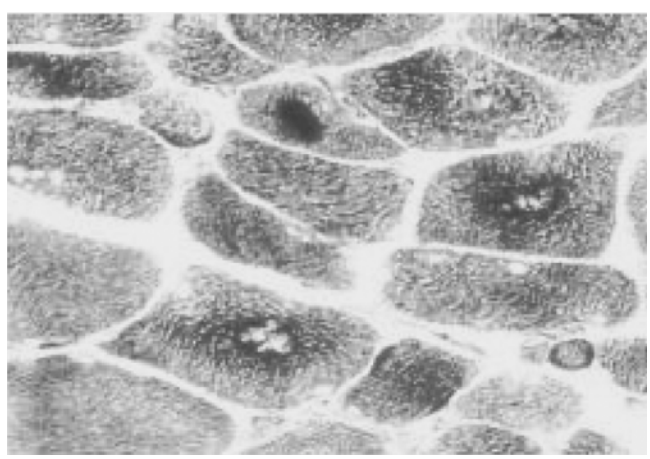


**FIG. 15-44.** See color insert.

**69.** Figure 15-45 illustrates

(A) ragged-red fibers
(B) dermatomyositis
(C) target fibers
(D) infantile spinal muscular atrophy
(E) polymyositis

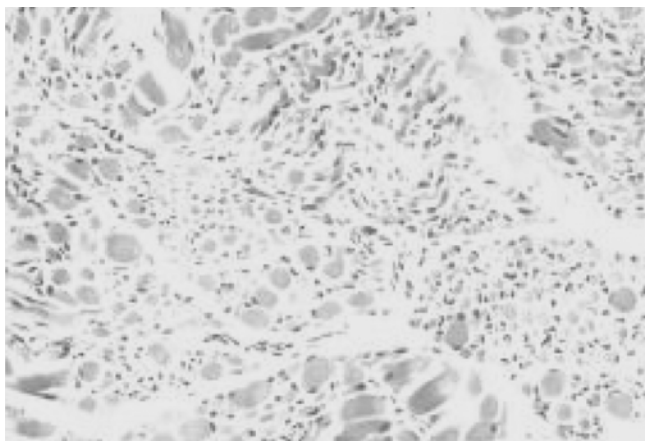


**FIG. 15-45.** See color insert.

**70.** Figure 15-46 illustrates

(A) normal muscle
(B) central core disease
(C) nemaline myopathy
(D) ragged-red fibers
(E) dermatomyositis

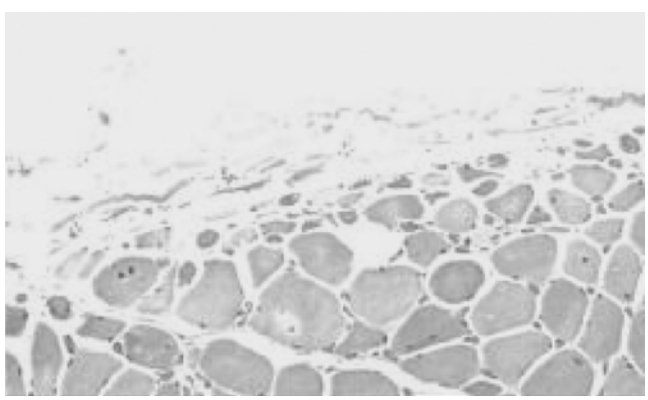


**FIG. 15-46.** See color insert.

**71.** Figure 15-47 illustrates

(A) ragged-red fibers
(B) dermatomyositis
(C) target fibers
(D) infantile spinal muscular atrophy
(E) polymyositi

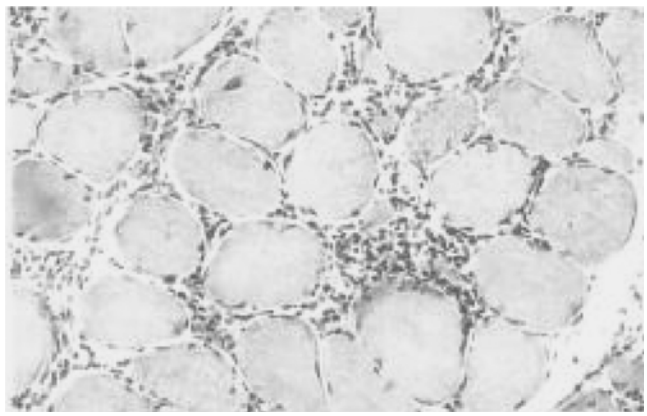


**FIG. 15-47.** See color insert.

**72.** Figure 15-48 illustrates

(A) normal muscle
(B) central core disease
(C) nemaline myopathy
(D) ragged-red fibers
(E) dermatomyositis

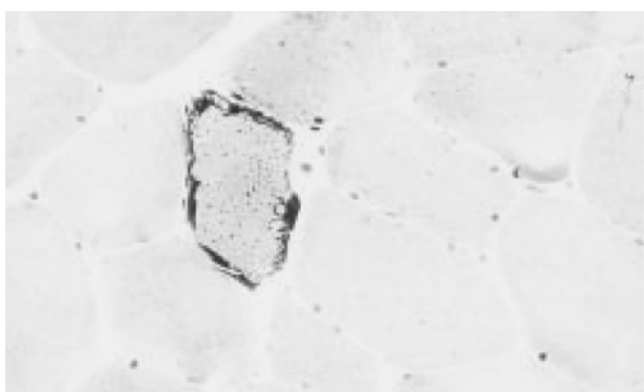


**FIG. 15-48.** See color insert.

# Answers and Explanations

1. **(C)** Figure 15-1 illustrates a modified Gomori–trichome stain of a muscle biopsy. It reveals a ragged-red fiber in a patient with mitochondrial myopathy. *(Amato, 73)*

2. **(B)** The myofibrillar adenosine triphosphatase (ATPase) is typically performed at three pHs: 4.3, 46, and 9.4 in order to assess the size and the distribution of different muscle fiber types. Individual muscle fibers can be classified into four different fiber types based on their staining characteristics and physiological properties: type I (slow-twitch, fatigue-resistant, with oxidative metabolism), 2A (fast-twitch, intermediate fatigue resistance, with oxidative and glycolytic metabolism), 2B (fast-twitch, poor fatigue resistance, with glycolytic metabolism), and 2C (undifferentiated and embryonic). The specific muscle fiber type is determined by the innervating motor neuron. The different muscle fibers type are distributed randomly. Figure 15-2 shows a muscle biopsy myofibrillary adenosine triphosphatase (ATPase) staining at a pH 9.4. Type 1 fibers are lightly stained while type 2 fibers are dark. *(Amato, 74–75)*

3. **(D)** Congo red stain was used in Figures 15-3A and B. It demonstrates amyloid deposition surrounding muscle fibers and blood vessels. Under routine light microscopy, the amyloid deposition stains pinkish red, as illustrated in Figure 5-3A; it is apple-green under polarized light but is most easily appreciated as bright red, using rhodamine optics, as illustrated in Figure 15-3B. *(Amato, 78)*

4. **(A)** A feature of muscle fiber denervation is the presence of target fibers. Reorganization of the cytoarchitecture within denervated muscle cells results in a rounded central zone of disorganized filaments that contain fewer mitochondria and glycogen. Target fibers have three zones that are circumferentially oriented; this is best seen on NADH-TR staining, as illustrated in Figure 15-4A. The innermost zone is devoid of mitochondria, glycogen, phosporylase, and ATPase enzymatic activity. The second zone has increased enzymatic activity, while the third zone exhibits intermediate enzymatic activity. Target fibers can also be appreciated on Gomori–trichome stain, as illustrated in Figure 15-4B, where they stain dark and are surround by a pale-staining zone. *(Amato, 81)*

5. **(A)** Figure 15-5 is an illustration of modified Gomori–trichome staining of a muscle biopsy cross section. It reveals a subsarcolemmal cluster of rods stained reddish-purple, suggestive of nemaline myopathy. *(Amato, 583)*

6. **(B)** Myosin storage or hyaline body myopathy is a rare congenital myopathy characterized by large areas devoid of sarcomeres in type I (slow) fibers on skeletal muscle biopsy. The term *hyaline body myopathy* was introduced because of the "glassy" appearance of the inclusions on trichrome stain. Myosin storage or hyaline body myopathy is a rare congenital myopathy characterized by large areas devoid of sarcomeres in type I (slow) fibers on skeletal muscle biopsy. The characteristic histological feature of myosin storage myopathy is the presence of subsarcolemmal hyalinized bodies in several muscle fibers that stain pale pink with hematoxylin and eosin (H&E), as illustrated in Figure 15-6A, and pale green with the modified Gomori–trichrome

stain, as illustrated in Figure 15-6B; they lack reactivity for glycogen and oxidative enzyme stains. On electron microscopy, the hyaline bodies are subsarcolemmal in location and not membrane-bound. They consist of an amorphous, granular substance. Disorganized delicate profiles of filaments visible at higher magnification have been described. *(Amato, 589)*

7. **(A)** Central core myopathy is a rare disorder characterized by the occurrence of weakness and hypotonia soon after birth and a general delay in motor development, particularly in walking, which is not achieved until the age of 4 to 5 years. The weakness is greater in proximal than in distal muscles. Facial, bulbar, and ocular muscles are spared. The disease has another remarkable attribute in that every patient is a potential candidate for the development of malignant hyperthermia. Pathologically, the majority of the muscle fibers appear normal in size or enlarged; no focal destruction or loss of fibers can be found. The unique feature of the disease is the presence in the central portion of each muscle fiber of a dense, amorphous condensation of myofibrils or myofibrillar material. This altered zone characteristically lacks mitochondria and other organelles and gives a reduced positive periodic acid–Schiff reaction and a dark blue coloration with the Gomori–trichrome stain, contrasting with the normal blue-green color of the peripheral myofibrils. Within the core, there is a lack of phosphorylase and oxidative enzymes. Most of the cores are in type 1 fibers, which predominate in muscle biopsies. These cores run the length of the muscle fiber, thus differing from the multiple cores or minicores seen in oculopharyngeal and multiminicore myopathy. Figure 15-7A and B shows a muscle biopsy stained with nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR). It demonstrates areas devoid of oxidative enzyme activity in the center of the fibers or sometimes in eccentric regions (Figure 15-7A) that extend the length of the fiber longitudinally (Figure 15-7B). *(Amato, 579)*

8. **(E)** The histopathological abnormalities in muscle biopsies of the various mitochondrial myopathies are nonspecific. The characteristic histological features are the presence of ragged-red fibers on modified Gomori–trichome stain. Oxidative enzyme stains with nicotinamide adenine dinucleotide dehydrogenase (NADH), succinate dehydrogenase (SDH), and cytochrome c oxidase (COX). The ragged-red fibers and small arteries intensely react with NADH and SDH stains, forming ragged-blue fibers. Some patients with mitochondrial myopathies may have no ragged-red fibers and normal NADH and SDH staining. COX stain (directed against one of the subunits encoded by mitochondrial DNA) appears to be the most sensitive stain and can demonstrate scattered muscle fibers with reduced or absent stain, as illustrated in Figure 15-8. *(Amato, 632)*

9. **(C)** Muscle biopsies in statin myopathy reveal muscle fiber necrosis with phagocytosis and small regenerating fibers, as illustrated in Figure 15-9, which is a muscle biopsy with modified Gomori–trichome staining. *(Amato, 739)*

10. **(A)** Astrocytomas (WHO grade II) are low-grade, diffusely infiltrative neoplasms composed of astrocytes. These tumors may occur in patients of all ages and may arise at any location of the neuraxis. However, site predilection varies according to the patient's age; in adults, they are more common in the cerebral hemispheres; in children, these tumors usually arise in the brainstem. Both grossly and microscopically, astrocytomas are ill-defined masses that diffusely infiltrate the surrounding brain. Histologically, low cellularity and minimal cellular–nuclear atypia characterize low-grade astrocytomas. Special stains are helpful in characterizing the astrocytic nature of low-grade astrocytomas. These tumors are conspicuously immunoreactive for GFAP, as illustrated in Figure 15-10, and vimentin in both cytoplasm and cellular processes. *(Schiff, 86)*

11. **(A)** Anaplastic astrocytomas (WHO grade III) constitute a group of astrocytic neoplasms that, although exhibiting more prominent histological features of anaplasia than low-grade astrocytoma, do not exhibit the degree of anaplasia seen in GBM. Similar to astrocytomas grade II, anaplastic astrocytomas arise most frequently in the cerebral hemispheres; however, they tend

to occur in patients a decade older than those with astrocytomas (median age 41 years).

Microscopically, anaplastic astrocytomas (Figure 15-11) are hypercellular compared with astrocytomas and exhibit a variable degree of cytoplasmic and nuclear pleomorphism. Gemistocytic elements are more commonly seen. (Gemistocytic cells are characterized by abundant eosinophilia, round to slightly angulated cytoplasm, and eccentric nuclei.) Anaplastic astrocytomas typically display increased mitotic activity and higher levels of Ki-67 than do low-grade astrocyotmas. *(Schiff, 85–86)*

**12. (B)** GBM is the most common and most aggressive type of primary brain tumor in humans, accounting for 52% of all primary brain tumors and 20% of all intracranial tumors. Despite being the most prevalent form of primary brain tumor, GBM occurs in only 2 to 3 cases per 100,000 people in Europe and North America. Microscopically, glioblastomas manifest a variety of histological aspects. The tumors are hypercellular and exhibit a high degree of cytoplasmic and nuclear polymorphism. Figure 15-12A illustrates increased mitotic activity and Figure 15-12B shows areas of necrosis characteristic of glioblastoma. *(Schiff, 87)*

**13. (A)** Glioblastoma multiforme (astrocytoma grade IV) is characterized by the presence of small areas of necrotizing tissue surrounded by anaplastic cells forming pseudopalisading necrosis. This characteristic, seen in Figure 15-3, as well as the typical hyperplastic blood vessels, differentiates the tumor from grade III astrocytoma, which does not have these features. *(Schiff, 87)*

**14. (B)** Figure 15-14 shows a pilocytic astrocytoma. These well-circumscribed tumors occur most frequently in children and young adults, with a peak incidence in the second decade of life. Pilocytic astrocytomas are typically located in midline structures, including the cerebellum, otic pathways, hypothalamus, third ventricle regions, and brainstem. Most are cystic lesions with a solid component or mural nodule. Microscopically, pilocytic astrocytomas typically demonstrate a biphasic pattern of growth with bipolar piloid cells arranged in dense fascicles alternating with a loose microcytic tissue formed by stellate astrocytic cells. *(Schiff, 90–91)*

**15. (D)** The oligodendroglioma is derived from oligodendrocytes or their precursor cells and may occur at any age, most often in the third or fourth decade, with an earlier peak at 6 to 12 years. It is relatively infrequent, constituting approximately 5% to 7% of all intracranial gliomas. Males outnumber females 2:1. In some cases the tumor may be recognized at surgery by its pink–gray color and multilobular form, relative avascularity, and firmness (slightly tougher than surrounding brain); it has a tendency to encapsulate and form calcium and small cysts. The neoplastic oligodendrocyte has a small round nucleus and a halo of unstained cytoplasm, giving the appearance of a fried egg, as illustrated in Figure 15-5. The cell processes are few and stubby, visualized only with silver carbonate stains. Some of the oligodendrocytes have intense immunoreactivity to GFAP, similar to normal myelin-forming oligodendrocytes. Microscopic calcifications are observed frequently, both within the tumor and in immediately adjacent brain tissue. The most common sites of this tumor are the frontal and temporal lobes (40% to 70%), often deep in the white matter, with one or more streaks of calcium but little or no surrounding edema. *(Ropper, chapter 31; Schiff, 94–95)*

**16. (B)** Figure 15-16 illustrates dense areas of fibrillary cells with the formation of Rosenthal fibers in a pilocytic astrocytoma. *(Schiff, 91)*

**17. (C)** Ependymomas are derived from ependymal cells—that is, the cells lining the ventricles of the brain and the central canal of the spinal cord; they are the most common gliomas of the spinal cord. The cells have both glial and epithelial characteristics. As one might expect, the tumors grow either into the ventricle or adjacent brain tissue. The most common cerebral site is the fourth ventricle; less often, they occur in the lateral or third ventricles. Grossly, those in the fourth ventricle are grayish pink, firm, cauliflower-like growths; those in the cerebrum, arising from the wall of the lateral ventricle, may be

large (several centimeters in diameter), reddish gray, and softer and more clearly demarcated from adjacent tissue than astrocytomas, but they are not encapsulated. The tumor cells tend to form rosettes with central lumens or, more often, circular arrangements around blood vessels (pseudorosettes), as illustrated in Figure 15-17. *(Ropper, chapter 31; Schiff, 98–99)*

**18.** **(D)** Figure 15-18A and B illustrates a central neurocytoma. This is a rare tumor of the CNS with neurocytic differentiation and a favorable prognosis. Although neurocytoma comprises only 0.25% to 0.5% of all intracranial tumors, they are the most frequent intraventricular tumor in adults. They occur predominantly in the third and fourth decades but can be seen in other age group. About three quarter of the cases occur in the lateral ventricles or the foramina of Monro; the remaining one quarter occur in the third ventricle. Rarely, they can occur in the cerebral hemispheres. Their ventricular location makes symptoms and signs of hydrocephalus the most common manifestations. The acuteness of clinical manifestations is variable. Central neurocytoma is distinguished histologically by a homogenous population of cells with round, lobulated nuclei and scant cytoplasm in a conspicuously fibrillated matrix, as seen in Figure 15-18A and B. Histologically, the tumor is composed of solid sheets of small, round to polygonal isomorphic tumor cells with a distinct cell membrane. Within the neoplastic cells is a delicate vascular network. Microcalcifications, when present, are distributed throughout the tumor. The cytoplasm is fine and amphophilic. A perinuclear halo is usually present and prominent, leading to an impression of a clear cell tumor. The summation of these features generates a "honeycomb" pattern similar to that of oligodendroglioma and clear cell ependymoma. The nuclei of neurocytomas are round, small, and contain fine speckled chromatin. Nucleoli are indistinct. Mitotic figures are not readily seen or infrequent. Irregular small islands of neuropils are present. The perivascular arrangement of neuropils in some areas may closely mimic the coronary perivascular fibrillary hypocellular mantles (perivascular pseudorosettes) that are considered evidence of ependymoma. The real ependymal pseudorosettes are more orderly and fibrillary. *(Schiff, 100–102)*

**19.** **(D)** Medulloblastoma is the most common malignant tumor of the CNS arising in childhood. This is an invasive and rapidly growing tumor that arises in the posterior part of the cerebellar vermis and neuroepithelial roof of the fourth ventricle, accounting for 20% of childhood brain tumors. Rarely, it presents elsewhere in the cerebellum or other parts of the brain in adults. Medulloblastomas are hypercellular neoplasms composed of relatively small cells with scant cytoplasm and hyperchromatic nuclei, as illustrated in Figure 15-19A and B. The cells are usually arranged n sheets, although focal formation of rhythmic nuclear palisades can be seen. The tumor cells diffusely infiltrate the cerebellar cortex with obliteration of the granular and molecular layers. *(Schiff, 105)*

**20.** **(C)** Meningiomas represent approximately 15% of all primary intracranial tumors; they are more common in women than in men (2:1) and have their highest incidence in the sixth and seventh decades of life. Some are familial. The histological hallmark of meningiomas remains the cellular meningothelial whorl. The meningotheliomatous and transitional meningiomas display the most typical meningothelial appearance. These are characterized by groups of cells with poorly defined cell borders, forming the typical whorls around individual cells, blood vessels, and stromal elements. Psammoma bodies, lamellated, calcified structures normally seen intermixed with meningioepithelial cells in the arachnoid membrane, are commonly seen in these tumors, but when psammoma bodies are the predominant feature, as seen in Figure 15-20, the tumor is designed a psammomatous meningioma. *(Schiff, 108–109)*

**21.** **(E)** Figure 15-21 showed alternation of hypercellular areas (Antoni A) and loose areas (Antoni B) of the spindle-shaped cells typically seen in schwannomas. *(Schiff, 111)*

**22.** **(A)** Figure 15-22 illustrates a primary CNS lymphoma, Histologically, these lymphomas are characteristically angiocentric neoplasms with

tumor cells arranged in vascular concentric cuffings with invasion of the vascular walls and increased reticulin deposition. The tumor cells also diffusely infiltrate the brain parenchyma. *(Schiff, 113)*

**23.** **(D)** Figure 15-23 illustrates a neurofibroma, a complex mixture of Schwann cells, fibroblasts, and perineurial cells that expands a diffuse segment of nerve. Neurofibromas display a uniform array of delicately waving Schwann cells with comma-shaped nuclei intermixed with perineurial-like cells and fibroblasts, often within a background myxoid matrix. *(Schiff, 111–112)*

**24.** **(D)** Nuclear inclusions are divided into pathological and nonpathological types. Nonpathological nuclear inclusions include:

- The nucleolus: it is the site of processing and partial assembly of ribosomes, which are required for cytoplasmic protein synthesis. It is prominent in large neurons, including motor neurons and Purkinje cells.
- The Marinesco body: a small round eosinophilic paranucleolar inclusion seen in normal aging. It stains with ubiquitin. Its ultrastructure is composed of intermediate filaments. It is commonly located in pigmented neurons of the substantia nigra, pyramidal cells of the hippocampus, and tegmentum of the brainstem.

Pathological nuclear inclusions include viral inclusions:

- Cowdry type A is an amorphous, large, spherical eosinophilic inclusion that displaces the nucleus and chromatin to the periphery and may be surrounded by a halo. It is usually indicative of viral infection.
- Cowdry type B is a small eosinophilic inclusion that does not displace the nucleus. Its origin may be viral or nonviral.

Lipofuscin is a normal cytoplasmic inclusion. It is composed of lipid, protein, and carbohydrate. It is produced by lysosomes by oxidation of lipid and lipoproteins. Hippocampal pyramidal neurons, thalamus, and motor neurons of the brainstem and spinal cord are among the common locations of lipofuscin cytoplasmic inclusions.

Hirano bodies are cytoplasmic inclusions. They are eosinophilic refractile inclusions found within the cytoplasm and adjacent to neurons. They stain positively for actin, tau protein, and vinculin. They are seen most frequently in Pick and Alzheimer diseases and are most commonly located in the hippocampus. Lewy bodies are eosinophilic cytoplasmic inclusions that consist of a dense core surrounded by a halo of wide radiating fibrils. *(Davis, 3–5; Sandberg, 7–8)*

**25.** **(C)** Neurofibrillary tangles are abnormal, coarse, fibrillary cytoplasmic inclusions, some of which are composed of hyperphosphorylated tau proteins that may be ubiquitinated or glycated. They are flame-shaped in pyramidal neurons and take on a globose appearance in neurons of the locus ceruleus. Commonly located in the hippocampus and the temporal lobe, they are seen in normal aging, progressive supranuclear palsy, postencephalitic Parkinson disease, Alzheimer disease, and ALS–parkinsonism–dementia complex of Guam. *(Davis, 28–30; Sandberg, 9)*

**26.** **(B)** Bunina bodies are abnormal cytoplasmic inclusions. They are small bead-like eosinophilic inclusions most commonly found in motor neurons of patients with ALS. *(Davis, 42–44; Sandberg, 9–10)*

**27.** **(A)** Alzheimer type II cells are astrocytic cells with enlarged nuclei and marginated chromatin. They are commonly located in the globus pallidus, cerebellar dentate nucleus, and cerebral cortex. They are seen in hepatic encephalopathy, Wilson disease, and Canavan disease. *(Davis, 470–471; Sandberg, 13)*

**28.** **(A)** Fungating herniation is a herniation of the brain through a defect in the skull secondary to trauma or surgery. It is caused by increased intracranial pressure and often has a fatal outcome. *(Sandberg, 5)*

**29.** **(C)** The pathological hallmarks of herpes encephalitis are necrotizing lesions of the limbic areas and Cowdry type A intranuclear inclusion bodies, which are amorphous, large, spherical eosinophilic inclusion that displace the nucleolus and chromatin to the periphery. *(Davis, 977–981, 1002–1010, 1018–1022, 1032–1034)*

**30.** **(E)** Microglial nodules and necrotizing lesions in the region of the conus medullaris, cauda equina, and the periventricular areas are characteristic of central nervous CMV infection. They are associated with the presence of cytomegalic cells, also known as owl's-eye cells. *(Davis, 977–981, 1002–1010, 1018–1022, 1032–1034)*

**31.** **(B)** In most cases, rabies encephalitis is transmitted to humans through infected saliva injected into soft tissue at the site of a bite from an animal such as a fox or a dog. The etiological agent of rabies is a rhabdovirus that contains a single-stranded RNA. Histopathological features of rabies encephalitis are cytoplasmic negri bodies, best seen in large neurons of the hippocampus, brainstem, and Purkinje cells. *(Davis, 977–981, 1002–1010, 1018–1022, 1032–1034)*

**32.** **(D)** Progressive multifocal leukoencephalopathy (PML) is an infection caused by the JC virus, a papova (papilloma–polyoma–vacuolating) virus. The hallmark pathological features of PML are oligodendrocytes with inclusion bodies and multiple frequently coalescing large and small foci of demyelination. JC virus causes lytic infection of oligodendrocytes, leading to demyelination and to the development of corresponding signs. The cut surface of the fixed brain affected by PML appears asymmetrically pitted by small foci of gray discoloration mixed with larger confluent areas of abnormal parenchyma, which may be centrally necrotic. The lesions tend to be most numerous in the cerebral white matter but also involve the cerebral cortex and deep gray matter. On microscopic examination, there are multiple foci of demyelination. Some are small and rounded, others confluent and irregular and occasionally centrally necrotic. The homogeneous amphophilic inclusions, seen in oligodendrocytes, largely fill the nuclei and consist of closely packed polyomavirus particles, which can be identified on electron microscopy. *(Davis, 977–981, 1002–1010, 1018–1022, 1032–1034)*

**33.** **(A)** The neuropathological characteristics of Creutzfeldt–Jacob disease are spongiform changes in the cortex, subcortical astrogliosis, and deposition of prion proteins. The normal prion protein is encoded by a gene located on chromosome 20 and converted into an abnormal one. Partial breakdown of prion protein may produce protein products that spontaneously polymerize into amyloid fibers. *(Davis, 977–981, 1002–1010, 1018–1022, 1032–1034)*

**34.** **(C)** Mumps virus infects ependymal cells. Herpes and polioviruses infect neuronal cells, whereas JC virus attacks both astrocytes and oligodendrocytes. Microglial cells are preferentially infected by herpesvirus. *(Takano, 2215–2221)*

**35.** **(A)** The combination of multinucleated giant cells, microglial nodules, and perivenular inflammation has been termed HIV encephalitis and has been identified in 30% to 90% of patients dying with AIDS. There is frequently a diffuse pallor of the myelin, particularly in deep areas of the centrum semiovale, with microscopic evidence of macrophage activation, astrocytosis, and productive HIV infection. Cerebral atrophy is common in patients with HIV dementia (HIV-D), often occurring in a frontotemporal distribution. The pathology of HIV-D is that of a chronic encephalitis with marked macrophage activation. Multiple small nodules containing macrophages, lymphocytes, and microglia are scattered throughout gray and white matter of the brain, appearing more commonly in white matter and subcortical gray matter of the thalamus, basal ganglia, and brainstem. These inflammatory nodules are not specific to HIV-1 infection and occur in other infections, including toxoplasmosis and CMV encephalitis.

Multinucleated giant cells are also characteristically seen; their presence correlates with the degree of dementia and the detection of HIV-1 DNA. These giant cells are thought to reflect HIV-1 replication because giant multinucleated cells form in HIV-infected macrophage cultures.

Gross pathological examination of primary CNS lymphoma (PCNSL) reveals a bulky tumor with indistinct borders, often contiguous with meningeal or ventricular surfaces. Most lesions are supratentorial. Whereas solitary lesions occur in one third of cases, multiple lesions are evident in most cases. These lesions are histologically diffuse, with perivascular involvement, high mitotic rates, and variable degrees of necrosis and microglial reaction. Immunohistochemical

studies of PCNSL identify these tumors as B cells in origin.

Cytomegalovirus has been identified in astrocytes, neurons, oligodendroglia, and capillary endothelia. Four pathological lesions are associated with CMV encephalitis in patients with AIDS:

1. Isolated cytomegalic cells: cytomegalic cells without associated microglial nodules or inflammation.
2. Microglial nodules: dense cellular aggregates of macrophages, rod cells, or both; typically well demarcated from the adjacent parenchyma and more common in gray matter than in white matter. Few microglial nodules (only 7% to 12%) contain cytomegalic inclusions.
3. Focal parenchymal necrosis: discrete foci of parenchymal necrosis with cytomegalic cells and macrophages.
4. CMV ventriculoencephalitis: focal or diffuse destruction of the ependymal lining and necrosis of periventricular parenchymal tissue associated with dense accumulation of cytomegalic cells in the ependymal and periependymal areas. Ventriculomegaly, necrosis, and hemorrhage or fibrinous exudates covering the ventricular system may be evident on gross inspection.

Varicella zoster virus causes meningoencephalitis with ventriculitis. CNS toxoplasmosis is the most common cause of focal brain lesions in patients with AIDS. The pathology of CNS toxoplasmosis may include necrosis and hemorrhage of choroid plexus. *(Arribas, 577–587; Ciacci, 213–221; McArthur, 129–150)*

**36.** **(D)** Lipohyalinosis, a destructive vasculopathy linked to severe hypertension, affects arteries 40 to 200 μm in diameter. The arterial lumen is compromised not by an intimal process but by thickening of the vessel wall itself. Subintimal lipid-laden foam cells and pink-staining fibrinoid material thicken the arterial walls, sometimes compressing the lumen. In places the arteries are replaced by tangles and wisps of connective tissue that obliterate the usual vascular layers. The small, deep infarcts that result from occlusion of these arteries are usually called lacunes. Small, deep infarcts can also result from miniature atheromas (microatheromas) that form at the origin of penetrating arteries, as well as by plaques within the parent arteries that obstruct or extend into the branches (junctional plaques). Rarely, they are occluded by microemboli. *(Goetz, 913–914)*

**37.** **(E)** Cytokeratin immunohistochemical stains are useful in the diagnosis of craniopharyngioma, carcinoma, chordoma, and epithelial cyst. *(Kubo, 131–134)*

**38.** **(D)** Immunohistochemistry is the most common method used to identify cell types and tumor phenotypes and to classify tumors. Endodermal sinus tumor stains positively for alpha fetoprotein. *(McKeever, 19–21)*

**39.** **(E)** Desmin is used to identify rhabdosarcoma and medullomyoblastoma. *(McKeever, 19–21)*

**40.** **(E)** Cytokeratin is used to identify craniopharyngioma as well as chordoma and epithelial cysts. *(McKeever, 19–21)*

**41.** **(A)** Meningioma, carcinoma, and epithelial cysts stain positively for epithelial membrane antigen. *(McKeever, 19–21)*

**42.** **(E)** L 26 identifies B-cell lymphoma. *(McKeever, 19–21)*

**43.** **(B)** Transthyretin stains choroid plexus tumors. *(McKeever, 19–21)*

**44.** **(D)** HMB 45 identifies melanoma. *(McKeever, 19–21)*

**45.** **(C)** Neurofilament stains neurofibroma, ganglion cell tumors, and pineocytoma. *(McKeever, 19–21)*

**46.** **(C)** Several genetic alterations are known to exist in human gliomas. In brief, these include alterations of chromosomes 9p, 10p, 10q, 11p, 13q, 17p, 19q, and 22p in diffuse fibrillary astrocytomas and the loss of 1p and 19q combined or in isolation in both pure and mixed oligodendrogliomas. The loss of heterozygosity (LOH) of 1p and 19q appears to be specific to tumors of

oligodendroglial origin, and this change is shared in both the astrocytic and the oligodendroglial portion of mixed oligoastrocytomas, suggesting that these are clonal. The high frequency of 1p and 19q loss in oligodendrogliomas suggests that these regions also harbor tumor suppressor genes. *(Perry, 705–710)*

**47.** **(A)** Cellular monotony is the main microscopic feature of oligodendroglioma. This is formed by monomorphous cells, characterized by uniformly round more often than oval nuclei with open chromatin. Nuclei are surrounded by either a rim of clear cytoplasm, resulting in the classic fried-egg appearance or a scant, slightly eccentric rim of pink cytoplasm and few processes. *(Parisi, 1–2)*

**48.** **(E)** This slide illustrates a brain with disseminated cysticercosis. It is the commonest parasitic infection of the CNS in Mexico as well as in other parts of the world, such as South America, India, and some European countries. The number of cysts within the CNS varies from one to several hundred. They occur in the parenchyma (especially the gray matter), meninges, or ventricles. The viable intraparenchymal cysticerci are usually 1 to 2 cm in diameter and contain a single invaginated scolex. After degeneration, they become fibrotic and are represented by a firm white nodule. *(Davis, 896–898)*

**49.** **(B)** This slide illustrates temporal arteritis (giant cell arteritis), an autoimmune disease involving large and medium-sized arteries, including the carotid and vertebral arteries and their major branches. On pathological examination, temporal arteritis is characterized by a widespread granulomatous inflammation of the arterial walls; it can cause cerebral infarction. Multinucleated giant cells are usually evident, and their cytoplasm may contain fragments of elastic lamina. *(Davis, 800–801)*

**50.** **(A)** This slide shows various stages of demyelination and remyelination with myelin loss, which may result in naked axons. This is highly suggestive of acute demyelinating inflammatory polyneuropathy. The pathological examination is characterized also by macrophages, which penetrate the Schwann cell basal lamina, displace a rim of Schwann cell cytoplasm, and strip away otherwise normal-appearing myelin. *(Schmidt, 5–6)*

**51.** **(C)** This slide shows axonal demyelination and remyelination with the development of concentric periaxonal Schwann cell processes in the form of an onion bulb. This is highly suggestive of hypertrophic neuropathy such as Charcot–Marie–Tooth neuropathy. *(Schmidt, 9–10)*

**52.** **(D)** Vacuolar myelopathy is the most common disease of the spinal cord in AIDS patients. It is characterized by a spongy vacuolation of myelin sheets in the posterior and lateral columns, as illustrated in this slide. There is vacuolation of the spinal white matter in the posterior columns and lateral corticospinal tracts. Breakdown of myelin, and later axons, is accompanied by an accumulation of macrophages containing debris. *(Davis, 996–997)*

**53.** **(A)** The two slides illustrate pontine sections; the left image uses a LFB/PAS stain, demonstrating myelin loss, while the image on the right uses a Bielschowsky stain, showing relative preservation of axons. These slides are highly suggestive of central pontine myelinolysis (CPM), a monophasic demyelinating disease that predominantly involves the basis pontis. It usually occurs as a complication of rapid correction of hyponatremia. The mechanism of the demyelination is poorly understood. On macroscopic examination, the basis pontis typically includes a fusiform region of gray discoloration, which is abnormally soft and appears granular. On sectioning, the extent of the lesion is variable. Its cross-sectional area is usually greatest in the upper part of the pons, where only a narrow rim of subpial tissue may be spared. It may involve the middle cerebral peduncles but rarely extends rostrocaudally beyond the confines of the pons and lower midbrain. The lesion may be asymmetric, being largely or completely confined to one side of the pons. On microscopic examination, CPM appears as an active demyelination. The lesions contain reactive astrocytes and large numbers of foamy lipid-laden macrophages but only very scanty lymphocytes. *(Davis, 518–520)*

**54.** **(B)** This slide shows a neuritic plaque seen in Alzheimer disease (AD). Amyloid plaques are one of the pathological characteristics of AD. They are formed by extracellular proteinaceous deposits, either as amyloid filaments or in nonfilamentous form, with variable associated abnormalities involving neuronal processes that traverse the abnormal region. The abnormal neuronal processes are termed dystrophic neurites. Plaques associated with abnormal neurites are termed neuritic plaques. Plaques are widely distributed in the brain of patients with AD. The neocortex and hippocampus are always involved. Plaques may also be present in the basal ganglia, the hypothalamus, the tegmentum of the midbrain and pons, and the subcortical white matter. *(Davis, 1071–1073; Hart, 1–3)*

**55.** **(C)** This slide illustrates neurofibrillary tangles, intraneuronal abnormalities seen in AD. Neurofibrillary tangles (NFTs) are neuronal inclusions composed largely of filamentous aggregates of hyperphosphorylated tau proteins that are variably ubiquitinated and glycated. In silver preparation, several morphological forms of NFTs can be identified. The shape of the NFT is probably determined by that of the neuron containing it. Ultrastructural investigation reveals that NFTs are composed of paired helical neurofilaments with a maximum diameter of 20 nm and a periodic narrowing to 10 nm every 80 nm. *(Davis, 1073–1076; Hart, 1–3)*

**56.** **(E)** This slide shows eosinophilic cytoplasmic neuronal inclusions corresponding to a Lewy body. Lewy bodies are seen in idiopathic Parkinson disease as well as in diffuse Lewy body disease. *(Davis, 38–41; Hart, 5)*

**57.** **(A)** This is a coronal brain section showing confluent petechial hemorrhages in the mammillary bodies consistent with Wernicke encephalopathy. It is caused by deficiency of thiamine. Lesions are usually discernible in the mammillary bodies, but may also involve parts of the hypothalamus, the medial thalamic nuclei, the floor of the third ventricle, the periaqueductal gray, the colliculi, the nuclei in the pontomedullary tegmentum (particularly the dorsal motor nuclei of the vagus), the inferior olives, and the cerebral cortex. Typically, the involved regions are slightly shrunken and show brown discoloration due to hemosiderin deposition, and there may be petechial hemorrhages. The periventricular and periaqueductal lesions often spare a slender strip of subependymal tissue. In some patients, particularly those with previously treated disease, the mammillary bodies may be only mildly discolored and other lesions may be inconspicuous. On microscopic examination, acute lesions are edematous, with relative preservation of neurons, variable necrosis of intervening tissue, and loss of myelinated fibers. Capillaries may appear strikingly prominent owing to endothelial hyperplasia and cuffing by macrophages. *(Davis, 536–538; Rushing, 9)*

**58.** **(D)** This patient's FLAIR MRI of the head shows a bright signal in the putamen area that correlates with the ischemic necrosis seen in the brain coronal section, which also shows a left putamen hemorrhagic lesion. Selective bilateral lesions of the putamen are highly suggestive of methanol intoxication. Acute methanol intoxication causes generalized edema of the brain, which usually shows features of global hypoxic injury. There may be scattered petechial hemorrhages and larger, symmetric foci of hemorrhagic infarction in the putamen and claustrum. Some patients develop extensive white matter necrosis. Degeneration of retinal ganglion cells results in optic nerve atrophy and gliosis. *(Davis, 520–521; Rushing, 9)*

**59.** **(B)** The slide in this picture illustrates agyria. It results from injury of the germinal cells as they reach the cortex and leads to abnormalities of gyral development. The thick cortical ribbon is disproportionately represented compared with the relative paucity of the centrum semiovale. The characteristic histological appearance is a four-layer cortex instead of the six layers of the normal neocortical pattern:

- A mMolecular layer
- A thin external neuronal layer
- A sparsely cellular layer with a tangential myelin fiber plexus
- A thick inner neuronal layer, which splits in its deeper zone into columns of cells

*(Davis, 294–296; Henry, 13–14)*

**60.** **(A)** The slide in this question illustrates polymicrogyria, which is characterized by a hyperconvoluted cortical ribbon of miniature, individually thin gyri, often fused together or piled on top of one another. The macrogyric cerebral surface is irregular and has been likened to cobblestones. Sections of the cerebrum reveal heaped up or submerged gyri that widen the cortical ribbon. Polymicrogyria may be

- Widespread in one or both hemispheres
- Bilateral and symmetric in a particular arterial territory (usually the middle cerebral artery)
- Confined to the opercular region or depths of the insula
- Around porencephalic or hydranencephalic defects
- Focal in almost any neocortical area except the cingulate or striate cortex

On microscopic examination, the cortical gray matter is abnormally thin and excessively folded; there is fusion of adjacent gyri and abnormal cortical lamination. *(Davis, 294–296; Henry, 14)*

**61.** **(C)** This picture illustrates an agenesis of the corpus callosum. *(Henry, 16)*

**62.** **(D)** The head CT of the patient shows a tumor with a gyriform pattern of calcification involving the left frontal lobe. The microscopic features of the tumor include cellular monotony and cells with round nuclei and perinuclear halos, resulting in the classic fried-egg appearance. These findings are highly suggestive of oligodendrioglioma. *(Parisi, 1–3)*

**63.** **(E)** The slide in this question shows a colloid cyst. Its location in the third ventricle, usually near the choroid plexus and foramen of Monro, helps to distinguish the colloid cyst from other cysts that superficially resemble it (enterogenous cysts, ependymal cysts, and Rathke's cleft cysts), but these occur in different locations. The simple columnar and cuboidal epithelium, which may be flattened to simple squamous epithelium, often contains a mixture of ciliated and nonciliated cells. *(Parisi, 10–11)*

**64.** **(A)** The slide in this question shows psammoma bodies from a psammomatous meningioma. Meningothelial whorls and psammoma bodies typify meningiomas. Psammoma bodies are concentrically laminated calcifications and are crowded with psammoma bodies. They are often spinal in location. This benign variant is recognized as meningioma by finding syncytial cells between the conspicuous, concentrically laminated psammoma bodies. *(Davis, 212)*

**65.** **(A)** The slide in this question demonstrates a normal muscle. Normal frozen muscle stains for ATPase at pH 9.4, and this differentiates type I from type II fibers. At an alkaline pH, the type II fibers are dark and the type I fibers are light. There is a normal mosaic pattern of both types of fibers with approximately two thirds being type II and one third type I. *(Heffner, 1–13)*

**66.** **(B)** The slide in this question illustrates central core disease. This is an autosomal dominant disorder and the gene defect is located on chromosome 19. Mutation on the ryanodine receptor contains a Ca release channel. Type I fibers have a central pale area representing the lack of oxidative enzymes. The core tends to be single and central within the affected fiber. Structured cores have preserved cross banding, whereas unstructured cores have lost their cross binding. *(Heffner, 1–13)*

**67.** **(C)** The slide in this question shows nemaline rod myopathy, a congenital myopathy of autosomal or recessive inheritance. The diagnosis is suggested by the variable number of rods in the trichome stains. *(Heffner, 1–13)*

**68.** **(C)** The slide in this question shows target fibers in a denervating disease. Target fibers are seen in atrophic fibers and consist of central nonstaining areas surrounded by a darkened rim of oxidative enzymes. *(Heffner, 1–13)*

**69.** **(D)** The slide in this question shows panfascicular atrophy, suggestive of infantile muscular atrophy. *(Heffner, 1–13)*

**70.** **(E)** The slide in this question shows the perifascicular atrophy of dermatomyositis. *(Heffner, 1–13)*

**71.** **(E)** The slide in this question shows lymphocytes infiltrating the endomysium between fibers, suggesting the diagnosis of polymyositis. *(Heffner, 1–13)*

**72. (D)** The slide in this question shows a modified Gomori trichome stain of mitochondrial myopathy, which stains the mitochondria red, hence the term *ragged-red fibers*. *(Heffner, 1–13)*

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CHAPTER 16

# Neuroradiology
## Questions

**1.** These studies show

(A) infarction of the right middle cerebral artery
(B) bilateral infarction of the anterior cerebral artery
(C) infarction of the right anterior cerebral artery
(D) bilateral infarction of the middle cerebral artery
(E) subdural hematoma

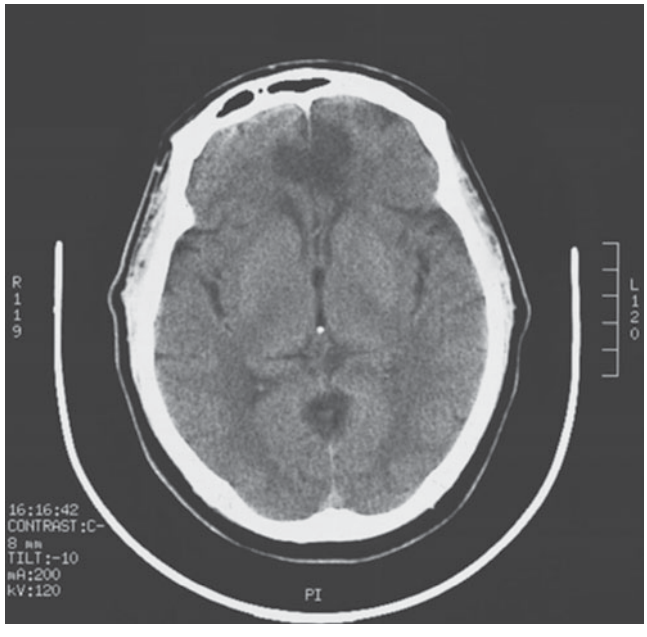


FIG. 1A

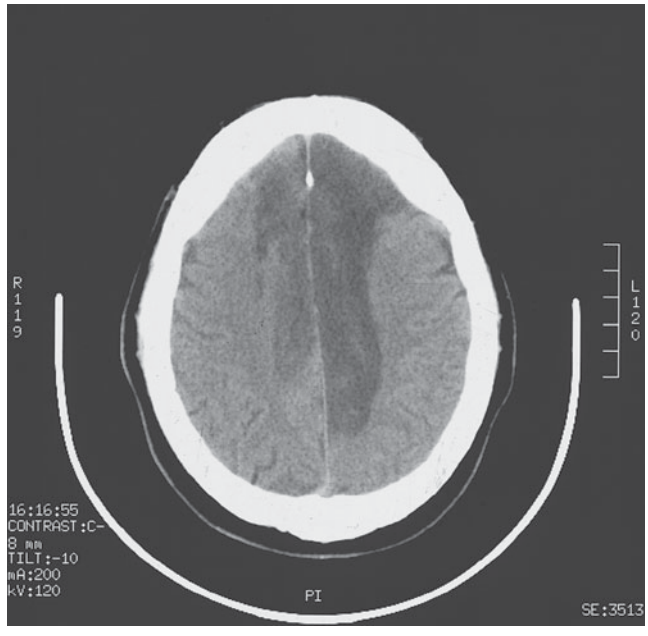


FIG. 1B

**2.** These are magnetic resonance images (MRIs) of the head of a 43-year-old man with a history of progressive ataxia. The most likely diagnosis is

(A) pilocytic astrocytoma
(B) hemangioblastoma
(C) medulloblastoma
(D) metastatic tumor
(E) meningioma

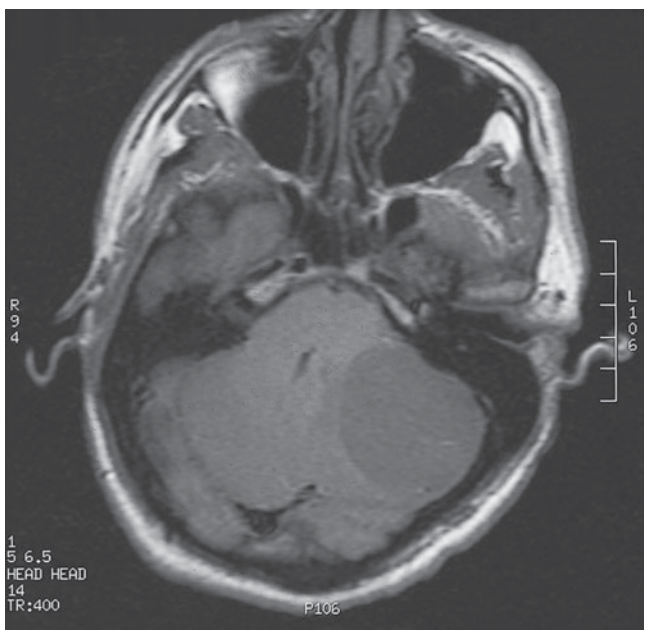


FIG. 2A

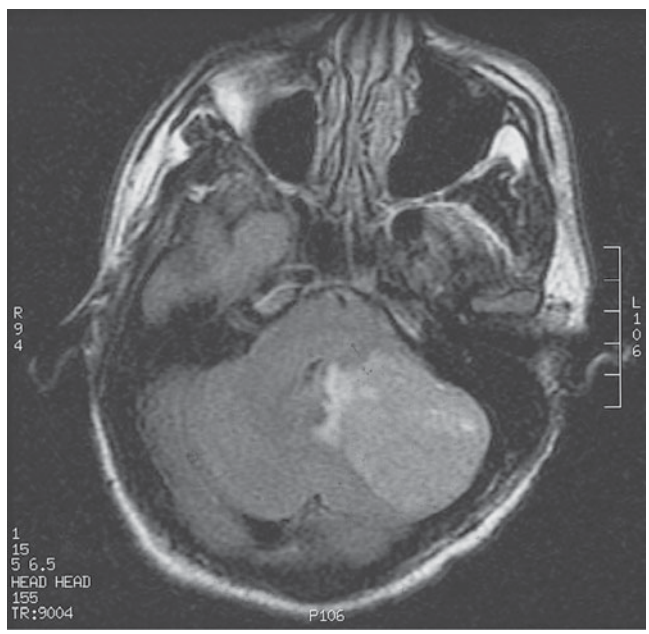


FIG. 2C

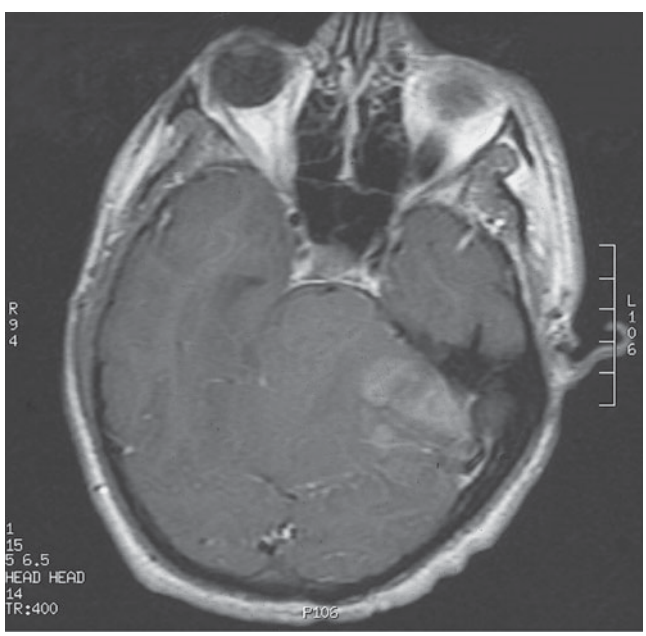


FIG. 2B

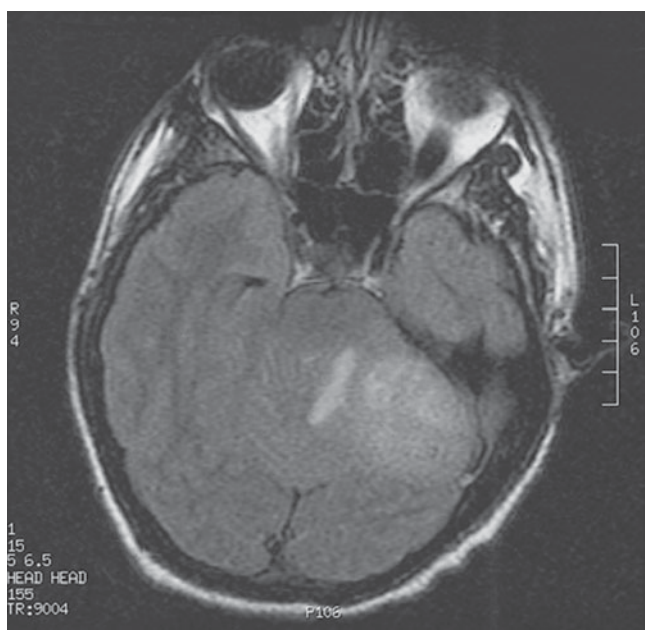


FIG. 2D

**3.** These images show the head MRI of a 65-year-old man who became acutely confused. The most likely diagnosis is

(A) amyloid angiopathy
(B) metastatic lung cancer
(C) metastatic melanoma
(D) glioblastoma multiforme
(E) hemorrhagic stroke

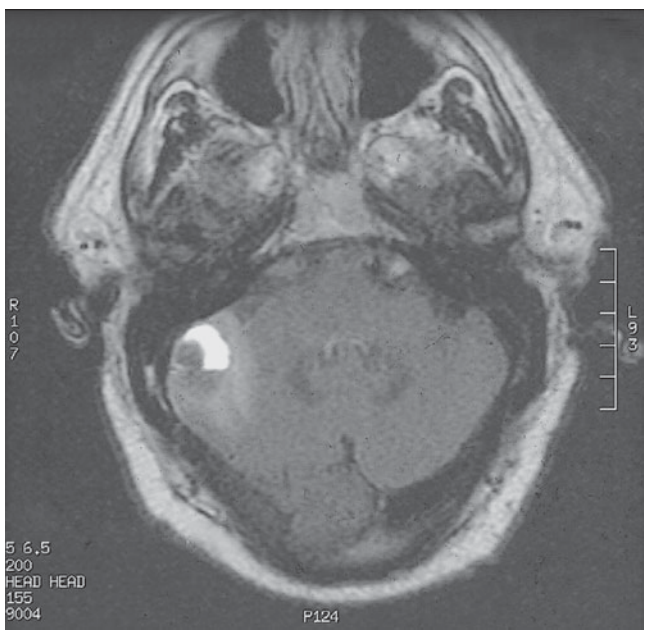


FIG. 3A

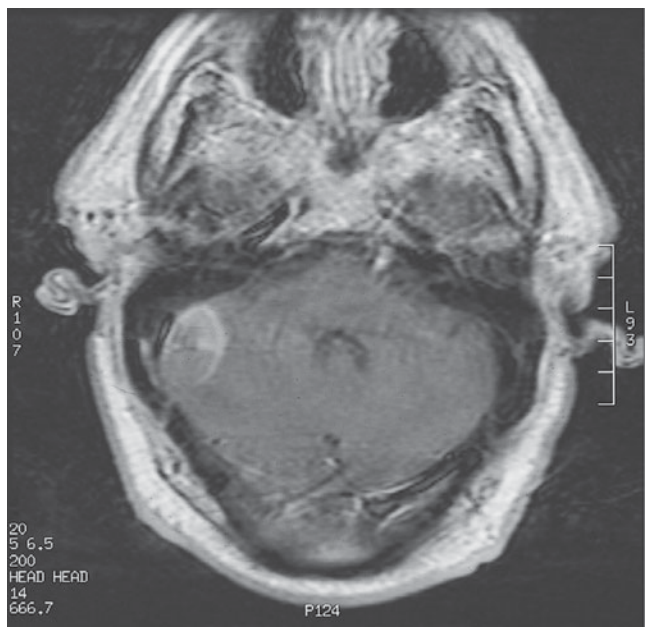


FIG. 3C

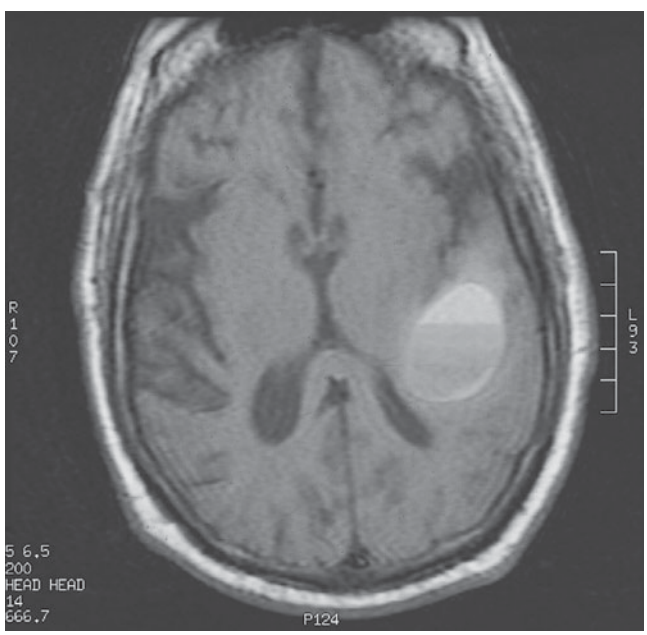


FIG. 3B

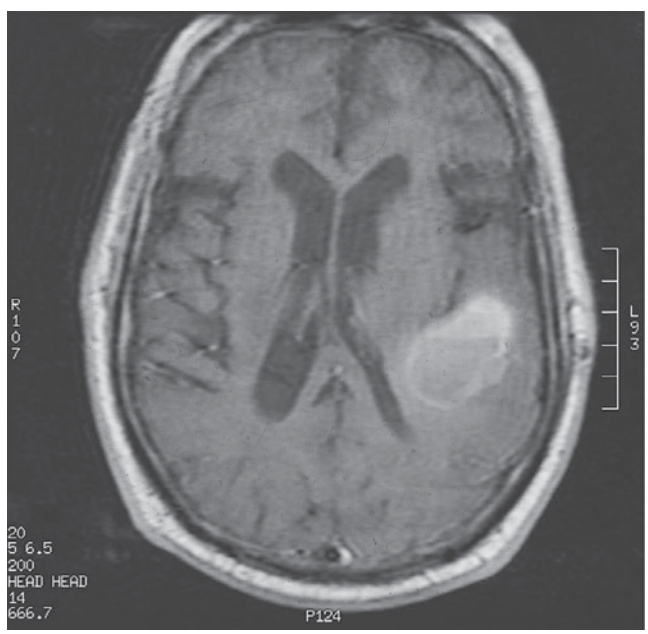


FIG. 3D

**4.** These are T1-weighted images of a gadolinium-enhanced head MRI of a 50-year-old asymptomatic man. The most likely diagnosis is

(A) anterior cerebral artery aneurysm
(B) arachnoid cyst
(C) ependymoma
(D) metastasis
(E) meningioma

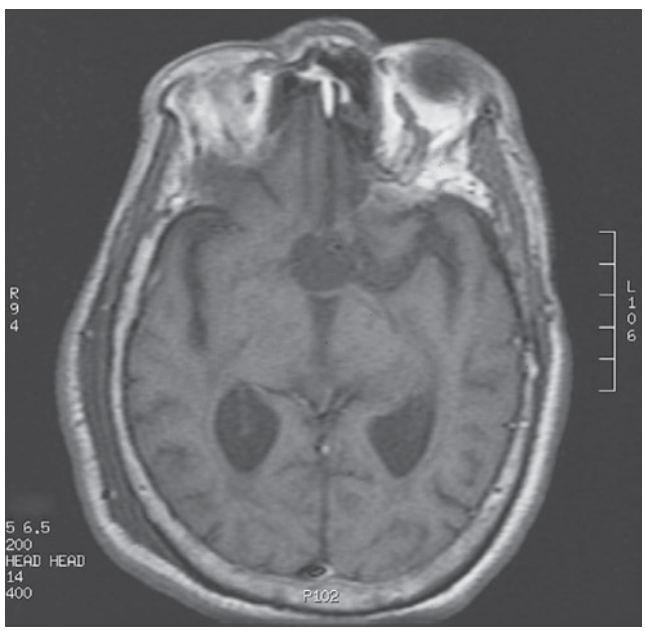


FIG. 4A

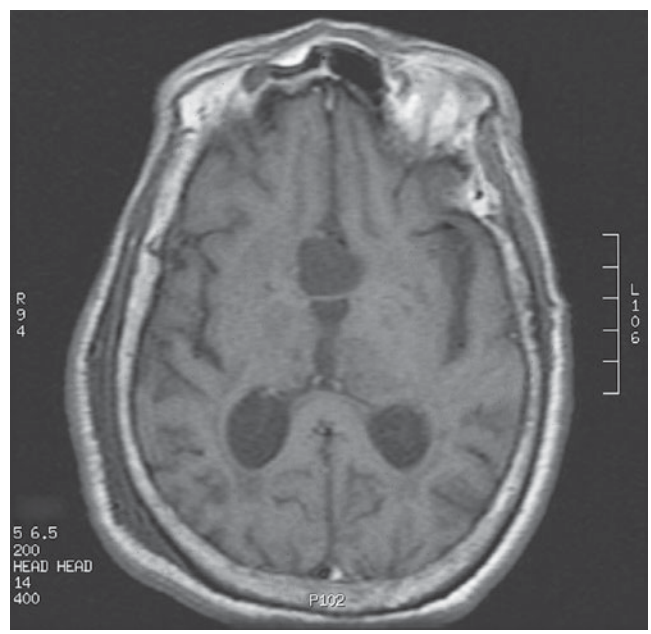


FIG. 4B

**5.** Which of the following clinical manifestations would one expect to see in a 56-year-old man with the following head MRI?

(A) Left-sided weakness
(B) Left oculomotor palsy
(C) Anosmia
(D) Left facial palsy
(E) Vertical gaze palsy

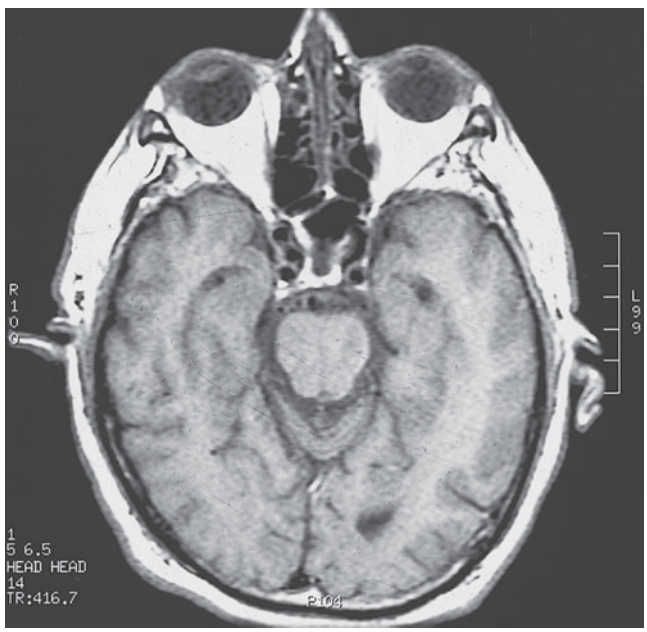


FIG. 5A

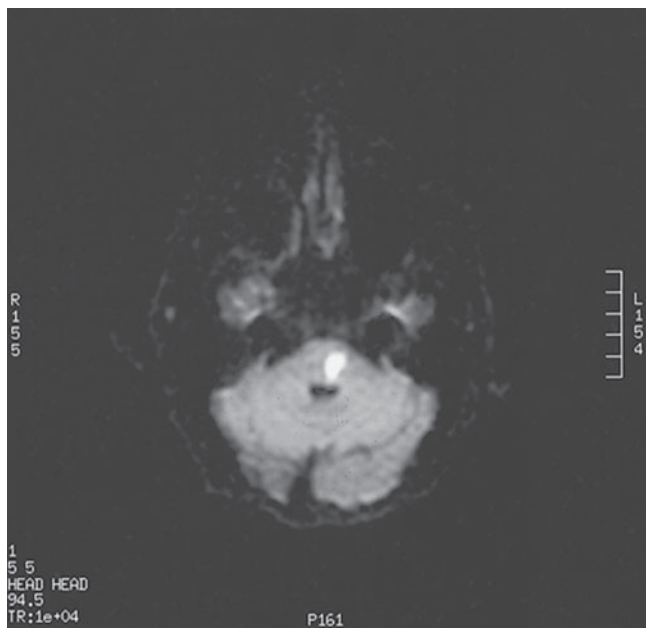


FIG. 5C

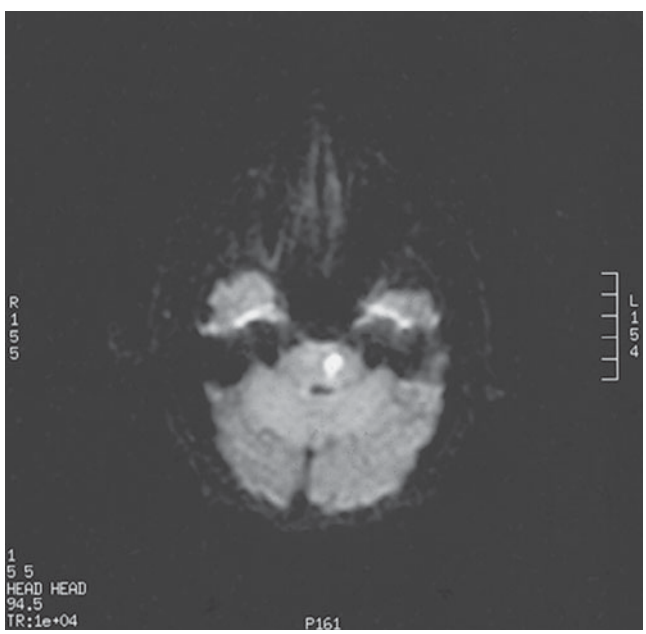


FIG. 5B

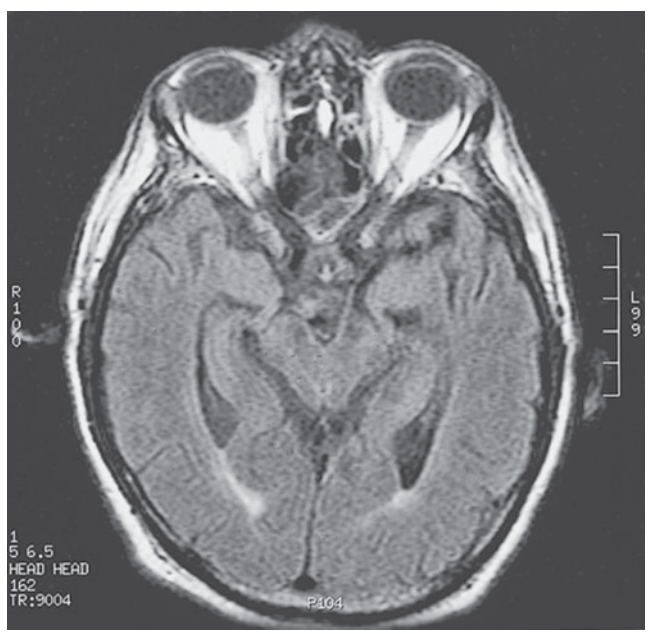


FIG. 5D

**6.** The most likely diagnosis suggested by this head MRI is

(A) craniopharyngioma
(B) pituitary adenoma
(C) thrombosed aneurysm
(D) brain metastasis
(E) primary central nervous system (CNS) lymphoma

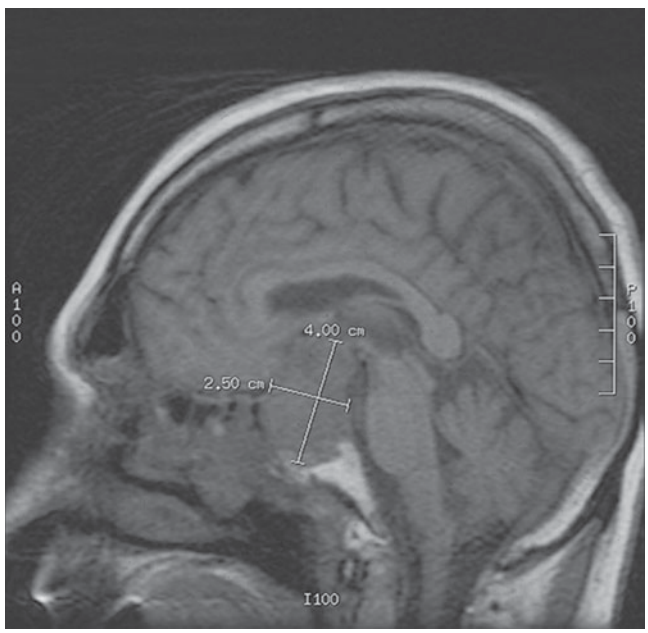


FIG. 6A

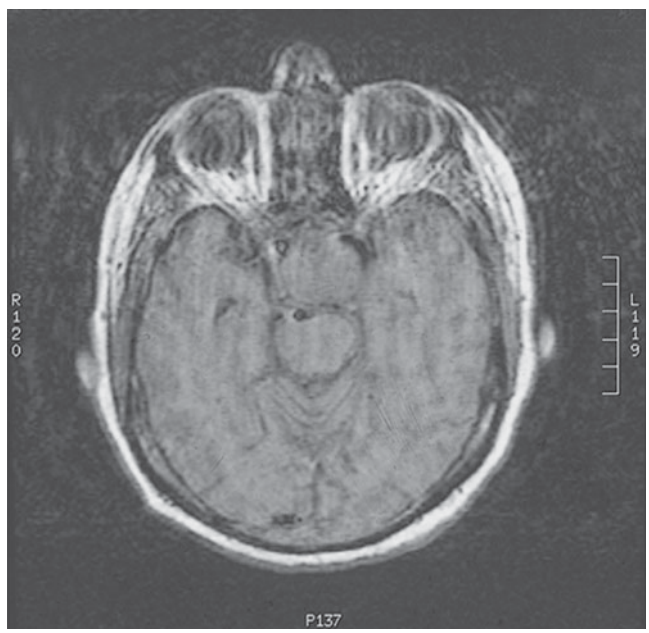


FIG. 6C

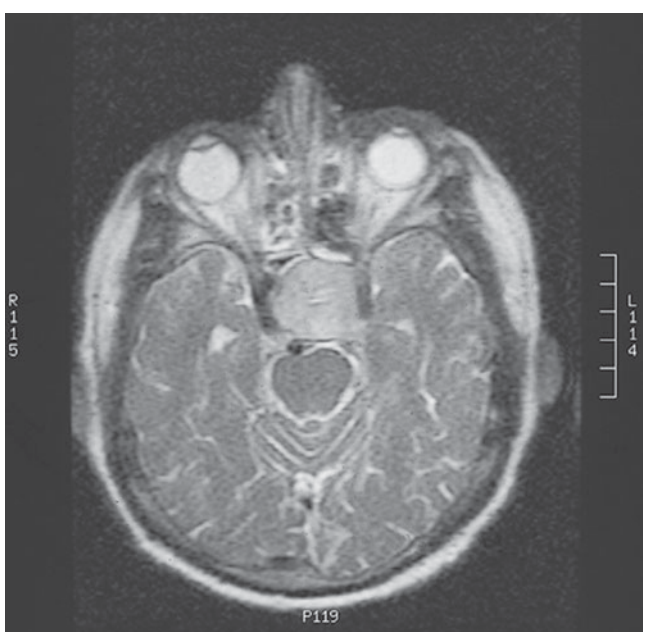


FIG. 6B

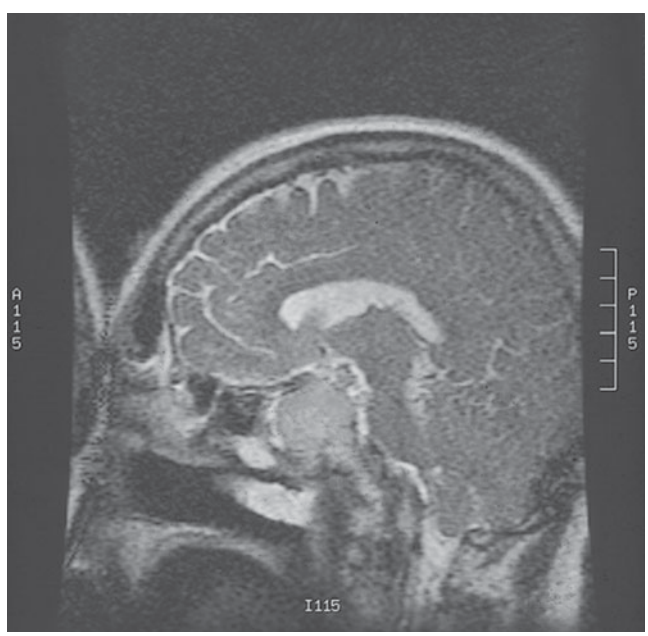


FIG. 6D

**7.** This head MRI of a newborn baby girl at 38 weeks' gestation shows

(A) cystic encephalomalacia
(B) lissencephaly
(C) polymicrogyria
(D) schizencephaly
(E) focal cortical dysplasia

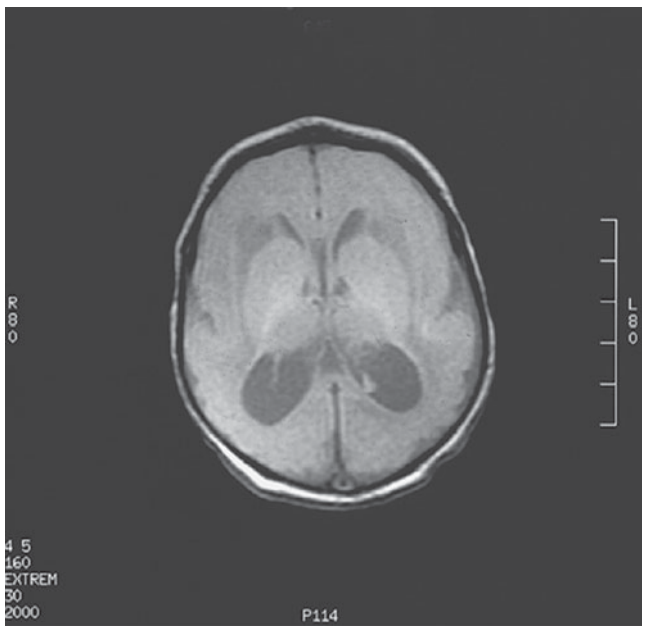


FIG. 7A

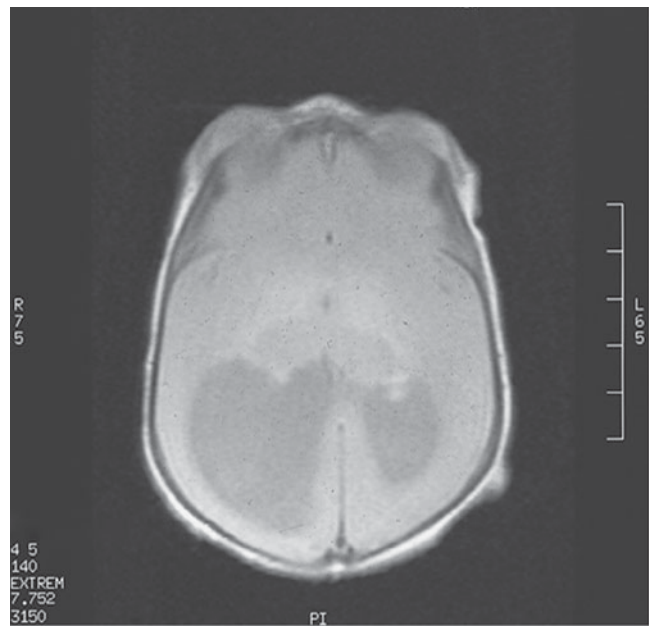


FIG. 7B

**8.** These are the imaging studies of an 80-year-old man with an acute onset of left-sided weakness and slurred speech. The most likely diagnosis is

(A) metastatic melanoma
(B) metastatic choriocarcinoma
(C) cavernous hemangiomas
(D) arteriovenous malformation
(E) aneurysm

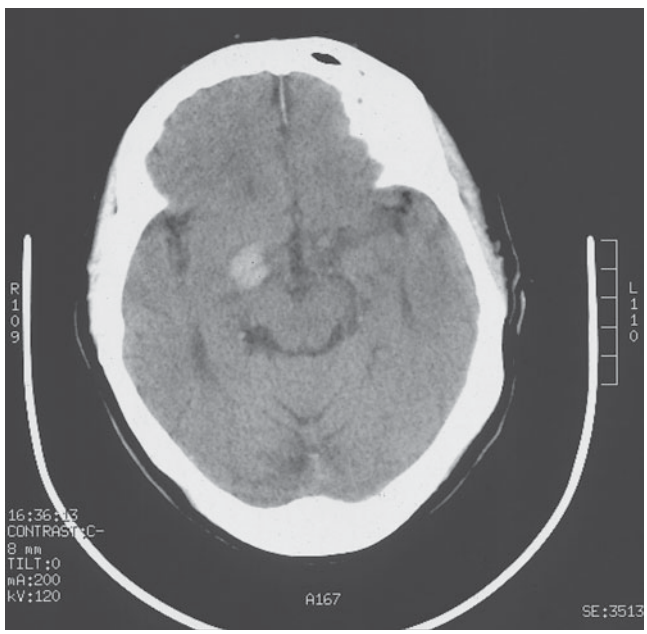


FIG. 8A

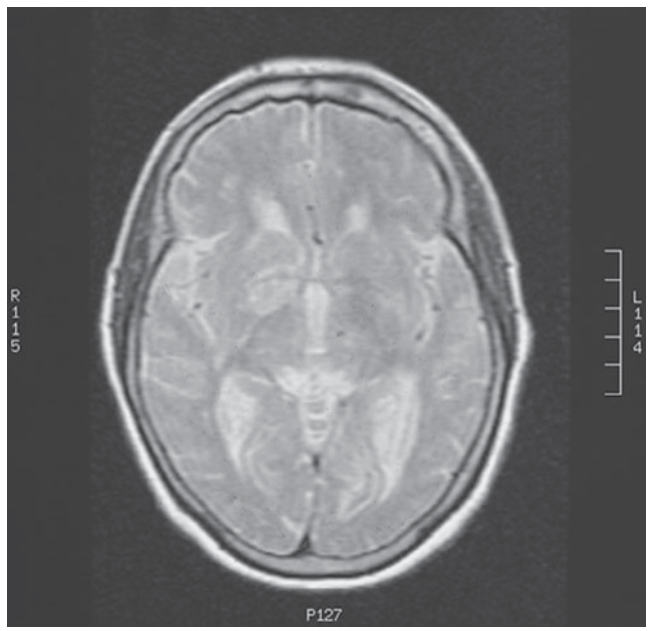


FIG. 8C

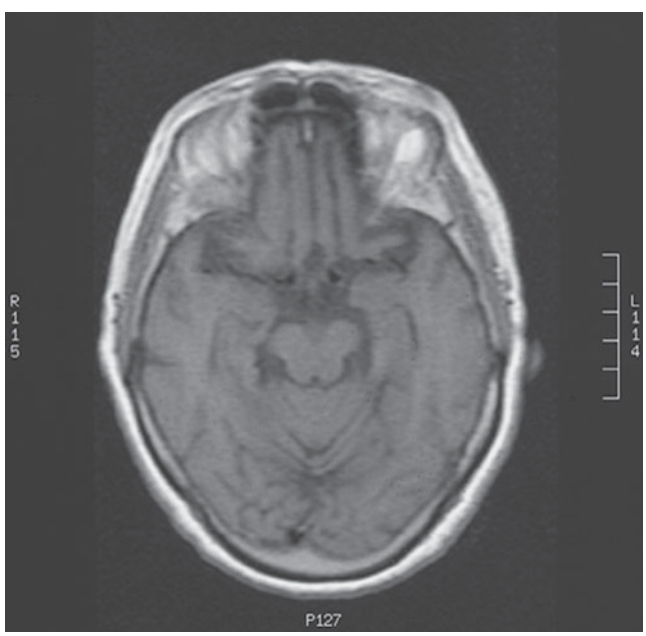


FIG. 8B

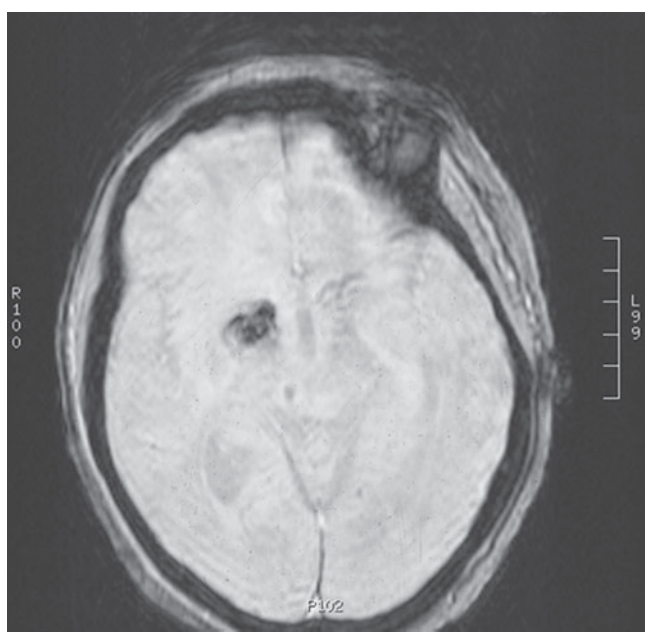


FIG. 8D

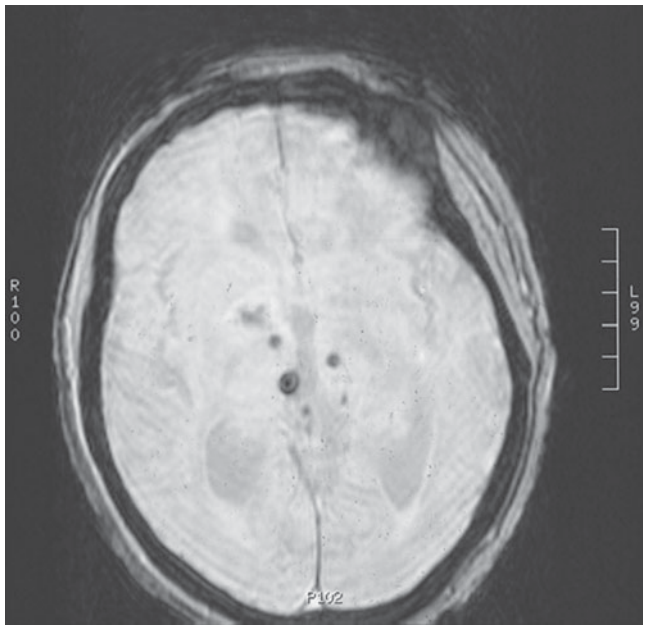


FIG. 8E

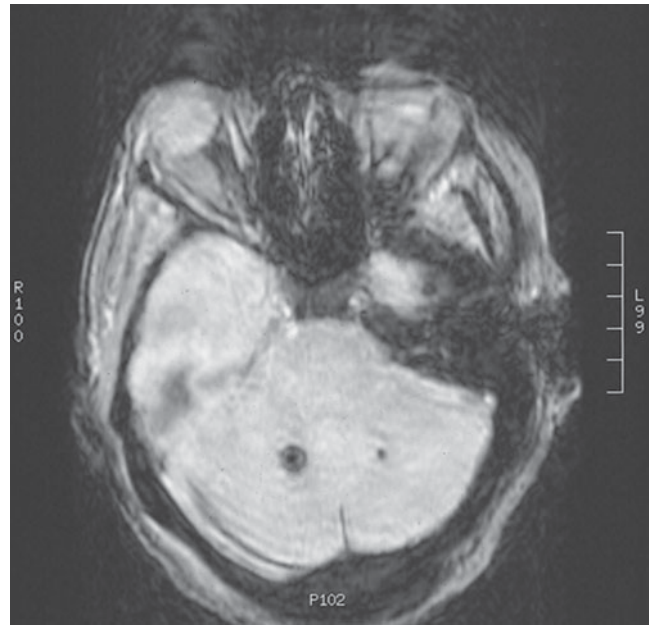


FIG. 8G

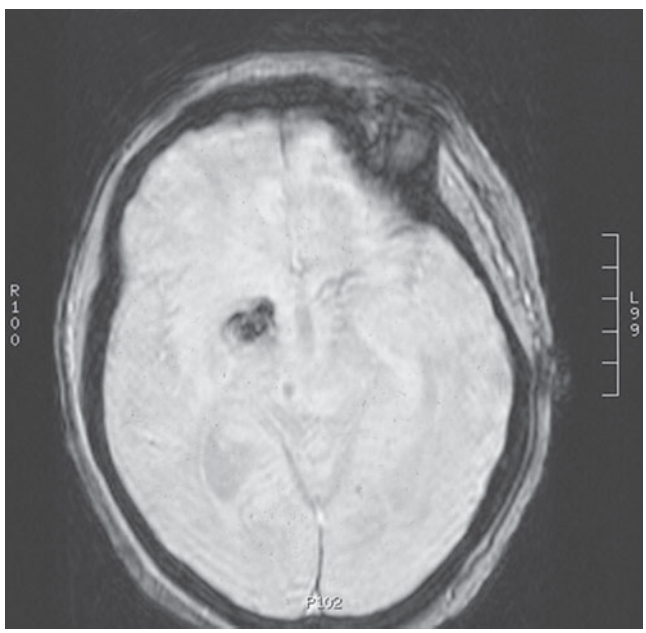


FIG. 8F

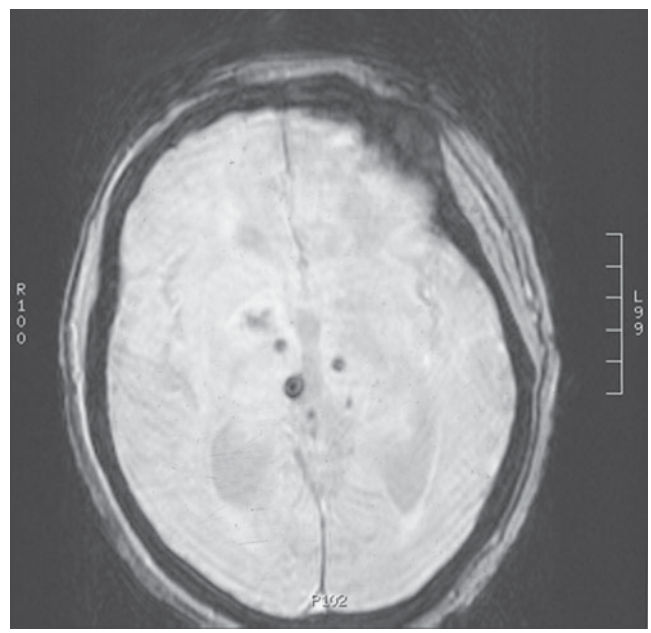


FIG. 8H

**9.** These are computed tomography (CT) images and MRIs of a 39-year-old woman with a history of AIDS who developed progressive left-sided weakness. The most likely diagnosis is

(A) progressive multifocal leukodystrophy (PLM)
(B) CNS lymphoma
(C) brain metastasis
(D) glioblastoma multiforme
(E) bacterial abscess

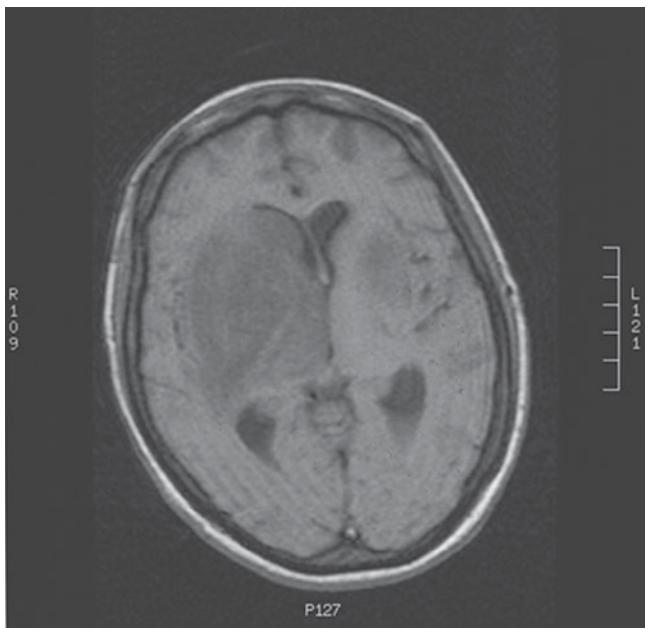


FIG. 9A

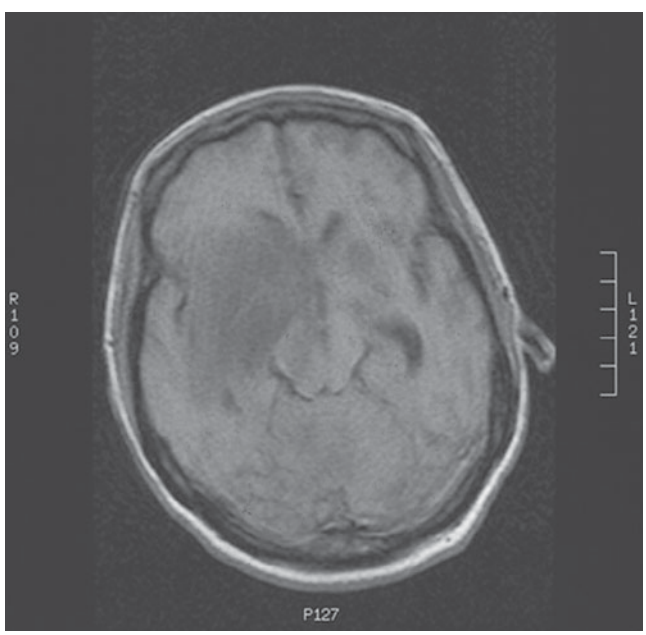


FIG. 9B

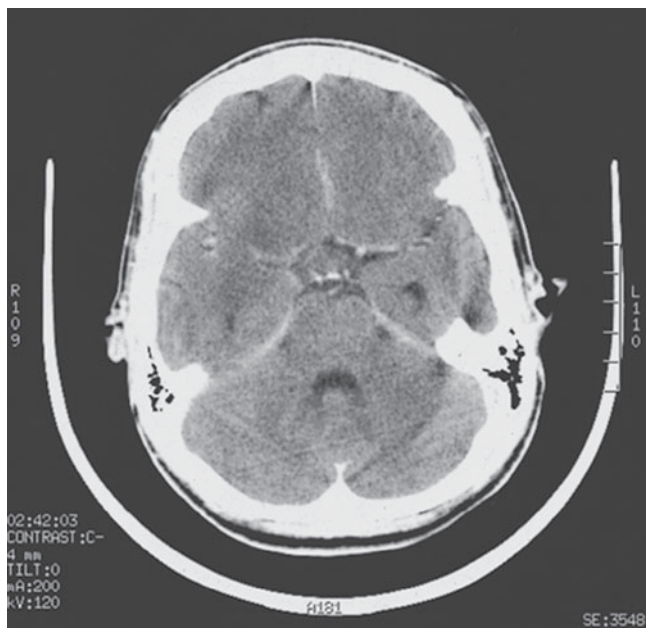


FIG. 9C

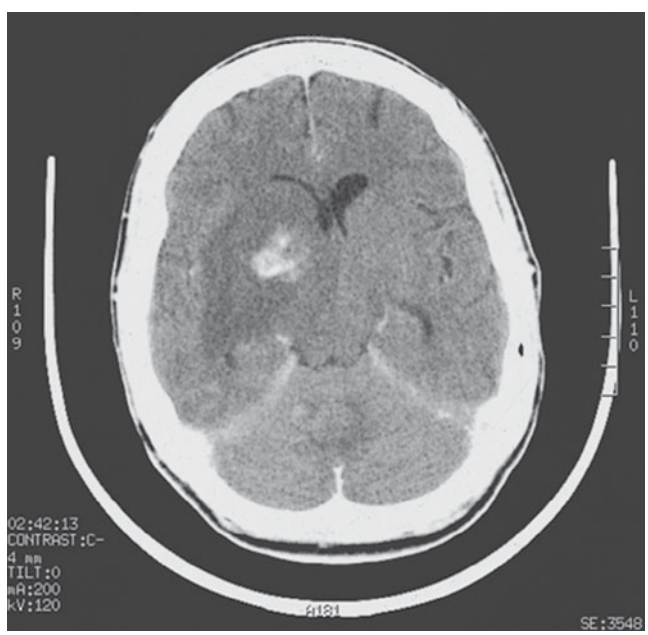


FIG. 9D

**10.** This is a head CT and MRI of a 62-year-old woman with no past medical history who was hospitalized with a chief complaint of change in her mental status. The most likely diagnosis is

(A) brain metastasis
(B) meningioma
(C) aneurysm
(D) oligodendroglioma
(E) pilocytic astrocytoma

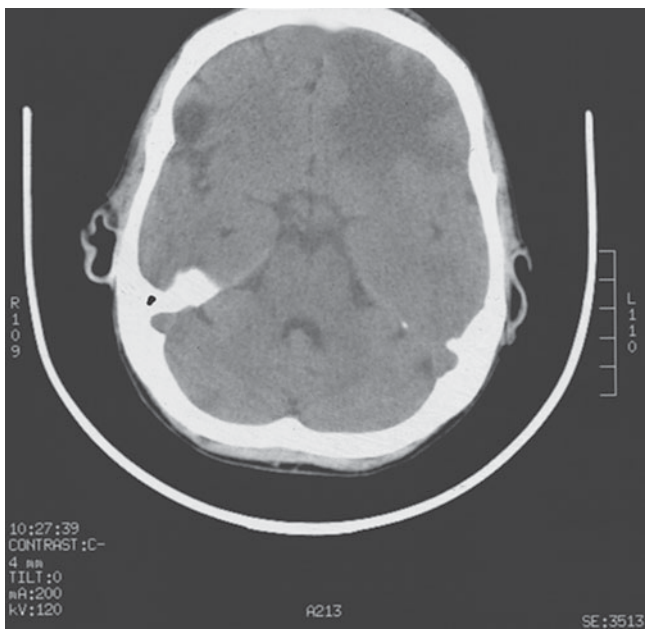


FIG. 10A

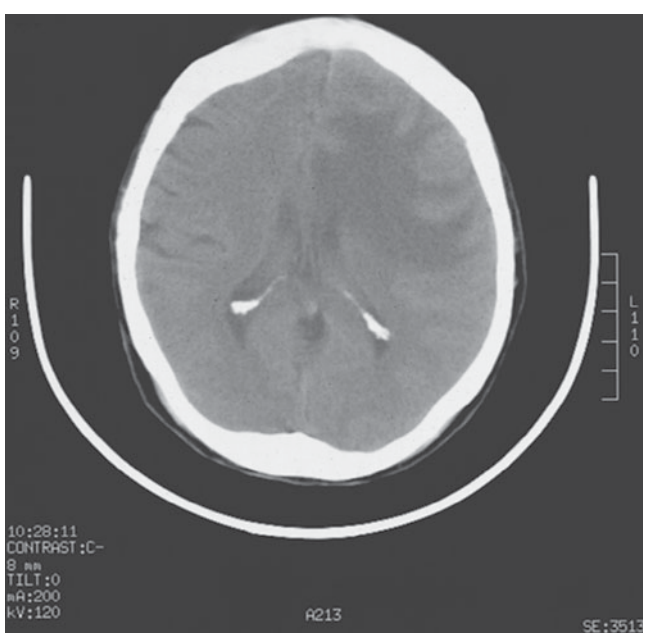


FIG. 10B

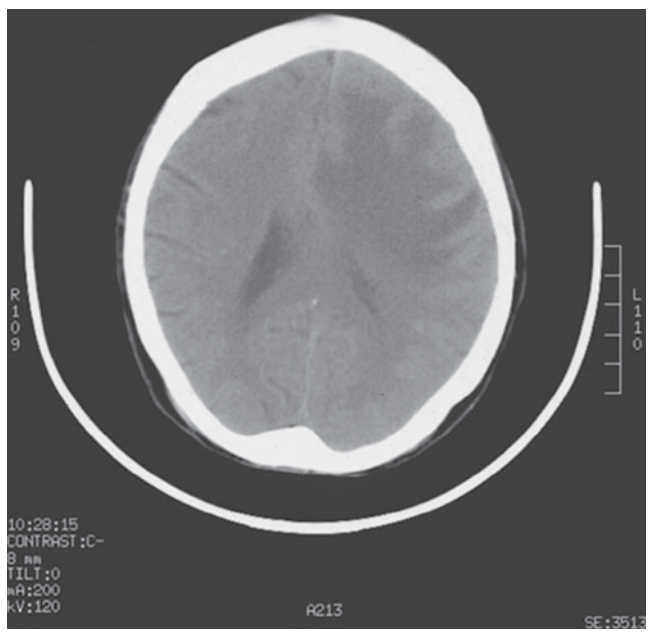


FIG. 10C

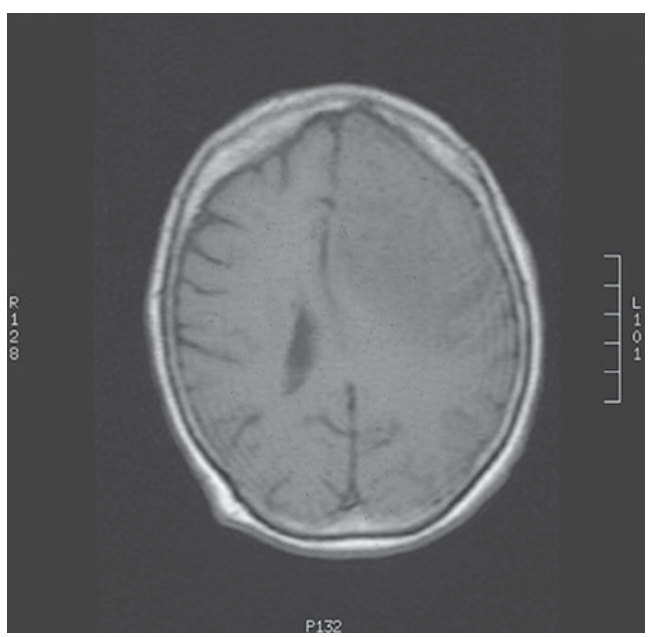


FIG. 10D

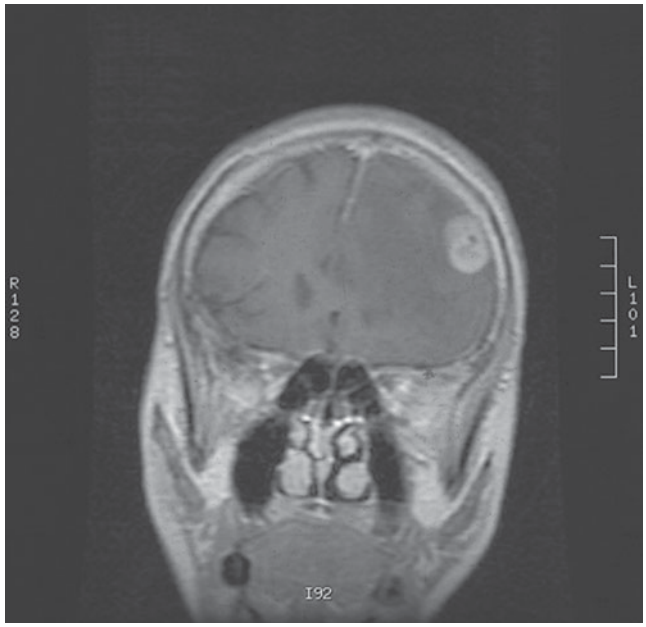


FIG. 10E

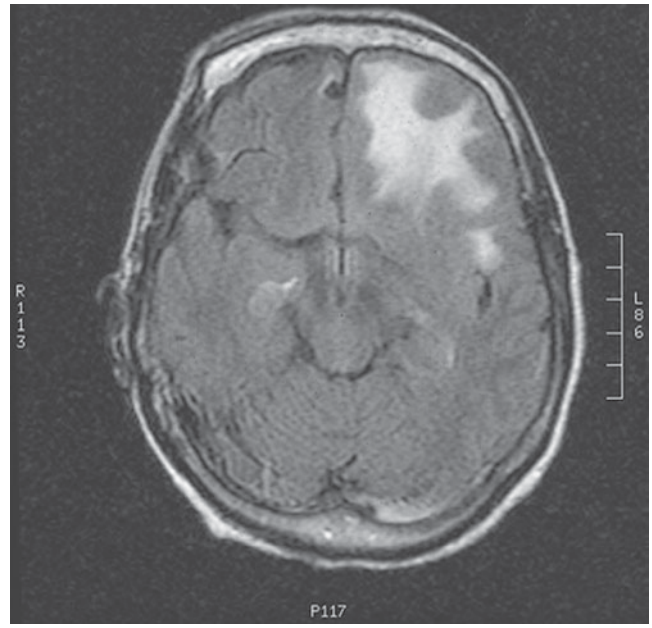


FIG. 10G

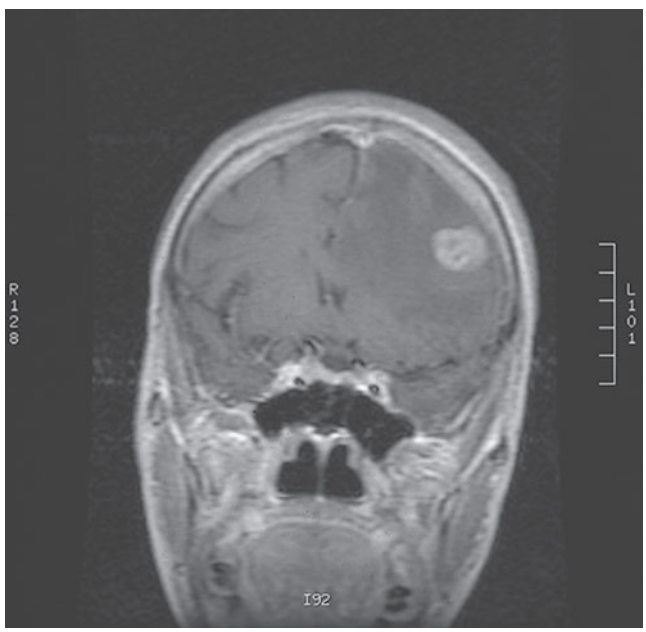


FIG. 10F

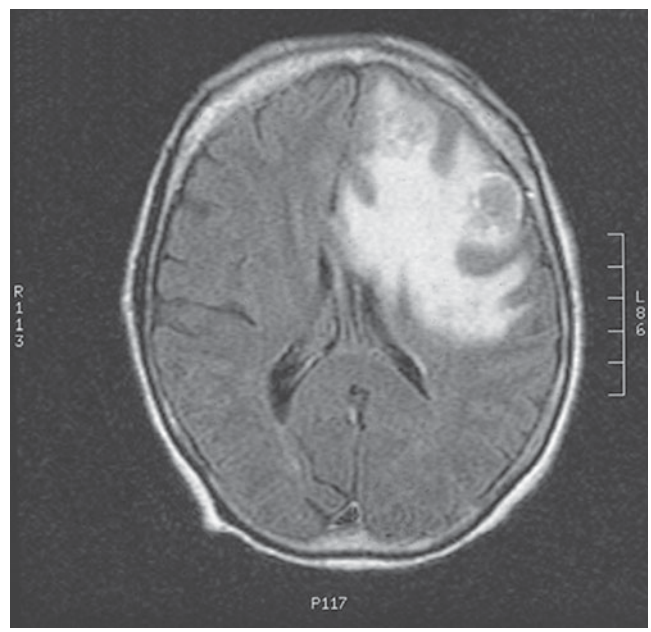


FIG. 10H

**11.** This is the imaging study of a 20-year-old woman with a new onset of acute headache, subacute fever, and new-onset seizures. The most likely diagnosis is

(A) normal head MRI
(B) viral meningitis
(C) left anterior cerebral artery stroke
(D) superior sagittal sinus thrombosis
(E) cortical dyplasia

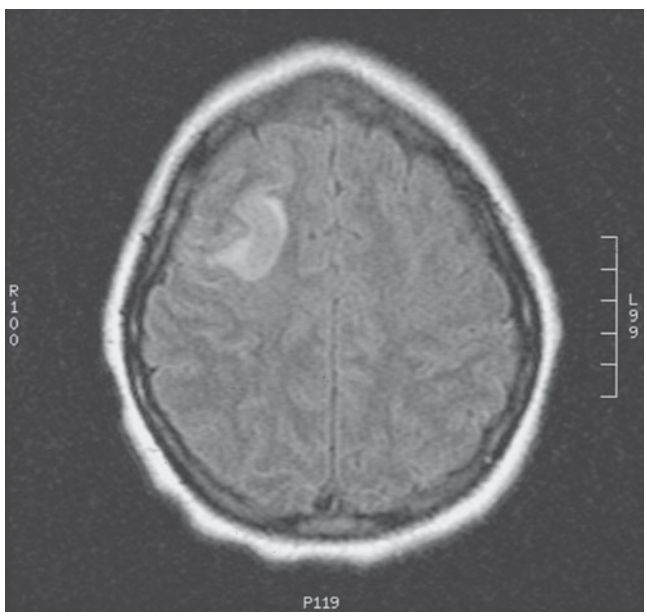


FIG. 11A

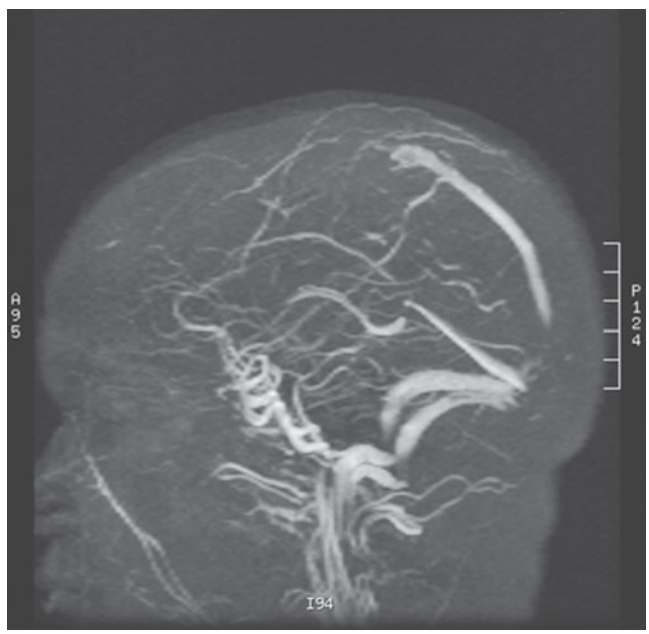


FIG. 11C

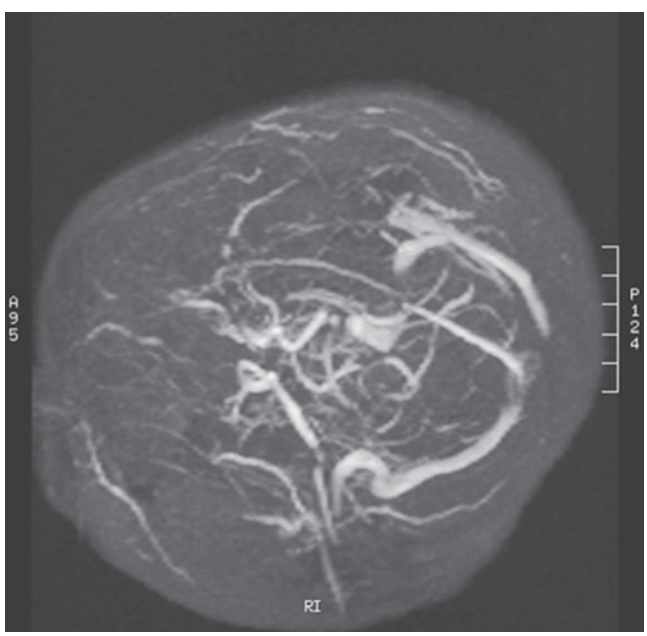


FIG. 11B

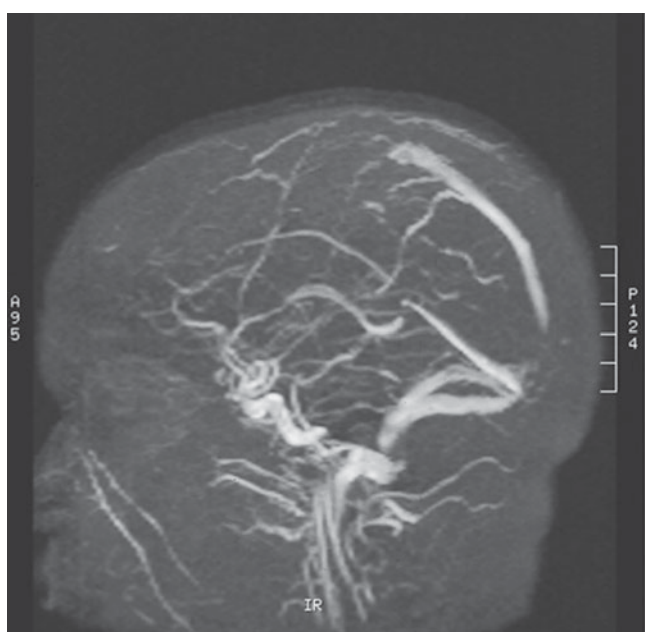


FIG. 11D

# Answers and Explanations

**1.** **(B)** This is an unenhanced CT scan of the head. It shows a large area of hypodensity within the left medial frontal lobe. There is a similar region of hypodensity within the right medial frontal region, which is smaller in size. These findings are typical of evolving infarcts within the territory of the left and right anterior cerebral arteries (ACAs). There is no mass or midline shift. The basal cisterns are intact. The ventricles are normal in size and shape.

Infarction in the ACA distribution is uncommon and bilateral infarction is rare. ACA infarctions are cortical or subcortical and are caused by embolism. The clinical spectrum of unilateral infarction in the ACA territory is broad and may include disinhibition and hemiparesis predominant in the leg. Bilateral infarction in the ACA territories causes a profound neurological syndrome, highlighted by akinetic mutism and poor recovery. *(Minagar, 886)*

**2.** **(D)** These are multiple axial images of the brain MRI, with and without contrast. There is a left cerebellar mass with low signal intensity on T1-weighted images, demonstrating minimal enhancement. This mass causes compression of the fourth ventricle. There is also increased signal intensity in the subependymal region, consistent with transependymal resorption of cerebrospinal fluid (CSF). The lateral and third ventricles are dilated. These findings are consistent with obstructive hydrocephalus.

This profile is suggestive of a metastatic tumor. Most brain metastases that present with an unknown primary tumor stem from lung cancer. A more extensive search for the primary tumor does not appear to improve overall survival. The search for a primary tumor should focus on tumors that are sensitive to systemic treatment. MRI is superior to (CT for the detection of metastatic disease. *(Van den Bent, 717–723)*

**3.** **(C)** MRI examination of the brain parenchyma demonstrates a right cerebellar lesion with a fluid level, surrounding edema, and minimal gadolinium enhancement. There is a lesion with a left posterior temporal fluid level and surrounding edema as well as mass effect on the posterior horn of the left lateral ventricle. There are multiple intracranial lesions demonstrating fluid levels and hemorrhagic components consistent with hemorrhagic metastasis.

Cerebral metastases from melanoma, renal cell carcinoma, thyroid carcinoma, and choriocarcinoma have a propensity to bleed. Although metastases from breast and lung cancer are less prone to bleed, a cerebral hemorrhagic metastasis is still more likely to originate from lung or breast cancer because these are the most frequently occurring malignancies. A single cerebral hemorrhagic mass should lead one to suspect a primary brain tumor such as glioblastoma multiforme. *(Grossman, 79–82)*

**4.** **(B)** This image shows a 2-cm nonenhancing suprasellar mass. It is rounded, with regular borders, and has signal characteristics similar to those of CSF. These characteristics are consistent with an arachnoid cyst.

Arachnoid cysts are usually congenital malformations derived from the meninx primitiva. Their most common location is the midcranial fossa. Less commonly, they may be seen in the cerebral convexities, the basal cisterns, and the retrocerebellar region. They result from a splitting of normal arachnoid membranes by congenital

aberrations of increased CSF pulsatile flow. They constitute 1% of all intracranial space-occupying lesions. On MRI, an arachnoid cyst follows the intensity of the CSF with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. The major differential diagnosis with arachnoid cyst is epidermoid cyst. The latter may show an internal matrix on T1-weighted nonenhanced MRI and hyperintense signal compared with CSF on FLAIR images. *(Grossman, 247–249; Pollice, 764–765)*

5. **(D)** This is an MRI study with T1-weighted, T2-weighted, FLAIR-, and diffusion-weighted images. There are areas of abnormal signal present on the FLAIR-weighted images in the pons; the left inferior pons is particularly bright on the diffusion-weighted images. The abnormal signals on the FLAIR- and T2-weighted images in the periventricular deep white matter, which are not seen on diffusion, correspond to small vessel ischemic changes. The ventricular system is normal in size and is midline. The subarachnoid spaces are unremarkable. These findings are compatible with the diagnosis of acute left pontine ischemic stroke.

   Clinical symptoms of pontine stroke are variable and depend on the location and extent of the ischemic damage. In a ventral pontine infarct, motor symptoms vary from mild hemiparesis in a small ventrolateral pontine infarction to contralateral hemiplegia with dysarthria and ataxia in a ventromedial infarction. Tegmental pontine lesions may cause sensory disturbances and ipsilateral cranial nerve dysfunction, such as facial palsy. Basilar artery branch disease is more commonly associated with pontine stroke than cardioembolism or large artery stenosis. Large ventral infarcts carry the worst prognosis. *(Bassetti, 165–175)*

6. **(B)** This is a head MRI study with T1- and T2-weighted images, including sagittal and coronal sections. It shows a large (4.0 by 2.5 cm) pituitary sellar mass, with suprasellar extension and bowing into the sphenoid sinus that has intermediate signal on T1 and T2. The mass protrudes ventrally into the sphenoid sinus and superiorly compresses the optic chiasm. There is no evidence of chronic hemorrhage or methemoglobin. This lesion is most consistent with pituitary macroadenoma. MRI of the sellar and parasellar regions is the imaging study of choice for the diagnosis of pituitary adenoma. The size of the pituitary gland is variable and depends on the age and sex of the patient. The maximum height allowed for the pituitary gland is 12 mm in women in late pregnancy and postpartum, 10 mm in other women of childbearing age, 8 mm in men and postmenopausal women, and 6 mm in children. Microadenomas are more common than macroadenomas; their MRI detection rate varies from 65% to 90%. MRI signs of microadenomas may include hypointensity on T1-weighted sequences, focal enlargement of the gland, and sella floor thinning or erosion. In case of macroadenomas, head MRI may show sellar enlargement in 94% to 100% of cases. It may also show a lobulated pituitary margin. MRI of the pituitary gland is a useful tool in defining the extent of a pituitary mass to the cavernous sinus and in following the effect of medical treatment on the size of the macroadenoma. *(Anderson, 703–721)*

7. **(B)** MRI of the brain shows a decrease in sulcation over the temporal, frontal, and right occipital lobes consistent with the diagnosis of lissencephaly. The ventricular system is in the midline. There is dilatation of both lateral ventricles; the right lateral ventricle is significantly more dilated than the left. Especially dilated are the occipital horns of both lateral ventricles. Lissencephaly is divided into two types based on histological criteria, extent of damage, and clinical features. In both types, the brain appears smooth on gross inspection. In lissencephaly type 1, the neocortex has 4 poorly organized layers instead of 6 well-organized layers. In type 2 lissencephaly, the cortex is unlayered, with a cobblestone surface and thickened meninges. The clinical spectrum of lissencephaly is heterogeneous and may include seizures, motor delay, hypotonia, and mental retardation. *(Porter, 361–365)*

8. **(C)** Figure 16-8A is a head CT upper left image without contrast. It shows a lesion approximately 1.2 cm in diameter with hyperdensity along the region of the genu of the right internal

capsule. This represents hemorrhage. There is no subarachnoid hemorrhage and no associated mass lesion. The rest of the imaging study comprises head MRI images that include T1, proton density, gradient-echo, and T2-weighted images. Gradient-echo images demonstrate multiple foci of markedly decreased signal. These are consistent with hemosiderin staining, likely related to multiple cavernous hemangiomas. Cavernous hemangioma is a benign vascular lesion that may occur at any site within the CNS. It is formed by ectatic endothelium-lined channels without mural muscular or elastic fibers and without any neuronal elements. It does not have a direct high-pressure arterial supply or distinct venous drainage, which distinguishes cavernous hemangioma from arteriovenous malformation. It is characterized, on T2-weighted MRI, by a reticulated core of mixed signal representing blood various state of degradation surrounded by a hypointense halo due to hemosiderin. *(Moran, 561–568)*

**9.** **(B)** This imaging study shows a contrast-enhancing lesion within the right basal ganglion with significant vasogenic edema and mass effect on the surrounding structures; there is compression of the anterior horn of the right lateral ventricle and midline shift. These findings are suggestive of either toxoplasmosis or lymphoma and less likely PLM. These three diagnoses are particularly increased in frequency in AIDS, whereas bacterial abscess, glioblastoma multiforme, and bacterial metastasis are not. Primary CNS lymphoma (PCNSL) accounts for 1% to 1.5% of all primary brain tumors. It is a common complication in HIV patients and occurs in as many as 20%. The most common presenting signs of PCNSL are altered level of consciousness, focal neurological deficits, and seizures. Radiological signs of PCNSL may include a homogeneous enhancing lesion on CT in the central gray matter or corpus callosum or a ring-enhancing lesion. Head MRI is more sensitive than CT for detecting CNS lymphoma. Most lesions are located close to the ependymal or meningeal areas. The main differential diagnosis of PCNSL in HIV patient is CNS toxoplasmosis and progressive multifocal leukoencephalopathy. Lesions in CNS toxoplasmosis may tend to include more multiple enhancing lesions of smaller size than PCNSL on CT. Positron emission tomography (PET) or single photon emission CT (SPECT) scanning can help confirm the diagnosis. Biopsy is now rarely performed. *(Ciacci, 213–221)*

**10.** **(A)** The head CT scan of this patient shows a large region of hypoattenuation within the anterior left frontal region, suggesting the presence of edema with mass effect on the lateral ventricle and a shift of the midline. MRI examination of the brain shows, within the superior left frontal lobe, in homogeneously enhancing lesions with edema and mass effect as well as minimal midline shift. These findings are suggestive of brain metastasis.

Brain metastasis is the most common cause of an intracranial mass in adults. It is an important cause of morbidity and mortality in cancer patients. These lesions are found at autopsy in approximately 25% of patients who die of cancer. Metastases are often multiple; however, in 30% to 50% of cases they may be solitary lesions on brain imaging. Cancers of the lung, breast, skin, kidney, and thyroid frequently metastasize to the brain. Most patients who present with a brain metastasis of unknown origin suffer from lung cancer. The typical location of brain metastasis is the gray–white matter junction because tumor cells lodge in the small-caliber vessels in this location. Head MRI with contrast is the imaging technique of choice in detecting brain tumors. It is more sensitive than head CT with contrast in detecting brain metastasis. A metastatic brain lesion typically appears as an enhanced, rounded, and circumscribed mass surrounded by a disproportionate vasogenic edema, which shows up as an increased signal on T2-weighted images. *(Van den Bent, 717–723)*

**11.** **(D)** The FLAIR head MRI of this patient shows a serpiginous right frontal hyperintensity signal. MR venography reveals cutoff of the anterior half of the superior sagittal sinus. These findings suggest a right frontal lobe infarction secondary to superior sagittal venous thrombosis. Cerebral venous thrombosis (CVT) is commonly underdiagnosed, causing a delay in recognizing this entity, which may lead to devastating disability, and even death. The clinical spectrum of the disease includes seizures, focal neurological

signs, headache, and papilledema related to increased intracranial pressure. CT (especially without contrast) as well as conventional T1- and T2-weighted MRI images have a low sensitivity for diagnosing CVT. Alteration in blood flow and hemoglobin degradation in cerebral venous thrombosis may produce signal changes in conventional MRI imaging that may suggest the diagnosis; however, these changes are often subtle. MR venography (MRV) and echo-planar T2-weighted imaging are becoming the techniques of choice to establish the diagnosis of CVT and should be performed when there is a high index of suspicion of the disease. *(Selim, 1021–1026)*

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CHAPTER 17

# Psychiatry
## Questions

**1.** The highest rate of completed suicide among adult males is at the age of

(A) 20 years
(B) 35 years
(C) 55 years
(D) 65 years
(E) 75 years

**2.** The peak of a panic attack is reached within

(A) 6 hours
(B) 3 hours
(C) 1 hour
(D) 20 seconds
(E) 10 minutes

**3.** At what age does an infant drink from a cup, walk, and say dada/mama nonspecifically?

(A) Four months
(B) Six months
(C) Eight months
(D) Ten months
(E) Twelve months

**4.** Autonomy versus shame and the doubt stage of Erikson's epigenetic model of development correspond to which stage of Freud's psychosexual model of development?

(A) Oral phase
(B) Anal phase
(C) Phallic phase
(D) Latency phase
(E) Adolescence phase

**5.** A 6-year-old boy was brought to the outpatient clinic by his mother because of easy distractibility and poor school performance. The mother states that for the past 12 months, her son experienced difficulty engaging in quiet leisure activities, talked excessively, and interrupted others frequently. In school, he was reported to avoid activities that require mental effort, to have poor concentration, and to be easily distracted. What is the most likely diagnosis?

(A) Oppositional defiant disorder
(B) Bipolar disorder
(C) Obsessive–compulsive disorder
(D) Conduct disorder
(E) Attention deficit–hyperactivity disorder (ADHD)

**6.** Which of the following medications is contraindicated in the management of acute agitation in an 84-year-old man with a history of normal-pressure hydrocephalus and coronary artery disease with arrhythmia?

(A) Midazolam
(B) Haloperidol
(C) Droperidol
(D) Morphine sulfate
(E) Lorazepam

**7.** The positive reinforcement of alcohol is mediated by

(A) activation of glutamate receptors
(B) activation of gamma aminobutyric acid A (GABA A) receptors
(C) decreased norepinephrine activity in the brain
(D) inhibition of dopamine release
(E) opioid release inhibition

**8.** A 30-year-old alcoholic man was admitted to the emergency room because he was found by his neighbors to be acting agitated and confused. Which of the following is more suggestive of delirium tremens rather than acute alcoholic hallucination?

(A) Mild tremor
(B) Auditory hallucination
(C) 20 days' duration
(D) Dilated pupils with slow reaction to light
(E) Clear sensorium

**9.** What is the mechanism of action of disulfiram?

(A) Inhibition of intestinal absorption of alcohol
(B) Inhibition of liver transport of alcohol
(C) Inhibition of alcohol dehydrogenase
(D) Inhibition of aldehyde dehydrogenase
(E) Increased renal excretion of alcohol

**10.** Which of the following questions is *not* a part of the CAGE questionnaire?

(A) Have you gotten into physical fights when drinking?
(B) Have you ever felt you should cut down on your drinking?
(C) Have people annoyed you by criticizing your drinking?
(D) Have you ever felt bad or guilty about your drinking?
(E) Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover?

**11.** The craving for alcohol is reduced by

(A) lorazepam
(B) naltrexone
(C) disulfiram
(D) diazepam
(E) amitriptyline

**12.** In the central nervous system (CNS), cocaine acts by

(A) blocking D1 dopamine receptors
(B) inhibiting acetylcholine esterase in the CNS
(C) mediating its rewarding effect through dopamine cells in the ventral tegmentum area that projects to the basal ganglia
(D) increasing the reuptake of norepinephrine
(E) activating GABA receptors

**13.** Epidemiological studies have shown that in schizophrenia,

(A) women tend to have earlier age of onset of the disease and poorer outcome than men
(B) the urban poor population has a lower incidence of the disease
(C) the majority of cases occurring after the age of 40 are men
(D) at risk children have a normal scholastic test
(E) children who have been abused have an earlier age of onset and a poorer outcome

**14.** Major depression is characterized by loss of interest or pleasure for more than

(A) 2 years
(B) 6 months
(C) 3 months
(D) 6 weeks
(E) 2 weeks

**15.** Which of the following statements about major depression is *true*?

(A) The lifetime prevalence rates for adult men range from 3% to 9%.

(B) Relapse after a single episode is about 50%.
(C) Thirty percent of individuals with a single episode of major depression develop bipolar disorder.
(D) The average age of onset of unipolar major depression is 50 years.
(E) Full recovery from major depression occurs in 25% of patients by 6 months.

**16.** A good correlation between the blood level and the clinical effect of an antidepressant is seen with

(A) imipramine
(B) fluoxetine
(C) paroxetine
(D) trazodone
(E) phenelzine

**17.** Which of the following is *not* a cardinal feature of mania?

(A) Insomnia
(B) Distractibility
(C) Low self-esteem
(D) Flight of ideas
(E) Thoughtlessness

**18.** The treatment of choice of rapid-cycling bipolar disorder is

(A) lithium
(B) valproic acid
(C) carbamazepine
(D) clonazepam
(E) haloperidol

**19.** Posttraumatic stress disorder spares the

(A) thalamus
(B) prefrontal cortex
(C) red nucleus
(D) hippocampus
(E) amygdale

**20.** "La belle indifference" is an associated feature of

(A) somatization disorder
(B) hypochondriasis
(C) major depression
(D) delusion disorder
(E) conversion disorder

**21.** Factitious disorder is differentiated from malingering by which of the following characteristics?

(A) The production of physical signs is under voluntary control.
(B) The absence of secondary gain.
(C) The presence of a serious organic disorder as a comorbid factor.
(D) The primary motivation of the patient is to assume the sick role.
(E) The patient may intentionally produce symptoms of another person who is under his or her care.

**22.** Which of the following anatomical structures is responsible for the genesis of rapid-eye-movement (REM) sleep?

(A) Ascending reticular activating system
(B) Thalamus
(C) Red nucleus
(D) Putamen
(E) Nucleus ceruleus (locus ceruleus)

**23.** Restless leg syndrome may be exacerbated by using

(A) fluoxetine
(B) L-dopa
(C) bromocriptine
(D) clonazepam
(E) pergolide

**24.** Neuroleptic malignant syndrome results from

(A) anaphylactic reaction to a neuroleptic medication
(B) depletion of synaptic dopamine stores in the CNS
(C) blockade of central dopamine receptors
(D) central dopamine receptor hypersensitivity to neuroleptics
(E) inhibition of serotonin reuptake in the CNS

**25.** Which of the followings is a marker of Tourette syndrome?

(A) Short arm of chromosome 4
(B) X chromosome
(C) 5 hydroxy indoleacetic acid
(D) A1 allele of D2 receptors
(E) Y chromosome

**26.** Which of the followings is a marker of infantile autism?

(A) Short arm of chromosome 4
(B) X chromosome
(C) 5 hydroxy indoleacetic acid
(D) A1 allele of D2 receptors
(E) Y chromosome

**27.** Which of the followings is a marker of Huntington disease?

(A) Short arm of chromosome 4
(B) X chromosome
(C) 5 hydroxy indoleacetic acid
(D) A1 allele of D2 receptors
(E) Y chromosome

**28.** Which of the following is a common marker of suicidal behavior?

(A) Short arm of chromosome 4
(B) X chromosome
(C) 5 hydroxy indoleacetic acid
(D) A1 allele of D2 receptors
(E) Y chromosome

**29.** Agranulocytosis is a major side effect of

(A) thioridazine
(B) haloperidol
(C) clozapine
(D) risperidone
(E) olanzapine

**30.** Akathisia is a major side effect of

(A) thioridazine
(B) haloperidol
(C) clozapine
(D) risperidone
(E) olanzapine

**31.** Prolongation of the QT interval and risk of arrhythmia is a major side effect of

(A) thioridazine
(B) haloperidol
(C) clozapine
(D) risperidone
(E) olanzapine

**32.** Thyroid dysfunction is a side effect observed with

(A) thioridazine
(B) haloperidol
(C) clozapine
(D) risperidone
(E) quetiapine

**33.** Orthostatic hypotension is a side effect observed with

(A) thioridazine
(B) haloperidol
(C) clozapine
(D) risperidone
(E) olanzapine

**34.** Elevation of hepatic transaminase is a side effect observed with

(A) thioridazine
(B) haloperidol
(C) clozapine
(D) risperidone
(E) olanzapine

**35.** Grand mal seizure is the most prominent side effect of

(A) bupropion
(B) phenelzine
(C) fluoxetine
(D) amitriptyline
(E) venlafaxine

**36.** Delirium with abnormal electroencephalographic (EEG) and renal function is seen at a minimal lithium level in the range of

(A) 1.2 to 1.5 mEq/L
(B) 1.6 to 1.9 mEq/L
(C) 2.0 to 2.5 mEq/L
(D) 2.6 to 3 mEq/L
(E) above 3 mEq/L

**37.** Stimulant drugs appear to be more effective in the treatment of which of the following symptoms of narcolepsy?

(A) Sleep paralysis
(B) Sleep attacks
(C) Cataplexy
(D) Hypnagogic hallucination
(E) Restless nighttime sleep

**38.** The lithium level increases with the coadministration of

(A) theophylline
(B) mannitol
(C) sodium chloride
(D) acetazolamide
(E) captopril

**39.** Drug-induced hypertension may be seen with the use of

(A) venlafaxine
(B) imipramine
(C) clozapine
(D) nortriptyline
(E) risperidone

**40.** A 30-year-old woman was evaluated over a 5-year period for various symptoms including headaches, arthralgia, and pain in the abdomen, chest, and pelvis. An extensive outpatient workup in different subspecialty clinics (neurology, cardiology, gastroenterology, rheumatology, pulmonary diseases, gynecology, and urology) has been negative. The patient reports a chaotic lifestyle because of her condition despite the absence of an organic abnormality. What is the most likely diagnosis?

(A) Somatization disorder
(B) Dysmorphic disorder
(C) Factitious disorder
(D) Malingering
(E) Conversion disorder

**41.** Weight gain is *least* likely to be caused by the long-term use of

(A) clozapine
(B) piperidine
(C) haloperidol
(D) molindone
(E) risperidone

**42.** A 10-year-old boy was brought to a psychiatric clinic by his mother because of marked impairment in his social interaction. He has no friends and does not make eye contact. He is unable to identify objects of interest to others and exhibits stereotyped and repetitive hand and finger flapping. He has normal language and cognitive development. Neurological examination is normal. What is the most likely diagnosis?

(A) Asperger syndrome
(B) Autism
(C) Pervasive developmental disorder not otherwise specified
(D) Schizoid personality disorder
(E) Rett syndrome

**43.** With kleptomaniacs,

(A) objects are stolen for their financial value
(B) thievery is pleasurable
(C) there is antisocial behavior
(D) there is a decreasing sense of tension immediately before the theft
(E) after the theft, there is anger and vengeance

**44.** Priapism is a serious side effect of

(A) haloperidol
(B) lorazepam
(C) trazodone
(D) risperidone
(E) valproic acid

**45.** The next step in the treatment of a child who has ADHD and who fails to respond to methylphenidate is to use

(A) bupropion
(B) clonidine
(C) magnesium pemoline
(D) dextroamphetamine
(E) guaifenesin

**46.** A 20-year-old woman with no past medical history consults a physician because of recurrent abdominal pain, nausea, vomiting, and weakness in the lower extremities. She also reports paranoid ideation and auditory hallucinations. What is the most likely diagnosis?

(A) Hepatic encephalopathy
(B) Acute intermittent porphyria
(C) Niacin deficiency
(D) Thiamine deficiency
(E) Cobalamin deficiency

**47.** What is the substance most likely to provoke an acute panic attack in a patient suffering from a panic disorder?

(A) Carbon dioxide inhalation
(B) Dopamine
(C) Lactate
(D) Caffeine
(E) Yohimbine

**48.** Which of the following medications is most appropriate for an 80-year-old man with major depression and history of glaucoma, orthostatic hypotension, and urinary hesitation?

(A) Nortriptyline
(B) Amitriptyline
(C) Trimipramine
(D) Doxepin
(E) Imipramine

**49.** Which of the following symptoms is the earliest indication of lithium intoxication?

(A) Impaired consciousness
(B) Myoclonus
(C) Seizures
(D) Coarse tremor
(E) Acute renal failure

**50.** Which of the following is *not* a sign of lithium toxicity?

(A) Dry mouth
(B) Seizure
(C) Constipation
(D) Delirium
(E) Polyuria

**51.** Neurotoxicity of lithium may increase with the coadministration of which of the following drugs?

(A) Sodium bicarbonate
(B) Caffeine
(C) Mannitol
(D) Acetazolamide
(E) Amlodipine

**52.** Which of the followings is a common side effect of lithium?

(A) Agranulocytosis
(B) Hepatoxicity
(C) Cardiac conduction disturbance
(D) Hypothyroidism
(E) Acute pancreatitis

**53.** In which stage of pregnancy do major pharmacokinetic changes of lithium metabolism occur?

(A) First trimester
(B) Second trimester
(C) Third trimester
(D) At delivery
(E) Postpartum and during breast-feeding

**54.** Functional neuroimaging of patients with ADHD shows decreased activity in which region of the brain?

(A) The prefrontal cortex
(B) The temporal lobe
(C) The parietal lobe
(D) The thalamus
(E) The amygdala

**55.** Irreversible pigmentation of the retina is seen as a side effect of the chronic use of

(A) chlorpromazine
(B) thioridazine
(C) lithium
(D) risperidone
(E) valproic acid

**56.** Which of the following is *true* about the effect of chronic alcohol consumption on sleep?

(A) Decreased REM sleep
(B) Increased stage IV sleep
(C) Decreased sleep fragmentation
(D) Increased sleep latency
(E) None of the above

**57.** Which of the following is a sign of acute alcohol intoxication?

(A) Impairment in attention or memory, slurred speech, euphoria, and pupillary vasoconstriction
(B) Anxiety, depression, paranoid ideation, subjective intensification of perceptions, hallucinations, tachycardia, and sweating
(C) Dysarthria, ataxia, muscle rigidity, decreased response to pain, vertical nystagmus, and labile affect
(D) Impaired judgment, slurred speech, incoordination, unsteady gait, and nystagmus
(E) Euphoria, tachycardia, elevated blood pressure, pupillary dilatation, and seizure

**58.** Acute cocaine intoxication causes

(A) impairment in attention or memory, slurred speech, euphoria, and pupillary vasoconstriction
(B) anxiety, depression, paranoid ideation, subjective intensification of perceptions, hallucinations, tachycardia, and sweating
(C) dysarthria, ataxia, muscle rigidity, decreased response to pain, vertical nystagmus, and labile affect
(D) impaired judgment, slurred speech, incoordination, unsteady gait, and nystagmus
(E) euphoria, tachycardia, elevated blood pressure, pupillary dilatation, and seizure

**59.** Heroin overdose may cause

(A) impairment in attention or memory, slurred speech, euphoria, and pupillary vasoconstriction
(B) anxiety, depression, paranoid ideation, subjective intensification of perceptions, hallucinations, tachycardia, and sweating
(C) dysarthria, ataxia, muscle rigidity, decreased response to pain, vertical nystagmus, and labile affect
(D) impaired judgment, slurred speech, incoordination, unsteady gait, and nystagmus
(E) euphoria, tachycardia, elevated blood pressure, pupillary dilatation, and seizure

**60.** Cannabis overdose may cause

(A) dysarthria, ataxia, muscle rigidity, decreased response to pain, vertical nystagmus, and labile affect
(B) impaired judgment, slurred speech, incoordination, unsteady gait, and nystagmus
(C) euphoria, tachycardia, elevated blood pressure, pupillary dilatation, and seizure
(D) excitement, restlessness, tachycardia, muscle twitching, insomnia, and diuresis
(E) euphoria, conjunctival injection, increased appetite, tachycardia, and impaired judgment

**61.** Acute phencyclidine intoxication may cause

(A) dysarthria, ataxia, muscle rigidity, decreased response to pain, vertical nystagmus, and labile affect
(B) impaired judgment, slurred speech, incoordination, unsteady gait, and nystagmus
(C) euphoria, tachycardia, elevated blood pressure, pupillary dilatation, and seizure
(D) excitement, restlessness, tachycardia, muscle twitching, insomnia, and diuresis
(E) euphoria, conjunctival injection, increased appetite, tachycardia, and impaired judgment

**62.** Acute intoxication with lysergic acid diethylamide (LSD) may cause

(A) impairment in attention or memory, slurred speech, euphoria, and pupillary vasoconstriction
(B) anxiety, depression, paranoid ideation, subjective intensification of perceptions, hallucinations, tachycardia, and sweating
(C) dysarthria, ataxia, muscle rigidity, decreased response to pain, vertical nystagmus, and labile affect
(D) impaired judgment, slurred speech, incoordination, unsteady gait, and nystagmus
(E) euphoria, tachycardia, elevated blood pressure, pupillary dilatation, and seizure

**63.** Acute caffeine intoxication may cause

(A) dysarthria, ataxia, muscle rigidity, decreased response to pain, vertical nystagmus, and labile affect
(B) impaired judgment, slurred speech, incoordination, unsteady gait, and nystagmus
(C) euphoria, tachycardia, elevated blood pressure, pupillary dilatation, and seizure
(D) excitement, restlessness, tachycardia, muscle twitching, insomnia, and diuresis
(E) euphoria, conjunctival injection, increased appetite, tachycardia, and impaired judgment

**64.** Signs of alcohol withdrawal are

(A) insomnia, transient visual, tactile or auditory hallucination, and autonomic hyperactivity
(B) dysphoric mood, fatigue, vivid, unpleasant dreams, and increased appetite
(C) headache, nausea, vomiting, marked fatigue and depression
(D) dysphoric mood, nausea, vomiting, muscle aches, pupillary dilation, piloerection, and sweating
(E) depressed mood, insomnia, decreased heart rate, and increased appetite

**65.** Signs of cocaine withdrawal are

(A) insomnia, transient visual, tactile, or auditory hallucination, and autonomic hyperactivity
(B) dysphoric mood, fatigue, vivid, unpleasant dreams, and increased appetite
(C) headache, nausea, vomiting, marked fatigue and depression
(D) dysphoric mood, nausea, vomiting, muscle aches, pupillary dilation, piloerection, and sweating
(E) depressed mood, insomnia, decreased heart rate, and increased appetite

**66.** Signs of heroin withdrawal are

(A) insomnia, transient visual, tactile or auditory hallucination, and autonomic hyperactivity
(B) dysphoric mood, fatigue, vivid, unpleasant dreams, and increased appetite
(C) headache, nausea, vomiting, marked fatigue and depression
(D) dysphoric mood, nausea, vomiting, muscle aches, pupillary dilation, piloerection, and sweating
(E) depressed mood, insomnia, decreased heart rate, and increased appetite

**67.** Signs of nicotine withdrawal are

(A) insomnia, transient visual, tactile, or auditory hallucinations, and autonomic hyperactivity
(B) dysphoric mood, fatigue, vivid, unpleasant dreams, and increased appetite
(C) headache, nausea, vomiting, marked fatigue and depression
(D) dysphoric mood, nausea, vomiting, muscle aches, pupillary dilation, piloerection, and sweating
(E) depressed mood, insomnia, decreased heart rate, and increased appetite

**68.** Signs of caffeine withdrawal are

(A) insomnia, transient visual, tactile. or auditory hallucinations, and autonomic hyperactivity
(B) dysphoric mood, fatigue, vivid, unpleasant dreams, and increased appetite
(C) headache, nausea, vomiting, marked fatigue and depression
(D) dysphoric mood, nausea, vomiting, muscle aches, pupillary dilation, piloerection, and sweating
(E) depressed mood, insomnia, decreased heart rate, and increased appetite

**69.** Electroconvulsive therapy is least likely to be successful in which of the following diseases?

(A) Major depression
(B) Acute schizophrenia
(C) Acute manic episodes
(D) Chronic schizophrenia
(E) Obsessive–compulsive disorder

**70.** The CAGE questionnaire is used in case of

(A) catatonic schizophrenia
(B) Pick disease
(C) mental retardation
(D) bipolar disorder
(E) alcohol abuse

**71.** Alprazolam's half-life increases with the coadministration of

(A) fluoxetine
(B) fluvoxamine
(C) paroxetine
(D) sertraline
(E) clozaril

# Answers and Explanations

1. **(E)** Suicide, the eighth leading cause of death in the United States, accounts for more than 30,000 deaths per year. The suicide rate in men (18.7 suicides per 100,000 men in 1998) is more than four times that in women (4.4 suicides per 100,000 women in 1998). In females, suicide rates remain relatively constant beginning in the mid-teens. In males, suicide rates are stable from the late teenage years until the late 70s, when the rate increases substantially to 41 suicides per 100,000 persons annually in men 75 to 84 years of age. *(Mann, 302–311)*

2. **(E)** Panic disorder is a syndrome characterized by unexpected and unprovoked attacks of anxiety that produce both cognitive and physical symptoms. The lifetime prevalence of panic disorder in the general population is 1.6%. The disorder has a unimodal distribution, peaking in the third decade of life. Panic disorder affects more females than males. The major distinguishing feature of panic disorder is the combination of cognitive and physical symptoms. Onset is rapid, peaking within 10 minutes, and the attack lasts about 60 minutes. The typical patient has 2 to 4 attacks per week, often accompanied by anticipatory anxiety. A patient who sustains 4 panic attacks in 4 weeks or 1 or more attacks followed by 4 weeks of continuous anticipatory anxiety may be said to have panic disorder. *(Zun, 92–96)*

3. **(E)** At the age of 12 months, an infant with normal psychomotor development can drink from a cup, walk, and say dada/mama nonspecifically. *(Stern, 25)*

4. **(B)** Erikson's formulations were based on the concept that epigenetic development occurs in sequential, clearly defined stages, and that each stage must be satisfactorily resolved for development to proceed smoothly. If successful resolution of a particular stage does not occur, all subsequent stages reflect the failure in the form of physical, cognitive, social, or emotional maladjustment. Erikson described eight stages of the life cycle:

Stage 1 corresponds to trust versus mistrust.
Stage 2 corresponds to autonomy versus shame and doubt.
Stage 3 corresponds to initiative versus guilt.
Stage 4 corresponds to industry versus inferiority.
Stage 5 corresponds to ego identity versus role confusion.
Stage 6 corresponds to intimacy versus isolation.
Stage 7 corresponds to generativity versus stagnation.
Stage 8 corresponds to ego integrity versus despair.

Stage 2, autonomy versus shame and doubt (about 1 to 3 years), corresponds to the anal phase of Freud's psychosexual model of development. Autonomy concerns children's sense of mastery over themselves and over their drives and impulses. For Erikson, it is the time for children either to retain feces (holding in) or to eliminate feces (letting go); both behaviors have an effect on the mother. Children in the second and third years of life learn to walk alone, feed themselves, control the anal sphincter, and talk. Muscular maturation sets the tone for this stage of development. When parents permit children to function with some autonomy and are supportive without being overprotective, toddlers gain self-confidence and feel that they can control themselves and their world. But if toddlers are

punished for being autonomous or are overcontrolled, they feel angry and ashamed. If parents show approval when children show self-control, children's self-esteem is enhanced and a sense of pride develops. *(Kaplan, 214–215, 233–239)*

**5. (E)** The patient in this vignette has symptoms of inattention (he was reported to avoid activities that require mental effort, to have poor concentration, and to be easily distractible), hyperactivity (had difficulty engaging in leisure activity quietly), and impulsivity (he grabbed things and interrupted others frequently). These symptoms are highly suggestive of ADHD.

ADHD is characterized by poor ability to attend to a task, motor overactivity, and impulsivity. Oppositional and aggressive behaviors are often seen in conjunction with ADHD. The cause of ADHD is unknown. Genetic factors as well as other factors affecting brain development during prenatal and early postnatal life are most likely responsible. An association of the dopamine receptor D4 gene with a refined phenotype of ADHD has been demonstrated. Growing evidence shows that children with ADHD differ from normal children on neuroimaging measures of brain structure and function. In particular, a prefrontal–striatothalamocortical circuit has been implicated. ADHD-afflicted children display various behaviors indicative of problems with attention, hyperactivity, and impulsivity.

According to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), inattentiveness is manifest when a child often or constantly (1) makes careless mistakes, failing to give close attention, (2) has difficulty sustaining attention, (3) does not seem to listen, (4) does not follow through on tasks, (5) has difficulty getting organized, (6) dislikes or avoids sustained mental effort, (7) loses things, (8) is easily distracted, and (9) is forgetful. Hyperactivity is evidenced when a child often or constantly (1) fidgets, (2) is out of his or her seat, (3) runs and climbs excessively, (4) has difficulty playing quietly, (5) is always on the go as though driven by a motor, and (6) talks excessively. Impulsivity is reflected in a child who often or constantly (1) blurts out answers, (2) has difficulty awaiting his or her turn, and (3) interrupts or intrudes on others.

Diagnosis of ADHD requires the presence of at least six manifestations from the inattentiveness cluster, the hyperactivity/impulsivity cluster, or both. Children whose symptoms are predominantly from one cluster are said to be primarily inattentive or hyperactive/impulsive. Clinical diagnosis requires that the symptoms be evident before age 7 and be constant for at least 6 months. *(Behrman, 107–110)*

**6. (B)** High doses of haloperidol have been associated with prolongation of cardiac conduction. Patients with a previous history of dilated ventricles, arrhythmia, or alcohol abuse have an increased risk of developing torsades de pointes. *(Stern, 392)*

**7. (B)** Addictive behavior associated with alcoholism is characterized by compulsive preoccupation with obtaining alcohol, loss of control over consumption, and development of tolerance and dependence as well as impaired social and occupational functioning. Like other addictive disorders, alcoholism is characterized by chronic vulnerability to relapse after cessation of drinking. To understand the factors that compel some individuals to drink excessively, alcohol research has focused on the identification of brain mechanisms that support the reinforcing actions of alcohol and the progression of changes in neural function induced by chronic ethanol consumption that lead to the development of dependence. More recently, increasing attention has been directed toward the understanding of neurobiological and environmental factors in susceptibility to relapse.

Ethanol interacts with dopamine function in the mesolimbic "reward" pathway by activating the dopaminergic neurons of the ventral tegmental area (VTA). Ethanol increases the firing of VTA DA neurons through direct excitation. The activation of GABA A receptors opens chloride channels, inducing a primary CNS depressant effect as well as inhibiting glutamate NMDA receptors; these effects comprise the positive reinforcement produced by the ingestion of alcohol. Other factors involved in the positive reinforcement of alcohol include interaction with serotonin systems and the release of opioid peptides. *(Stern, 73–74; Weiss, 3332–3337)*

**8.** **(D)** Both delirium tremens and acute alcoholic hallucinosis occur during the withdrawal period in an alcohol-dependent patient. Acute alcoholic hallucinosis may start without a drop in blood alcohol concentration and without delirium, tremor, or autonomic hyperactivity. Hallucinations are usually auditory and paranoid and may last more than 10 days. In delirium tremens, the patient is confused, with prominent tremor and psychomotor activity, disturbed vital signs, autonomic dysfunction with dilated pupils, and a slow reaction to light. Hallucinations are usually of the visual type. There is difficulty sustaining attention, disorganized thinking, and perceptual disturbance. The duration of symptoms is between 3 to 10 days, whereas in acute alcoholic hallucinosis symptom duration is between 5 to 30 days. *(Stern, 75)*

**9.** **(D)** Disulfiram is an alcohol-sensitizing agent that alters the response of the body to alcohol, making its ingestion unpleasant or toxic. It inhibits aldehyde dehydrogenase, the enzyme that catalyzes the oxidation of acetaldehyde, causing blood acetaldehyde levels to increase. The disulfiram–ethanol reaction (DER) varies inversely with the dose of disulfiram and the volume of alcohol consumed. The most common symptoms of the DER are warmness and flushed skin, especially in the upper chest and face; tachycardia; palpitations; and decreased blood pressure. Nausea, vomiting, shortness of breath, sweating, dizziness, blurred vision, and confusion may also occur. In addition to its effects on aldehyde dehydrogenase, disulfiram inhibits a variety of other enzymes, including dopamine beta-hydroxylase. Thus, in addition to the toxicity of the DER caused by the accumulation of acetaldehyde, adverse effects of disulfiram or its metabolites can occur as a result of multiple drug interactions. *(Kranzler, 401–423)*

**10.** **(A)** The CAGE test is a quick and reliable tool with which to assess alcohol abuse. It comprises four simple questions:

"C" Have you ever felt you should cut down on your drinking?
"A" Have people annoyed you by criticizing your drinking?
"G" Have you ever felt bad or guilty about your drinking?
"E" Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover?

A yes answer is scored 1 and a no answer is scored 0. A score of 2 or more is considered clinically significant.

*(Mayfield, 1121–1123)*

**11.** **(B)** Naltrexone is a pure competitive antagonist principally of m but also of k and d opioid receptors in the CNS. The effect of naltrexone on alcohol craving is not well understood but presumably involves antagonism of endogenous opioid agonists, which may be released on alcohol ingestion and may contribute to the subjective high. It aids in achieving the goal of abstinence by preventing relapse and decreasing alcohol consumption. *(Kaplan, 1064–1067)*

**12.** **(C)** Cocaine acts by blocking reuptake of neurotransmitters (norepinephrine, dopamine, and serotonin) at the synaptic junctions, resulting in increased neurotransmitter concentrations. Because norepinephrine is the primary neurotransmitter of the sympathetic nervous system, sympathetic stimulation results and leads to vasoconstriction, tachycardia, mydriasis, and hyperthermia. CNS stimulation may appear as increased alertness, energy, talkativeness, repetitive behavior, diminished appetite, and increased libido. Psychological stimulation by cocaine produces an intense euphoria that is often compared with orgasm. Pleasure and reward sensations in the brain have been correlated with increased neurotransmission in the mesolimbic or mesocortical dopaminergic tracts (or both). Cocaine increases the functional release of dopamine, which activates the ventral tegmental–nucleus accumbens pathway, which seems to be a major component of the brain reward system. Activation of this pathway is essential for the reinforcing actions of psychomotor stimulants. *(Warner, 226–235; Withers, 63–78)*

**13.** **(E)** The prevalence of schizophrenia varies by region in the United States. Its incidence appears to be higher among the urban poor. Males

manifest the illness between 18 and 25 years of age whereas females show their first symptoms between 26 and 45 years. Twenty percent of cases of schizophrenia occur after age 40; most are women. Children at risk of schizophrenia have a lower scholastic test score, abnormal affect, and thought disorder early in infancy. Those who are abused have an earlier onset and a worse course. *(Stern, 99)*

**14.** **(E)** Major depression is a cluster of psychological and physical symptoms that persist for 2 or more weeks and interfere with a person's ability to function or enjoy life. *(Kaplan, 534)*

**15.** **(B)** The National Comorbidity Survey carried out a structured psychiatric interview of a representative sample of the general population and reported a lifetime rate of major depression of 21.3% in women and 12.7% in men, producing a female-to-male ratio of 1.0 to 1.7. A gender difference was found beginning in early adolescence and persisting through the mid-50s. Although this increased tendency for depression in women reflects a long-term trend, an increase has also been seen in the rate of depression among young women over the short term. The highest rate occurs in adult women above 44 years of age. Major depression is a recurrent illness; the risk of relapse after one episode is about 50%, whereas it is greater than 80% after three episodes. The average lifetime number is four. The average age of onset of unipolar depression is 29 years. Some 5% to 10% of individuals with a single episode of major depression will eventually develop bipolar disease, whereas 50% of those experiencing major depression will recover fully by 6 months. *(Brown, 241–268; Stern, 104–105)*

**16.** **(A)** Blood levels can be obtained for all antidepressant drugs, but not all of them have shown a correlation between therapeutic effect and blood level. In 1985, a task force examined the present status of studies investigating the relationship between blood plasma concentrations of tricyclic antidepressants and clinical outcome. It discussed some of the discrepancies that have developed among various antidepressant drugs and evaluated the clinical implications of the current status of blood level monitoring. The task force concluded that plasma level measurements of imipramine, desmethylimipramine, and nortriptyline are unequivocally clinically useful in certain situations. For imipramine, the percentage of favorable responses correlates with plasma levels in a linear manner between 200 and 250 ng/mL, but some patients may respond at a lower level. At levels that exceed 250 ng/mL, there is no improved favorable response, and side effects increase. *(Task Force, 155–162)*

**17.** **(C)** The diagnosis of manic episodes is established by the presence of irritability or euphoria associated with 3 (euphoria) or 4 (irritability) of the 7 cardinal symptoms of mania. The cardinal symptoms of mania are distractibility, insomnia, grandiosity, flight of ideas, increased activities, pressured speech, and thoughtlessness. *(Stern, 116)*

**18.** **(B)** Divalproex sodium (valproic acid with sodium valproate) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute mania in 1995. A therapeutic blood-level window of 45 to 125 μg/mL has been demonstrated to correlate with antimanic response. Valproate may have better efficacy than lithium in the treatment of mixed manic states, rapid cycling mania or other complex, comorbid forms of bipolar disorder and thus may synergize with lithium to prevent relapses. Valproate can also be useful in the treatment of AIDS-related mania. *(Goldberg, 211–231)*

**19.** **(C)** The neurobiology of posttraumatic stress disorder (PTSD) involves the thalamus as a relay of information about a threat to the prefrontal cortex and amygdala. The hippocampus was found to be affected in adults with PTSD and appears to be related to increased exposure to excitatory amino acids and glucocorticoids. The amygdala plays a key role in consolidating the emotional significance of events. In fact, Vietnam combat veterans with PTSD showed left amygdala activation on single photon emission computed tomography (SPECT) study in response to exposure to combat sound, whereas combat veterans without PTSD and noncombatant controls did not exibit amygdala activation. *(Newport, 211–218)*

**20.** **(E)** Somatization disorder is characterized by the recurrence of multiple somatic complaints not accounted for by medical findings. It is a chronic condition with female predominance. Hypochondriasis is also a chronic condition characterized by a fear or the belief that one has a serious illness despite adequate medical evaluation. Its prevalence is 4% to 9% of medical outpatients, with equal incidence between men and women. Major depression is a comorbid condition of both somatization disorder and hypochondriasis. A family history of somatization disorder, antisocial disorder, and substance abuse is reported in somatization disorder, whereas a history of illness in family members is reported in hypochondriasis. "La belle indifference" is an associated feature of conversion disorder, where symptoms do not conform to anatomical pathways. Delusion is not a common feature of either somatization disorder or hypochondriasis. Delusional disorder may be a comorbid condition in body dysmorphic disorder. *(Stern, 144–146)*

**21.** **(B)** Absence of secondary gain is the main feature that differentiates factitious disorder from malingering. In factitious disorder, the patient intentionally produces physical or psychological signs or symptoms that are under voluntary control and not explained by any other underlying physical or mental disorder. The primary motivation of the behavior is to assume the sick role. There is no secondary gain such as economic benefit or avoidance of legal responsibilities. In malingering, the patient has an obvious recognizable secondary gain in producing signs and symptoms such as avoiding work or prosecution, or obtaining financial gain. *(Stern, 147–150)*

**22.** **(E)** Hobson proposed the most currently acceptable neuroanatomic model for wakefulness and sleep where REM is proposed to arise from the activation of the nucleus ceruleus and the gigantocellular tegmental field, whereas wakefulness is maintained by the ascending reticular activating system. *(Hobson, 1990, 371–382, 1975, 369–403; Stern, 76)*

**23.** **(A)** Serotonin reuptake inhibitors such as fluoxetine may exacerbate symptoms of restless leg syndrome, whereas medications such as benzodiazepines, levodopa, quinine, opioids, propranolol, and carbamazepine (Tegretol) have some benefit. *(Stern, 178)*

**24.** **(C)** Neuroleptic malignant syndrome is an uncommon but potentially fatal idiosyncratic reaction characterized by the development of altered consciousness, hyperthermia, autonomic dysfunction, and muscular rigidity on exposure to neuroleptic (and probably other psychotropic) medications. The pathophysiology of neuroleptic malignant syndrome (NMS) is poorly understood. The postulated mechanism involves blockade of central dopamine receptors in the basal ganglia and hypothalamus and peripherally in postganglionic sympathetic neurons and smooth muscle. The known plasticity of the mesostriatal–mesolimbic dopaminergic system is important in protecting the brain against severe biopsychosocial stressors by means of an appropriately timed receptor downregulation.

In most people, this homeostatic mechanism is sufficient to protect against psychosis; neuroleptics may help further decrease dopamine receptor sensitivity when the native mechanisms are insufficient. For some patients, however, this further reduction in general dopaminergic tone will result in NMS. As a corollary, it was suggested that the primary mesolimbic hyperdopaminergia might induce a homeostatic response, via GABAergic feedback from the nucleus accumbens, consisting of downregulation of dopamine receptors in the mesostriatum and hypothalamus. Such a response would then result in a reduction in local dopaminergic tone sufficient to produce lethal catatonia, despite the fact that such mesolimbic hyperdopaminergia would simultaneously cause psychosis. *(Longhurst, 537–538)*

**25.** **(D)** The prevalence of the D2A1 allele in a range of impulsive, compulsive, addictive disorders ranged from 42.3% to 54.5%. An indication of the importance of the dopamine D2 receptor in Tourette syndrome comes from SPECT studies of monozygotic twins discordant for tic severity. Differences in the D2 receptor density in the head of the caudate nucleus predicted differences in phenotypic severity with a high correlation

coefficient, suggesting that striatal dopamine D2 receptor density accounted for 98% of the variance of tic severity. Dopamine is a stress-responsive neurotransmitter. Some studies, using SPECT or positron emission tomography (PET), show increased density of the presynaptic dopamine transporter and the postsynaptic D2 dopamine receptor in Tourette syndrome. These studies suggest that there is abnormal regulation of dopamine release and uptake in this disease. *(Comings, 50–83; Margolis et al., 1019–1031; Oquendo, 11–25; Weeks, 401–408)*

**26. (B)** Fragile-X syndrome is primarily a disorder of neurodevelopment, although other organ systems are also involved. In addition to mental retardation, the mutation also predisposes affected individuals to a variety of psychiatric syndromes. A substantial number of males with the fragile-X mutation have autism. In one study, nearly 100% had one or more behaviors commonly observed in autism, such as hand flapping and biting, poor eye contact, or tactile defensiveness. *(Comings, 50–83; Margolis et al., 1019–1031; Oquendo, 11–25; Weeks, 401–408)*

**27. (A)** Huntington disease has an autosomal dominant transmission. Its gene is located on the short arm of chromosome 4. Huntington disease is caused by a mutation in the *IT15* gene, resulting in abnormal polyglutamine expansion in the N-terminal region of huntingtin protein (Htt). The expanded polyglutamine repeat alters the normal functions of Htt. In addition, the mutated protein, expanded Htt, is itself toxic. Htt interacts with an array of proteins in neuronal cells. One important characteristic of Huntington disease is the particular vulnerability of a particular brain region, the caudate–putamen, despite similar expression of the mutated protein in other parts of the brain. *(Roze, 497–503)*

**28. (C)** Platelet 5-$HT_{2A}$ receptors have been found to be increased in proportion to the lethality of the suicide attempt in depressed subjects. Approximately two thirds of studies comparing subjects who have attempted suicide versus nonattempters show that those who have attempted suicide have low levels of CSF 5-HIAA. One of the factors that is correlated with a low CSF 5-HIAA level is the medical severity of the attempt. CSF 5-HIAA is low in serious suicide attempters, even when the presence of a psychiatric illness (e.g., major depression) is controlled for and the patients are studied in a drug-free, controlled environment. *(Comings, 50–83; Margolis, 1019–1031; Oquendo, 11–25; Weeks, 401–408)*

**29. (C)** Clozapine is classified as an "atypical" antipsychotic drug because its profile of binding to dopamine receptors and its effects on various dopamine-mediated behaviors differ from those exhibited by more typical antipsychotic drug products. In particular, although clozapine does interfere with the binding of dopamine at D1, D2, D3, and D5 receptors and has a high affinity for the D4 receptor, it does not induce catalepsy. This evidence, consistent with the view that clozapine is preferentially more active at limbic than at striatal dopamine receptors, may explain the relative lack of clozapine-induced extrapyramidal side effects. Clozapine also acts as an antagonist at adrenergic, cholinergic, histaminergic, and serotonergic receptors. The incidence of clozapine-induced agranulocytosis is about 1.3% at 1 year, based on the occurrence of 15 U.S. cases out of 1743 patients in the premarketing period. This reaction could prove fatal if not detected early and therapy interrupted. The incidence rates of agranulocytosis based upon a weekly monitoring schedule rose steeply during the first 2 months of therapy, peaking in the third month. Among clozapine patients who continued the drug beyond the third month, the weekly incidence of agranulocytosis fell to a substantial degree, so that by the sixth month the weekly incidence of agranulocytosis was reduced to 3 per 1000 person-years. After 6 months, the weekly incidence of agranulocytosis declined still further; however, it never reached zero. *(Coyle, 34–42)*

**30. (B)** Haloperidol is a neuoleptic of high potency. Extrapyramidal syndrome (EPS) during its administration has been reported frequently, often during the first few days of treatment. EPS can be categorized generally as having Parkinson-like symptoms, akathisia, or dystonia (including opisthotonos and oculogyric crisis). While all can occur at relatively low doses, they occur more frequently and with greater severity at higher doses.

The symptoms may be controlled with dose reductions or administration of antiparkinson drugs such as benztropine. *(Coyle, 34–42)*

**31.** **(A)** Thioridazine is a D2 dopamine antagonist of low potency. CNS side effects include occasional drowsiness, especially where large doses are given early in treatment. Generally, this effect tends to subside with continued therapy or a reduction in dosage. Pseudoparkinsonism and other extrapyramidal symptoms may occur but are infrequent. Nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache have been reported but are extremely rare. Adverse cardiovascular reactions are the most serious side effects and include a dose-related prolongation of the QTc interval, which is associated with the ability to cause torsades de pointes–type arrhythmias, a potentially fatal polymorphic ventricular tachycardia, and sudden death. Autonomic nervous system side effects of thioridazine include dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, and urinary retention. *(Coyle, 34–42)*

**32.** **(E)** Quetiapine fumarate is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5HT_{1A}$ and $5HT_2$, dopamine D1 and D2, histamine $H_1$ and adrenergic $\alpha 1$ and $\alpha 2$ receptors. Clinical trials with quetiapine fumarate demonstrated a dose-related decrease in total and free thyroxin (T4) of approximately 20% at the higher end of the therapeutic dose range, which was maximal in the first 2 to 4 weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, and levels of TBG were unchanged. In nearly all cases, cessation of quetiapine fumarate treatment was associated with a reversal of the effects on total and free T4 irrespective of the duration of treatment. *(Coyle, 34–42)*

**33.** **(D)** Risperidone is an antipsychotic agent belonging to the benzisoxazole derivatives. The mechanism of action of risperidone, as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than D2 and $5HT_2$ may explain some of the other effects of risperidone. It may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% of risperidone-treated patients in phase 2 and phase 3 studies. *(Coyle, 34–42)*

**34.** **(E)** Olanzapine is an antipsychotropic agent that belongs to the thienobenzodiazepine class. Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin $5HT_{2(A)2C}$, dopamine D1-D4, muscarinic $M_{1\text{-}5}$, histamine $H_1$, and adrenergic $\alpha 1$ receptors. In placebo-controlled studies, clinically significant ALT (SGPT) elevations (equal to or greater than three times the upper limit of the normal range) were observed in 2% of patients exposed to olanzapine compared to none of the placebo patients. Periodic assessment of transaminases is recommended in patients with significant hepatic disease. *(Coyle, 34–42)*

**35.** **(A)** Bupropion is associated with grand mal seizures in approximately 0.4% (4 of 1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as four-fold. This relative risk is only an approximate estimate because of the lack of direct comparative studies. The estimated seizure incidence for Bupropion increases almost 10-fold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg). *(Coyle, 107)*

**36.** **(C)** Lithium adverse reactions may be encountered at serum levels below 1.5 mEq/L. Mild to moderate adverse reactions may occur at levels from 1.5 to 2.5 mEq/L and moderate to severe reactions may be seen at levels of 2.0 mEq/L and above. Fine hand tremor, polyuria, and mild thirst may occur during initial therapy for the acute manic phase and may persist throughout treatment. Transient and mild nausea and general discomfort may also appear during the first few days of lithium administration. Diarrhea,

vomiting, drowsiness, muscular weakness, and lack of coordination may be early signs of lithium intoxication and can occur at lithium levels below 2.0 mEq/L. At a level between 2 and 2.5 mEq/L, moderate to severe signs of toxicity may appear, such as delirium, abnormal EEG, abnormal renal function cardiac arrhythmia, and risk of coma. At a level above 2.5 mEq/L, signs of severe intoxication may appear that include acute renal failure seizure and death. Treatment is by dialysis. *(Coyle, 125–128; Kaplan, 1050)*

**37. (B)** Stimulants appear most effective against daytime somnolence and sleep attacks associated with narcolepsy; they are less beneficial for catalepsy. *(Stern, 177–178)*

**38. (E)** The lithium level decreases with the coadministration of mannitol, urea, theophylline and aminophyline, sodium chloride, acetazolamide, and sodium bicarbonate. It increases with the coadministration of angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, and nonsteroidal anti-inflammatory drugs. *(Stern, 385)*

**39. (A)** Venlafaxine is an effective antidepressant drug that acts by nonselective inhibition of the reuptake of three biogenic amines: serotonin, norepinephrine, and dopamine. An increase in blood pressure was seen in clinical trials in patients treated with venlafaxine. This occurred most often with doses above 200 mg per day and seems to be dose-dependent. *(Stern, 356)*

**40. (A)** The patient in this vignette has recurrent multiple chronic somatic complaints that started at the age of 25 years. This objective pathology is found despite evaluations; she also has a chaotic lifestyle. This is most suggestive of somatization disorder; the patient has a chronic condition without identifiable secondary gain. Dysmorphic disorder is unlikely, since the patient did not report an imagined ugliness. Conversion disorder is unlikely, because her condition is not self-limited. The absence of secondary gain makes the diagnosis of malingering unlikely. The absence of voluntary control of the symptoms makes the diagnosis of factitious disorder unlikely. *(Stern, 139–140)*

**41. (D)** A common adverse effect of treatment with dopamine receptor antagonists is weight gain, which can be significant in some cases. Molindone and, perhaps, loxapine are not associated with the symptom and may be indicated in patients for whom weight gain is a serious health hazard or a reason for noncompliance. *(Kaplan and Sadock, 1030)*

**42. (A)** Asperger syndrome is characterized by a severe, sustained impairment in social interaction and restricted, repetitive patterns of behavior, interests, and activities. Unlike autistic disorder, in Asperger syndrome there are no significant delays in language, cognitive development, or age-appropriate self-help skills. The cause is unknown, but family studies suggest a possible relation to autism. The similarity of Asperger syndrome to autism leads to genetic, metabolic, infectious, and perinatal hypotheses. The clinical features include at least two of the following indications of qualitative social impairment: markedly abnormal nonverbal communicative gestures, the failure to develop peer relationships, the lack of social or emotional reciprocity, and an impaired ability to express pleasure in other people's happiness. *(Kaplan, 1190–1191)*

**43. (B)** The essential feature of kleptomania is a recurrent failure to resist impulses to steal objects not needed for personal use or for monetary value. The objects taken are often given away, returned surreptitiously, or kept and hidden. People with kleptomania usually have the money to pay for the objects they impulsively steal. Like other impulse-control disorders, kleptomania is characterized by mounting tension before the act, followed by gratification and lessening of tension with or without guilt, remorse, or depression during the act. The stealing is not planned and does not involve others but is the goal of the patient with kleptomania. Although the thefts do not occur when immediate arrest is probable, people with kleptomania do not always consider their chances of being apprehended, even though repeated arrests lead to pain and humiliation. These people may feel guilt and anxiety after the theft, but they do not feel anger or vengeance. Furthermore, when the stolen object is itself the goal, the diagnosis is not

kleptomania; in kleptomania only the act of stealing is the goal. *(Kaplan, 763–764)*

**44. (C)** Trazodone is associated with the rare occurrence of priapism, the symptom of prolonged erection in the absence of sexual stimuli. That symptom appears to result from the alpha$_2$-adrenergic antagonism of trazodone. *(Kaplan, 1098–1100)*

**45. (D)** Dextroamphetamine is usually the second line of pharmacological treatment when methylphenidate is not effective. Pemoline has the advantage of a longer half-life and thereby allows less frequent dosing and round-the-clock effects, but there have been some recent reports of serious liver failure in patients being treated with pemoline. *(Kaplan, 1198)*

**46. (B)** The most likely diagnosis here is acute intermittent porphyria. It is a disorder of heme biosynthesis, which results in excessive accumulation of porphyrin. It is characterized by the triad of symptoms: acute abdominal pain, motor polyneuropathy, and psychosis. Acute intermittent porphyria is an autosomal dominant disorder that affects more women than men; its onset is between ages 20 and 50. The psychiatric symptoms include anxiety, insomnia, lability of mood, depression, and psychosis. Some studies have found that between 0.2% and 0.5% of chronic psychiatric patients may have undiagnosed porphyria. Barbiturates precipitate or aggravate the attacks of acute porphyria, and the use of barbiturates for any reason is absolutely contraindicated in a person with acute intermittent porphyria and in anyone who has a relative with the disease. Niacin deficiency is unlikely to be the diagnosis. The neuropsychiatric symptoms of pellagra include apathy, irritability, insomnia, depression, and delirium; the medical symptoms include dermatitis, peripheral neuropathy, and diarrhea.

Thiamine deficiency is unlikely, because there is no history of ethanol abuse and no signs of or psychiatric symptoms such as apathy, depression, irritability, nervousness, and poor concentration. The presence of a clear sensorium and the associated clinical and psychiatric symptoms argue against the diagnoses of hepatic encephalopathy and cobalamin deficiency, respectively. *(Kaplan, 362–363)*

**47. (C)** Up to 72% of patients with panic disorder have a panic attack when administered an intravenous injection of sodium lactate. Therefore lactate provocation is used to confirm a diagnosis of panic disorder. Hyperventilation, another known trigger of panic attacks in predisposed persons, is not as sensitive as lactate provocation in inducing panic attacks. Carbon dioxide ($CO_2$) inhalation also precipitates panic attacks in those so predisposed. *(Kaplan, 262)*

**48. (A)** Amitriptyline, imipramine, trimipramine, and doxepin have the most anticholinergic side effects of the tricyclic antidepressants. Amoxapine, nortriptyline, and maprotiline are less anticholinergic; and desipramine may be the least anticholinergic. Anticholinergic effects include dry mouth, constipation, blurred vision, and urinary retention. Narrow-angle glaucoma can also be aggravated by anticholinergic drugs, and the precipitation of glaucoma requires emergency treatment with a miotic agent. Severe anticholinergic effects can lead to a CNS anti-cholinergic syndrome with confusion and delirium, especially if tricyclic and tetracyclic drugs are administered with antipsychotics or anticholinergic drugs. The most common autonomic effect of tricyclic antidepressant medications, partly because of alpha$_1$-adrenergic blockade, is orthostatic hypotension, which can result in falls and injuries in affected patients. Nortriptyline may be the drug least likely to cause the problem, and some patients respond to fludrocortisone (Florinef), 0.05 mg twice a day. Other possible autonomic effects are profuse sweating, palpitations, and increased blood pressure. *(Kaplan, 1104)*

**49. (D)** The early signs and symptoms of lithium toxicity include coarse tremor, dysarthria, and ataxia; the later signs and symptoms include impaired consciousness, muscular fasciculations, myoclonus, seizures, and coma. The higher the lithium levels (and the longer they have been elevated), the worse the symptoms of lithium toxicity. *(Kaplan and Sadock, 1050)*

**50. (C)** Diarrhea, vomiting, drowsiness, muscular weakness and lack of coordination may be early signs of lithium intoxication, and can occur at lithium levels below 2.0 mEq/L. At higher levels,

ataxia, giddiness, tinnitus, blurred vision and a large output of dilute urine may be seen. Serum lithium levels above 3.0 mEq/L may produce a complex clinical picture, involving multiple organs and organ systems. Serum lithium levels should not be permitted to exceed 2.0 mEq/L during the acute treatment phase. *(Coyle, 125–127)*

**51. (E)** Concurrent use of calcium channel blocking agents with lithium may increase the risk of neurotoxicity in the form of ataxia, tremors, nausea, vomiting, diarrhea, and tinnitus. Caution should be used when lithium and diuretics are used concomitantly because diuretic-induced sodium loss may reduce the renal clearance of lithium and increase serum lithium levels with risk of lithium toxicity. Patients receiving such combined therapy should have serum lithium levels monitored closely and the lithium dosage adjusted if necessary. Lithium levels should be closely monitored when patients initiate or discontinue the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Concurrent use of metronidazole with lithium may provoke lithium toxicity due to reduced renal clearance. There is evidence that ACE inhibitors, such as enalapril and captopril, may substantially increase steady-state plasma lithium levels, sometimes resulting in lithium toxicity. When such combinations are used, lithium dosage may need to be decreased and plasma lithium levels should be measured more frequently. The concomitant administration of lithium with selective serotonin reuptake inhibitors should be undertaken with caution, as this combination has been reported to result in symptoms such as diarrhea, confusion, tremor, dizziness, and agitation. The following drugs can lower serum lithium concentrations by increasing urinary lithium excretion: acetazolamide, urea, xanthine preparations, and alkalinizing agents such as sodium bicarbonate. *(Coyle, 127; Stern, 366–367)*

**52. (D)** Hepatotoxicity has been reported with the use of pemoline. Agranulocytosis has been estimated to occur in association with clozapine use at a cumulative incidence at 1 year of approximately 1.3% of patients. Its incidence rate based upon a weekly monitoring schedule rose steeply during the first 2 months of therapy, peaking in the third month. Lithium use has been associated with the formation of euthyroid goiter, hypothyroidism accompanied by lower T3 and T4. Imipramine use may be associated with cardiovascular side effects such as arrhythmias, heart block, ECG changes, orthostatic hypotension, hypertension, tachycardia, palpitation, and myocardial infarction. *(Coyle, 38, 126; Kaplan, 566–569, 953)*

**53. (D)** The maternal lithium level must be monitored closely during pregnancy and especially after delivery because of the significant change in renal function with massive fluid shift that occurs over that time period. Lithium should be discontinued shortly before delivery, and the drug should be restarted after an assessment of the usually high risk of postpartum mood disorder and the mother's desire to breast-feed her infant. *(Kaplan, 1051)*

**54. (A)** Functional neuroimaging studies of people with ADHD have either been normal or have shown decreased volume of the right prefrontal cortex and the right globus pallidus. In addition, whereas normally the right caudate nucleus is larger than the left caudate nucleus, people with ADHD may have caudate nuclei of equal size. These findings suggest dysfunction of the right prefrontal–striatal pathway for control of attention. *(Kaplan, 1194)*

**55. (B)** Thioridazine is associated with irreversible pigmentation of the retina when given in dosages of more than 800 mg/day. An early symptom of this effect can sometimes be nocturnal confusion related to difficulty with night vision. The pigmentation is similar to that seen in retinitis pigmentosa; it can progress even after the thioridazine is stopped and can finally result in blindness. In contrast, chlorpromazine is associated with benign pigmentation of the eyes. Most patients who show the deposits are those who have ingested 1 to 3 kg of chlorpromazine throughout their lives. *(Kaplan, 1030)*

**56. (A)** Although alcohol consumed in the evening usually results in an increased ease of falling asleep (decreased sleep latency), alcohol also has adverse effects on sleep architecture. Specifically,

alcohol use is associated with decreased REM or dream sleep, decreased deep sleep (stage 4), and increased sleep fragmentation, with more and longer episodes of awakening. *(Kaplan, 396)*

**57. (D)** The CNS effects of acute alcohol intoxication depend on the blood level of alcohol. Signs of intoxication include loss of inhibition, slurred speech, staggering gait, euphoria, nystagmus, motor incoordination, confusion, stupor, and coma with high levels of alcohol in the blood. *(Kaplan, 379–383; Stern, 73, 85, 89)*

**58. (E)** Signs of cocaine intoxication include vasoconstriction, increased heart rate and blood pressure, chest pain, pupillary dilation, muscle weakness, respiratory depression, euphoria, increased energy, anxiety, and increased risk of psychosis. *(Kaplan, 379–383; Stern, 73, 85, 89)*

**59. (A)** Acute heroin intoxication results in an initial euphoria followed by apathy, dysphoria, psychomotor agitation, or retardation. Other signs include pupillary constriction, slurred speech, impaired attention or memory, and drowsiness or coma depending on the severity of the heroin overdose. *(Kaplan, 379–383; Stern, 73, 85, 89)*

**60. (E)** Acute cannabis intoxication results in clinically significant maladaptive behavioral or psychological changes such as impaired motor coordination, euphoria, anxiety, sensation of slowed time, and impaired judgment. Other symptoms of cannabis intoxication include conjunctival injection, increased appetite, dry mouth, and tachycardia. *(Kaplan, 379–383; Stern, 73, 85, 89)*

**61. (A)** Symptoms of phencyclidine intoxication include clinically significant maladaptive behavioral changes such as belligerence, assaultiveness, impulsiveness, unpredictability, vertical or horizontal nystagmus, hypertension or tachycardia, numbness or diminished responsiveness to pain, ataxia, dysarthria and muscle rigidity, hyperacusis. Seizure and coma may occur in case of severe intoxication. *(Kaplan, 379–383; Stern, 73, 85, 89)*

**62. (B)** LSD intoxication is characterized by marked behavioral abnormalities such as marked anxiety or depression, ideas of reference, fear of losing one's mind, paranoid ideation, and impaired judgment. Perceptual changes may occur in a state of full wakefulness and alertness: the patient may express a subjective intensification of perceptions, depersonalization, derealization, illusions, and hallucination. Other physical signs of LSD intoxication include pupillary dilation, tachycardia, blurred vision, incoordination, and sweating. *(Kaplan, 379–383; Stern, 73, 85, 89)*

**63. (D)** Caffeine overdose results in restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, and muscle twitching. *(Kaplan, 379–383; Stern, 73, 85, 89)*

**64. (A)** Signs of alcohol withdrawal are divided into minor and major groups. Minor symptoms start 8 to 9 hours after the last drink. The patient may have insomnia, sweating, hallucinations, and seizures. Major symptoms occur 48 to 96 hours after the last drink. The patient may have increased psychomotor activity, tremor, hallucinations, profound disorientation, and increased autonomic activity. *(Kaplan, 379–383; Stern, 75, 85, 89)*

**65. (B)** Cocaine withdrawal involves a dysphoric mood, fatigue, vivid and unpleasant dreams, insomnia or hypersomnia, increased appetite, and agitation or psychomotor retardation. *(Kaplan, 379–383; Stern, 75, 85, 89)*

**66. (D)** Heroin withdrawal is characterized by a dysphoric mood, nausea or vomiting, muscle aches, lacrimation, pupillary dilation, fever diarrhea, piloerection, and sweating. *(Kaplan, 379–383; Stern, 75, 85, 89)*

**67. (E)** Signs of nicotine withdrawal include dysphoric or depressed mood, insomnia, irritability, frustration, or anger, anxiety, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or weight gain. These symptoms are associated with significant distress or impairment in social functioning. *(Kaplan, 379–383; Stern, 75, 85, 89)*

**68.** **(C)** Abrupt cessation of caffeine use or reduction in the amount of caffeine used causes headache associated with marked fatigue and anxiety, possible depression, and nausea or vomiting, as well as clinically significant distress and impaired social functioning. *(Kaplan, 379–383; Stern, 75, 85, 89)*

**69.** **(D)** Catatonia, mania, major depression, and acute exacerbation of schizophrenia are well-established indications for electroconvulsive therapy (ECT). Other indications for ECT with less evidence of its effectiveness include Parkinson disease, obsessive–compulsive disorder, neuroleptic malignant syndrome, and intractable epilepsy. ECT is effective only in the treatment of the acute symptoms of schizophrenia, not those of chronic schizophrenia. *(Kaplan, 1116–1118; Stern, 360)*

**70.** **(E)** Four clinical interview questions, the CAGE questions, have proved useful in helping to make a diagnosis of alcoholism. The questions focus on Cutting Down, Annoyance by Criticism, Guilty Feeling, and Eye-Openers. The acronym CAGE helps the physician recall the questions, which are as follows:

"C": Have you ever felt you should cut down on your drinking?
"A" Have people annoyed you by criticizing your drinking?
"G" Have you ever felt bad or guilty about your drinking?
"E" Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover?

*(Ewing, 1905–1907)*

**71.** **(B)** Among the selective serotonin reuptake inhibitors (SSRIs), fluvoxamine appears to present the greatest risk of drug–drug interactions. Fluvoxamine is metabolized by CYP 3A4. Fluvoxamine may increase the half-lives of alprazolam and diazepam and should not be coadministered with these agents. Fluvoxamine may increase theophylline concentrations threefold and warfarin concentrations twofold, with important clinical consequences. Fluvoxamine raises concentrations and may increase the activity of clozapine, carbamazepine, methadone, propranolol, and diltiazem. *(Kaplan, 1090)*

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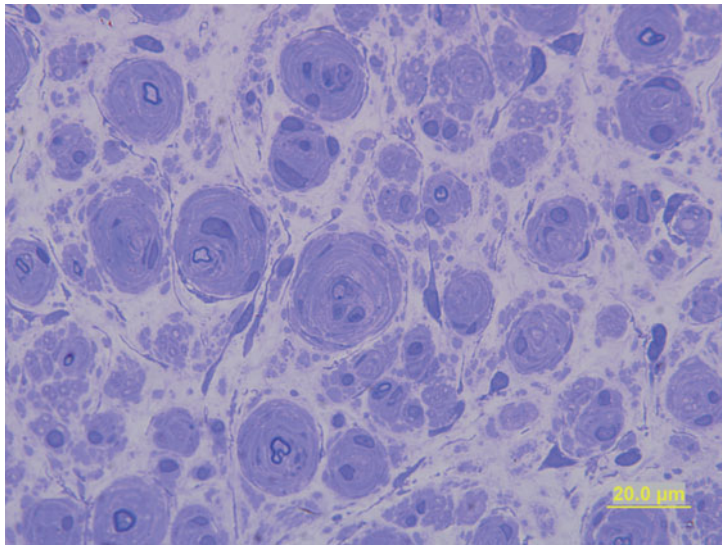


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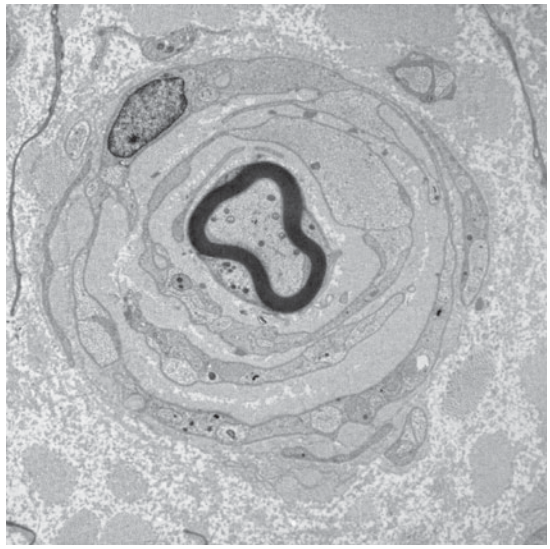

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**Figure 5-4:** Chapter 5, question 15

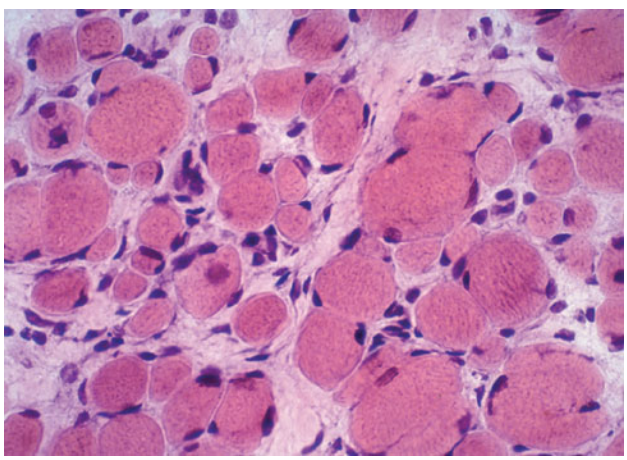


**Figure 5-6:** Chapter 5, question 28

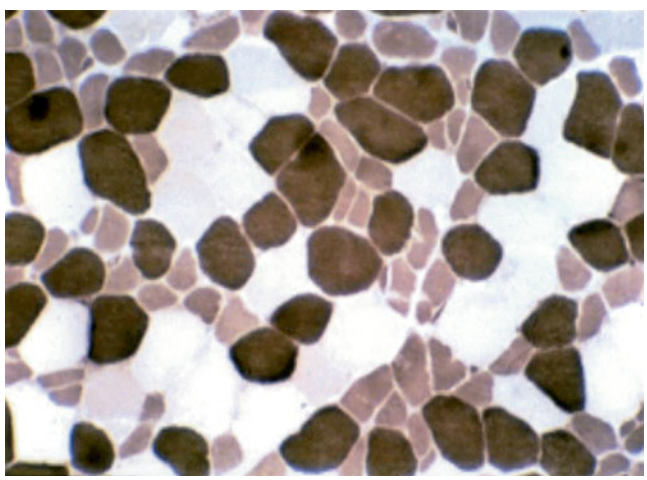
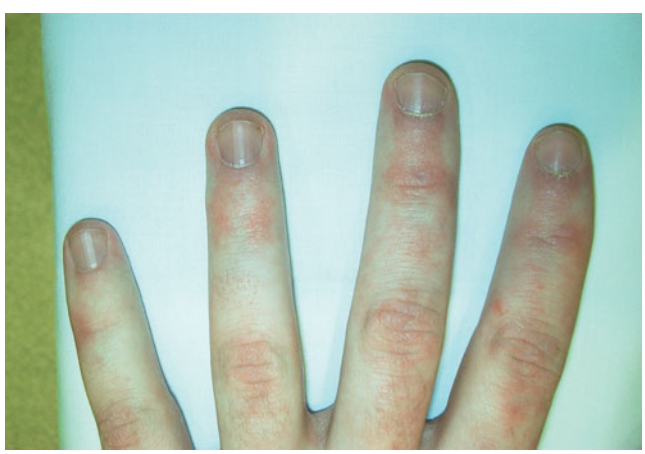


**Figure 5-9:** Chapter 5, question 31



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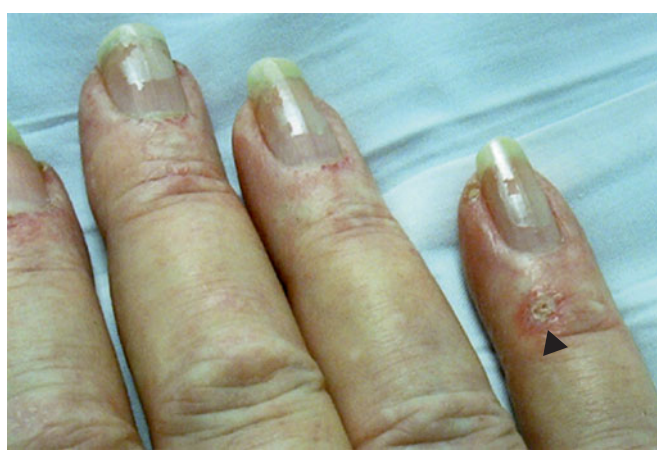


B

**Figure 5-8:** Chapter 5, question 30

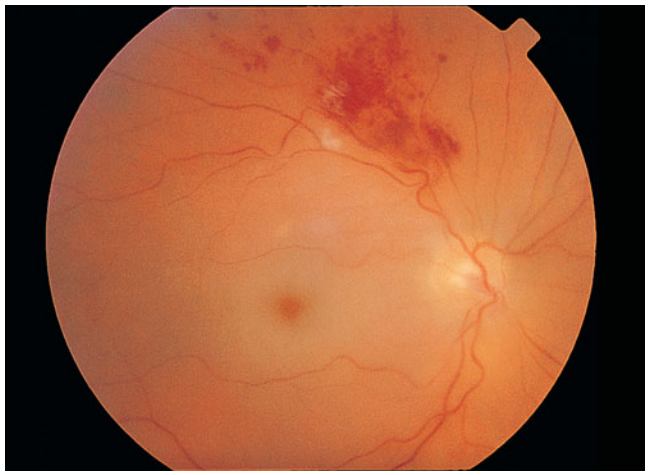


**Figure 12-1:** Chapter 12, question 33

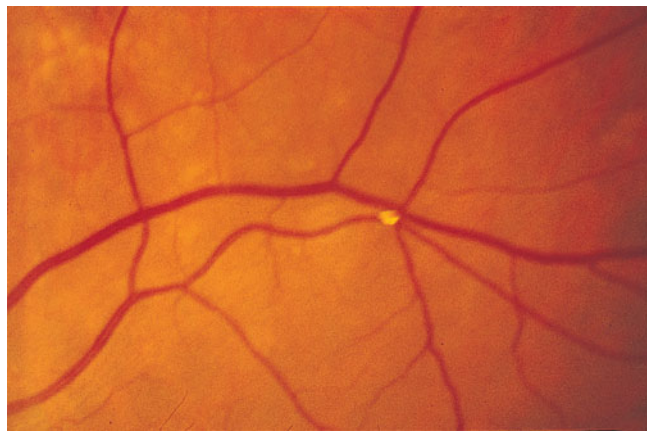


**Figure 12-2:** Chapter 12, question 34

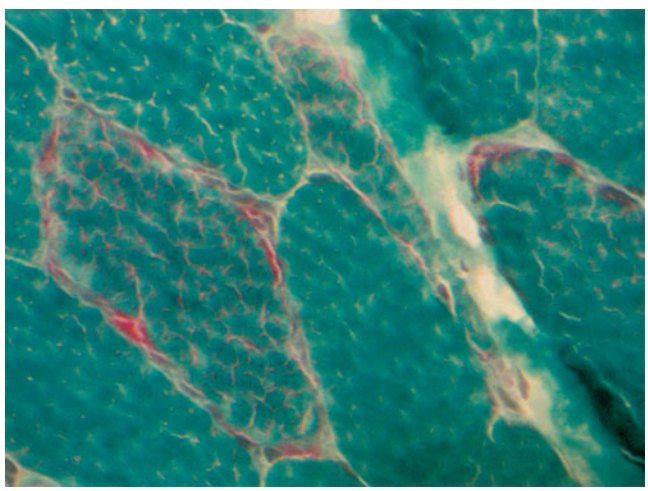


**Figure 15-1:** Chapter 15, question 1

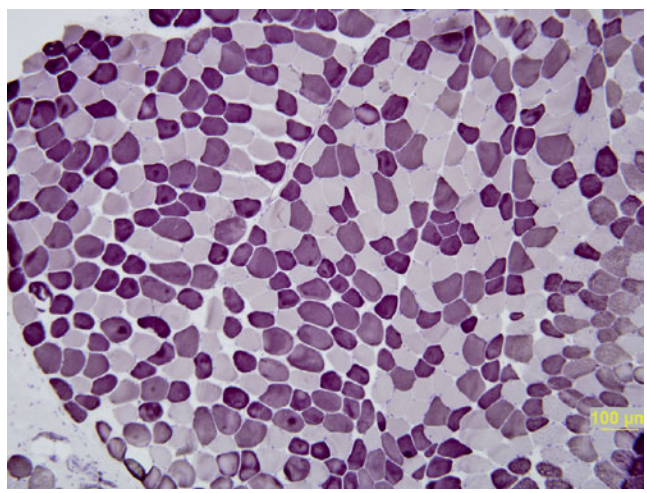
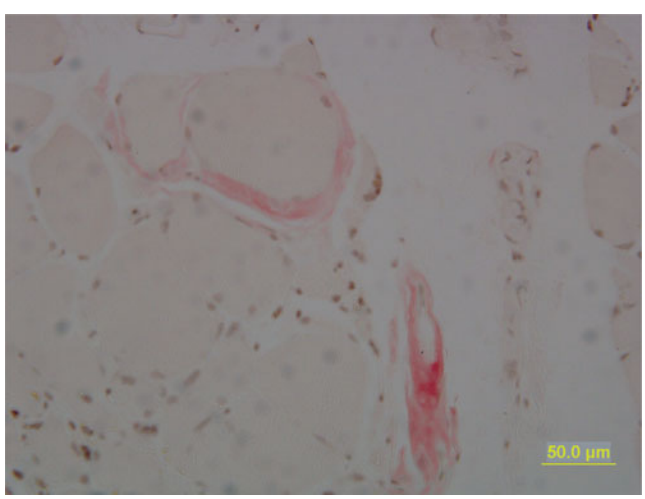



**Figure 15-2:** Chapter 15, question 2

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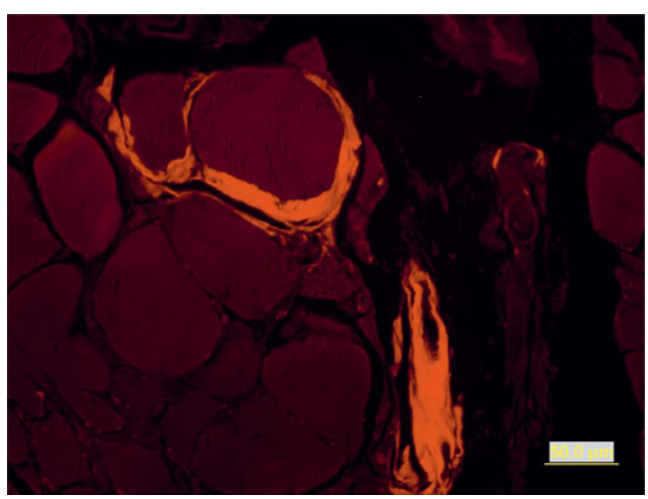


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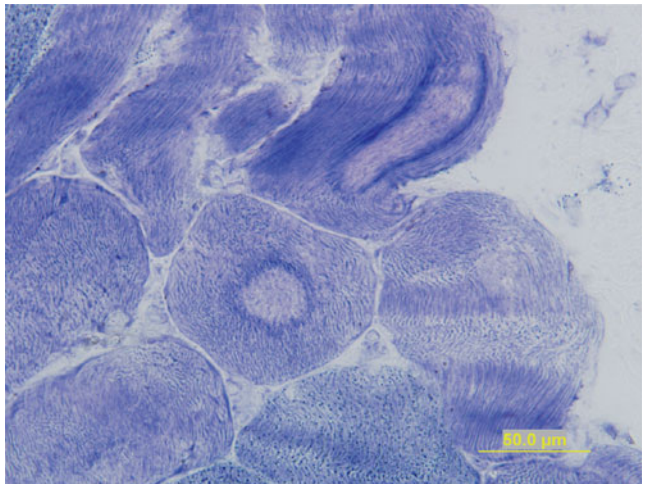
**Figure 15-3:** Chapter 15, question 3

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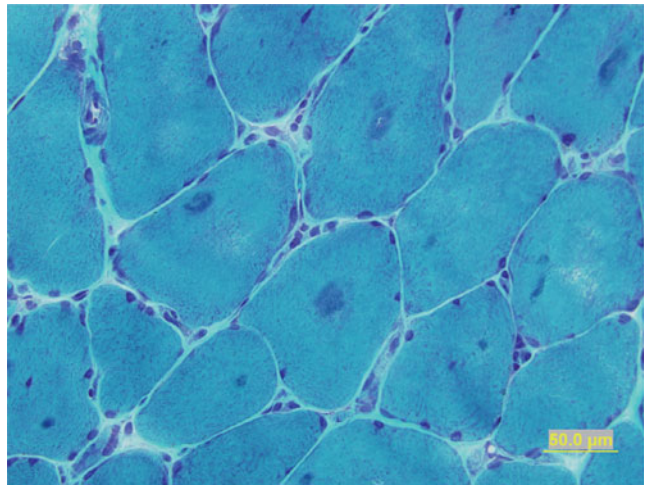



B

**Figure 15-4:** Chapter 15, question 4

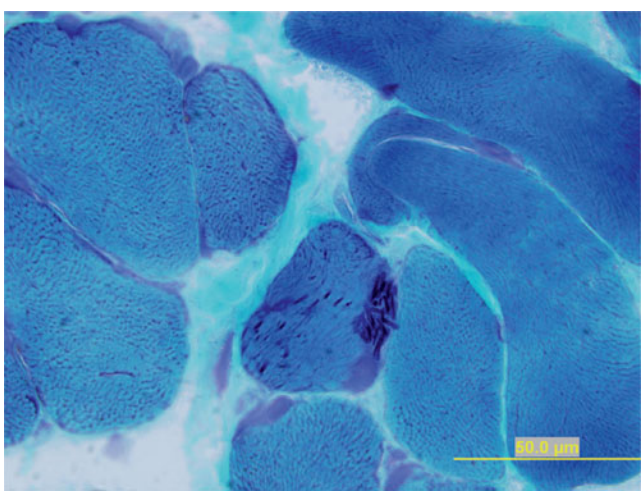



**Figure 15-5:** Chapter 15, question 5

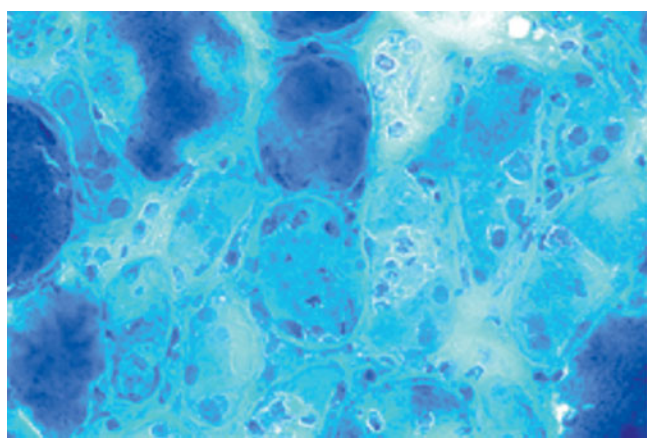
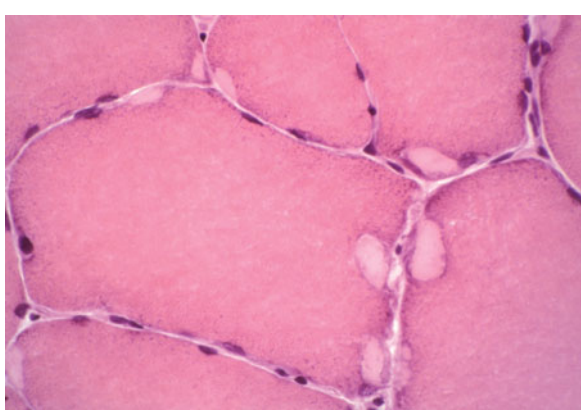


**Figure 15-9:** Chapter 15, question 9



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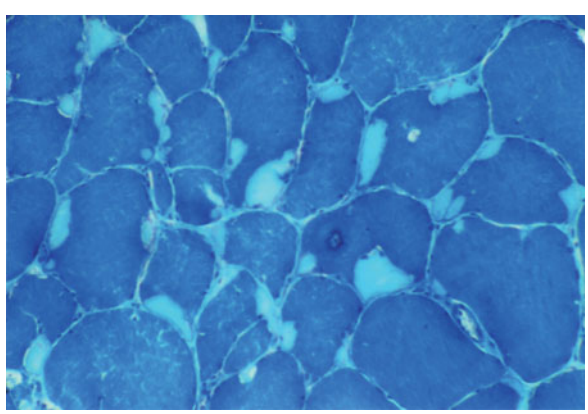


B

**Figure 15-6:** Chapter 15, question 6

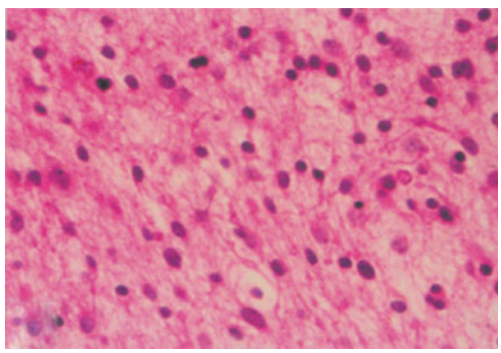


**Figure 15-10:** Chapter 15, question 10

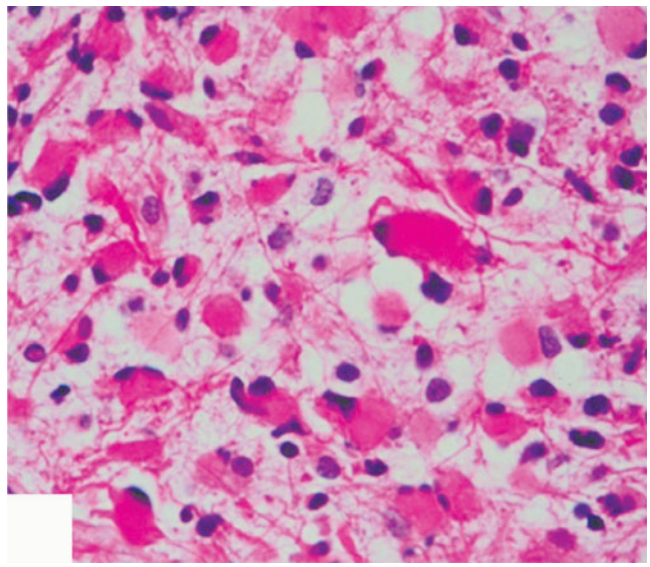
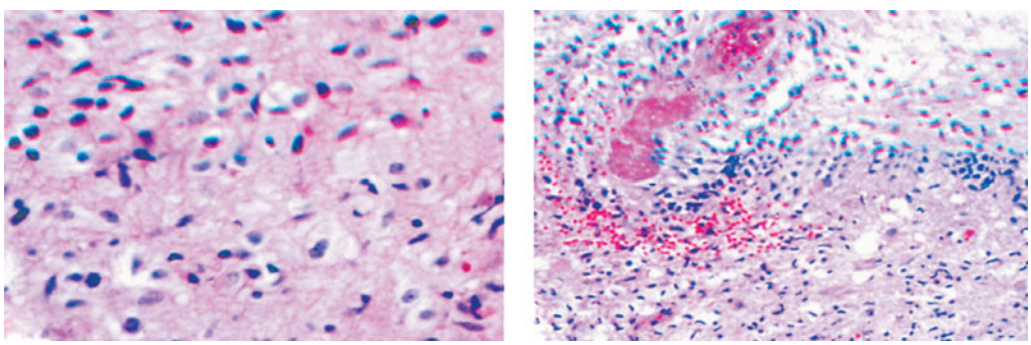


**Figure 15-11:** Chapter 15, question 11



A B

**Figure 15-12:** Chapter 15, question 12

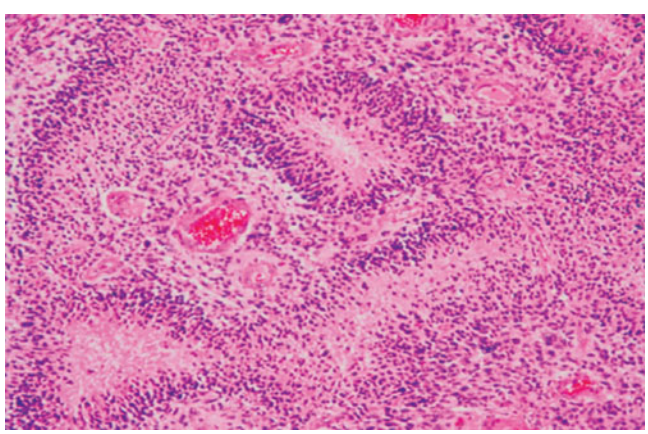


**Figure 15-13:** Chapter 15, question 13

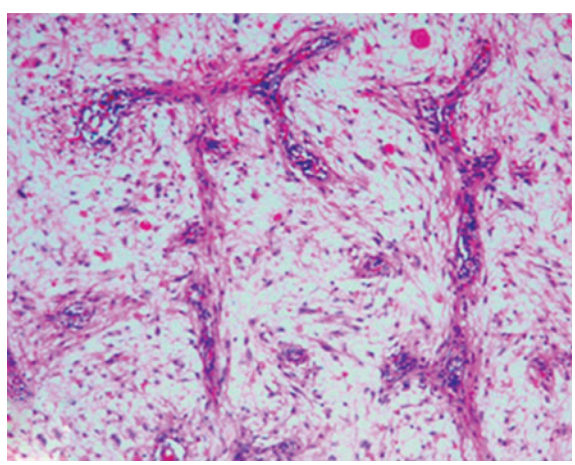


**Figure 15-14:** Chapter 15, question 14

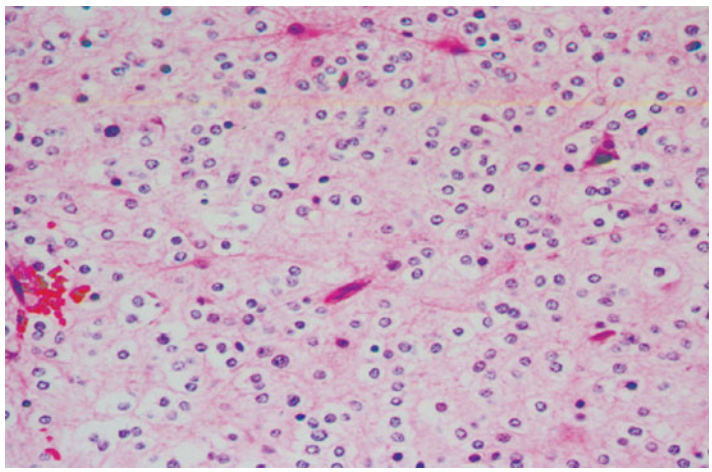


**Figure 15-15:** Chapter 15, question 15

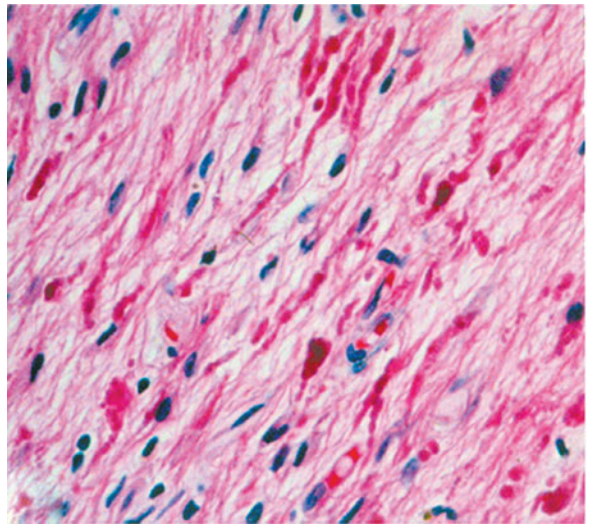


**Figure 15-16:** Chapter 15, question 16

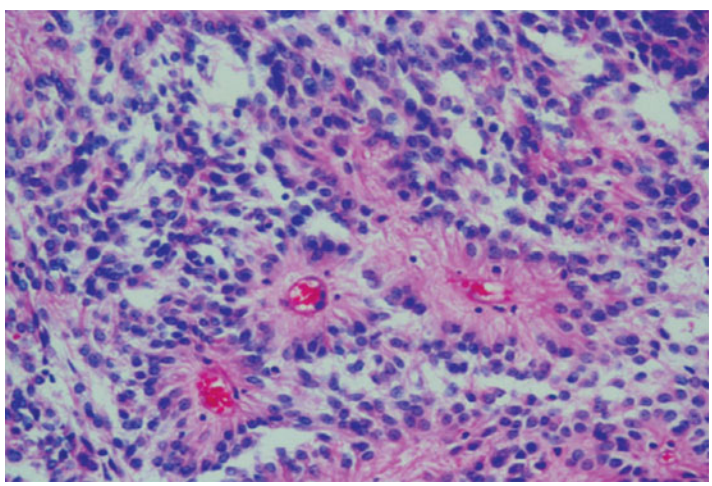


**Figure 15-17:** Chapter 15, question 17

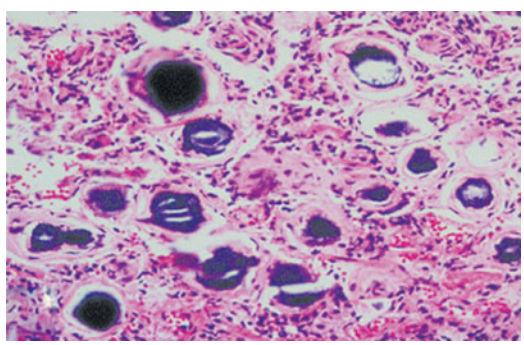


**Figure 15-20:** Chapter 15, question 20

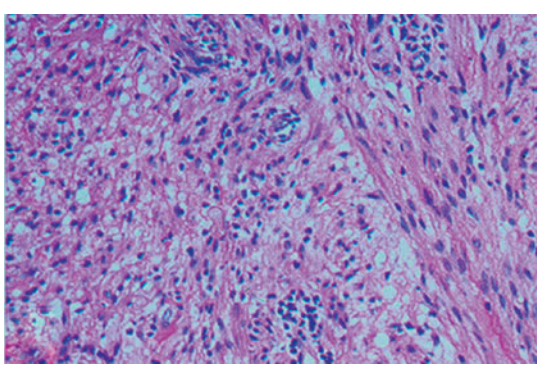


**Figure 15-21:** Chapter 15, question 21

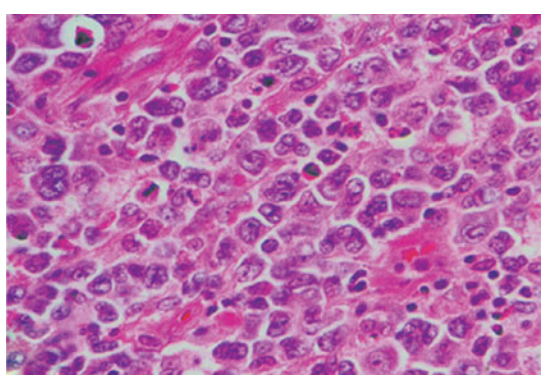


**Figure 15-22:** Chapter 15, question 22

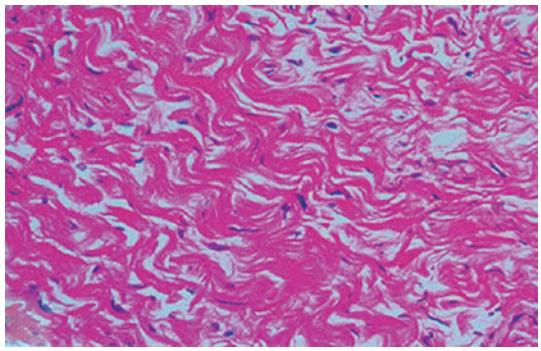


**Figure 15-23:** Chapter 15, question 23

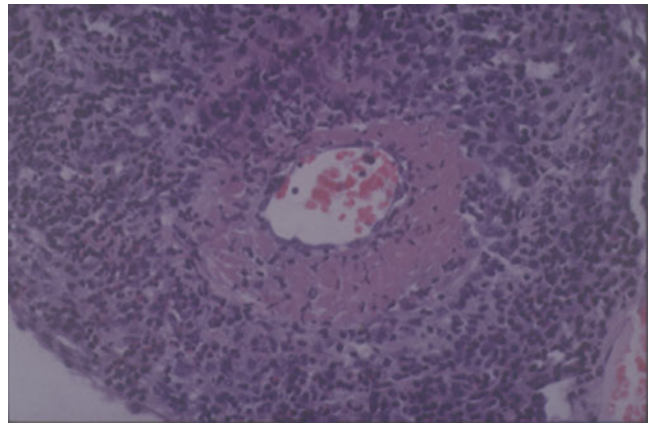


**Figure 15-25:** Chapter 15, question 49

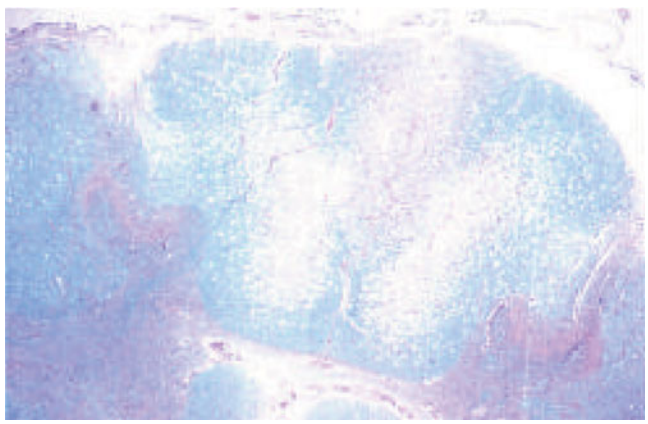


**Figure 15-28:** Chapter 15, question 52

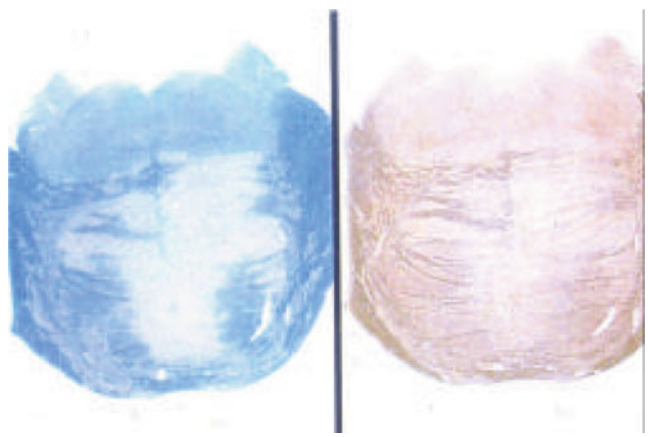


**Figure 15-29:** Chapter 15, question 53

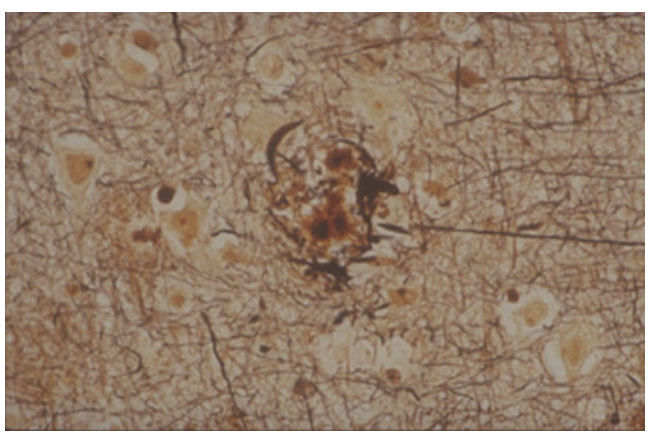


**Figure 15-30:** Chapter 15, question 54

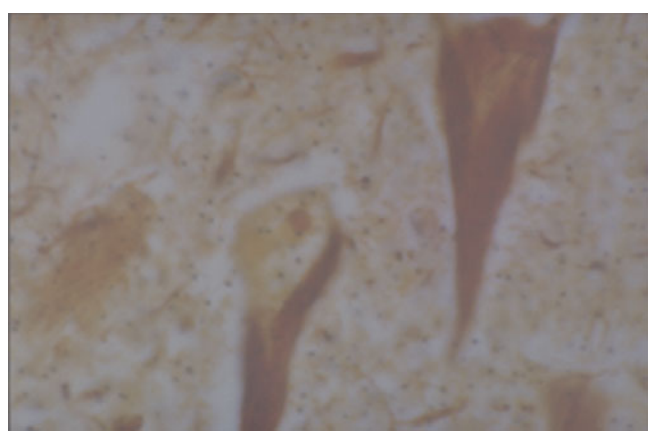


**Figure 15-31:** Chapter 15, question 55

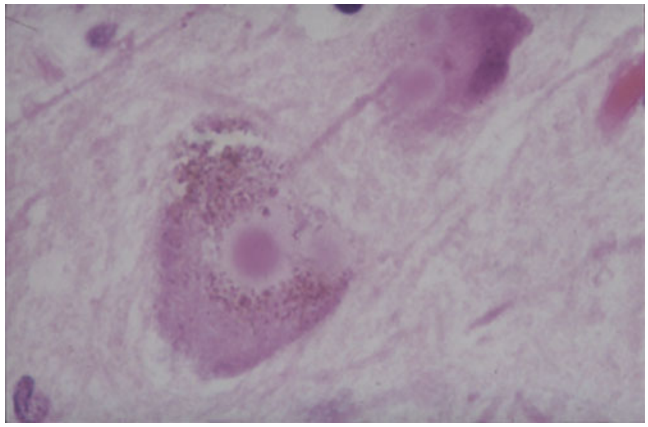


**Figure 15-32:** Chapter 15, question 56

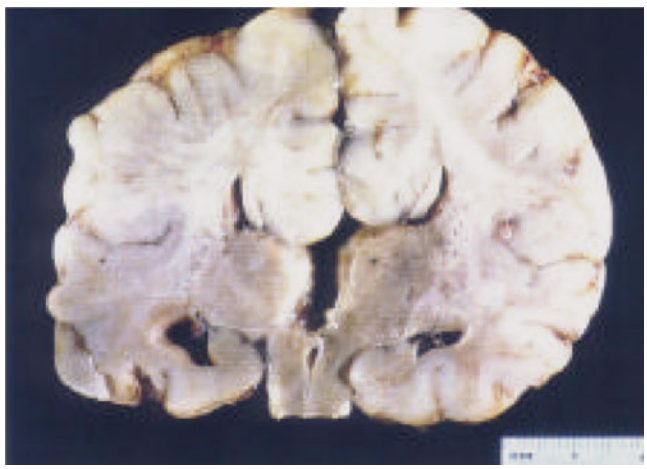


**Figure 15-37:** Chapter 15, question 61

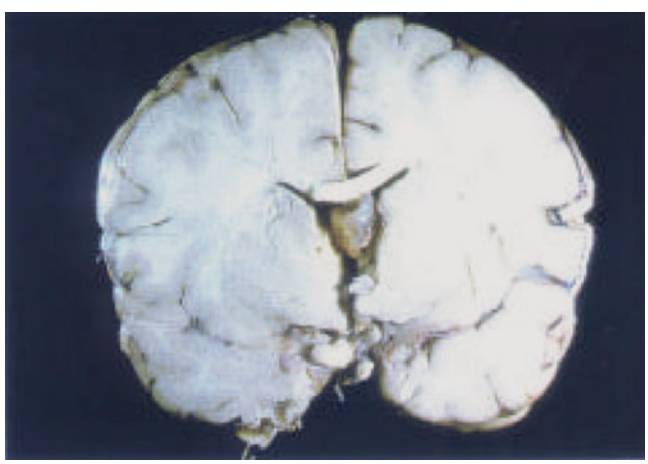


**Figure 15-39:** Chapter 15, question 63

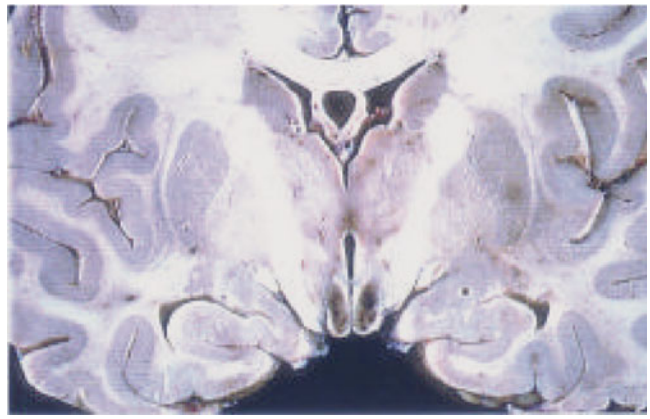


**Figure 15-33:** Chapter 15, question 57

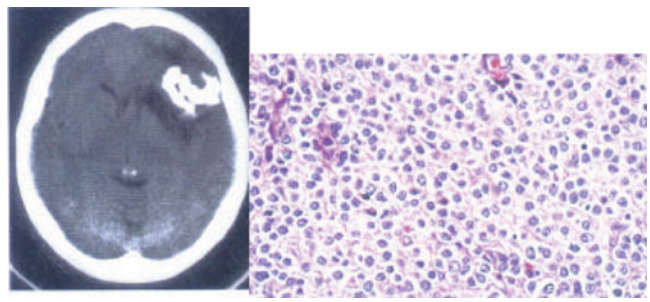


**Figure 15-38:** Chapter 15, question 62

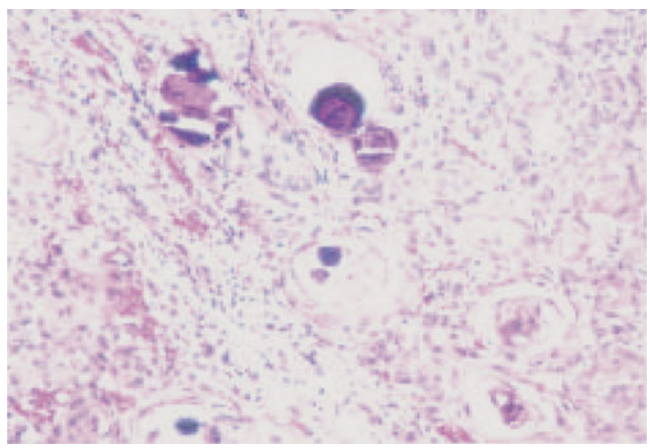


**Figure 15-40:** Chapter 15, question 64

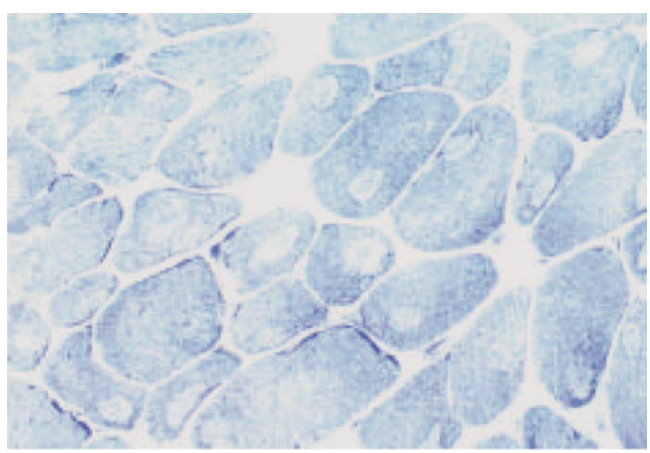


**Figure 15-42:** Chapter 15, question 66

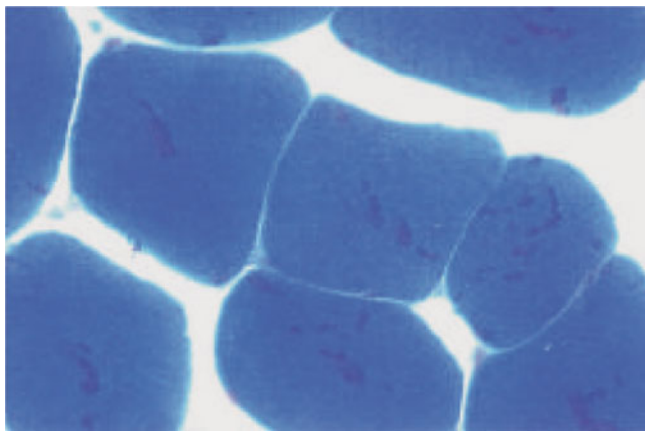


**Figure 15-43:** Chapter 15, question 67

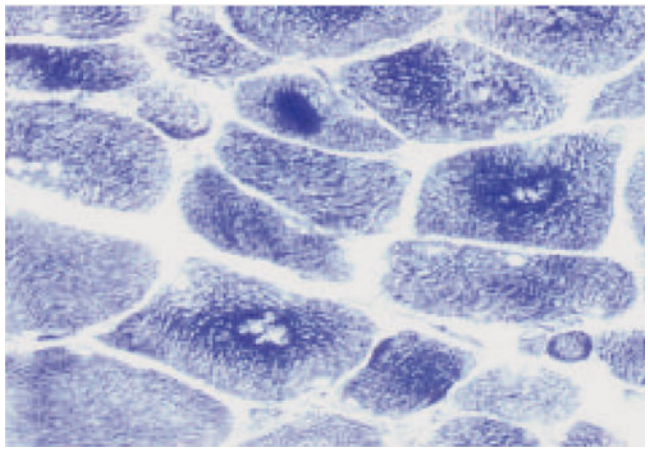


**Figure 15-44:** Chapter 15, question 68

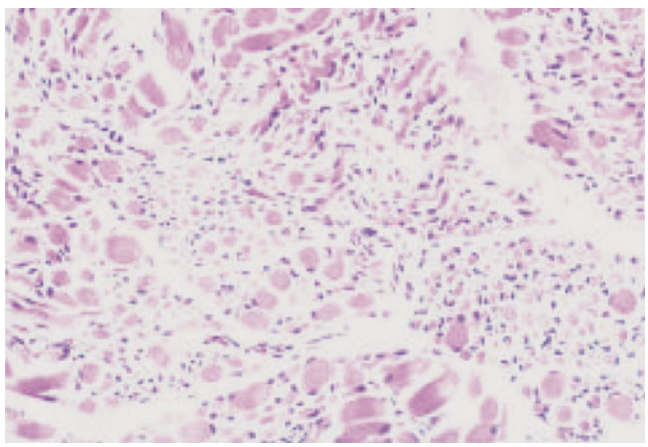


**Figure 15-45:** Chapter 15, question 69

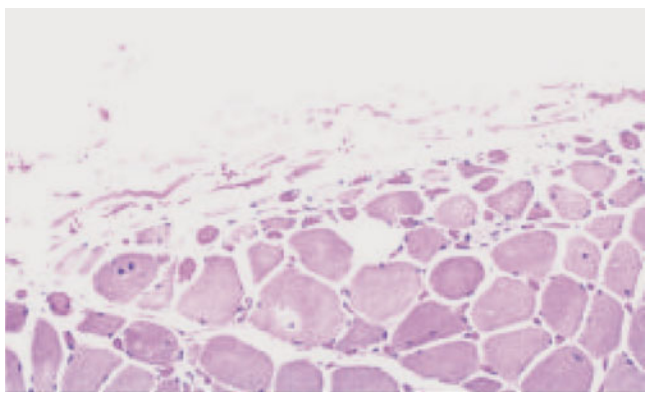


**Figure 15-46:** Chapter 15, question 70

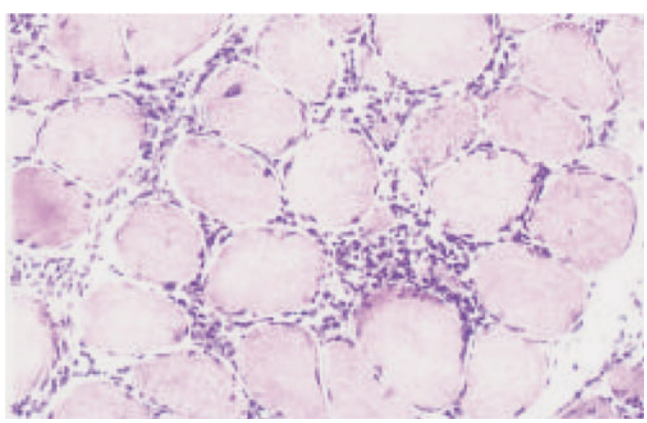


**Figure 15-47:** Chapter 15, question 71

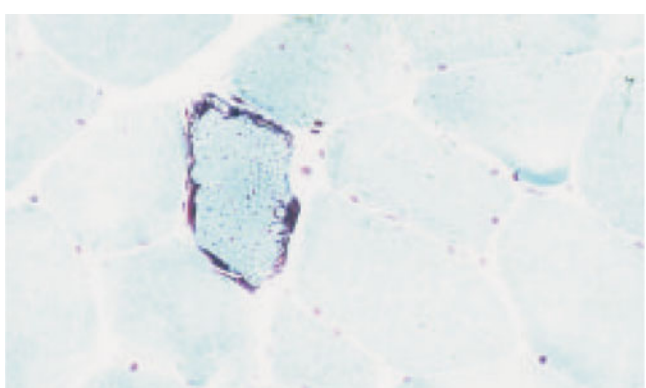


**Figure 15-48:** Chapter 15, question 72