Handbook of Neurodevelopmental and Genetic Disorders in Adults

Edited by

Sam Goldstein and Cecil R. Reynolds

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Sam Goldstein
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Editors

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For Janet, Allyson, and Ryan.

Children come into this world with their own unique qualities and temperaments. This volume is dedicated to a celebration of individual differences and an appreciation of the work of parents and educators in preparing every child for adulthood.

S. G.

To my wife and partner, Julia, for all of her good work in healing families.

C. R. R.

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ABOUT THE EDITORS

Sam Goldstein, PhD, is a member of the faculty at the University of Utah School of Medicine and practices at the Neurology, Learning, and Behavior Center in Salt Lake City, where he provides assessment, case management, and treatment for individuals experiencing diverse neuropsychological impairments throughout the lifespan. He has authored or edited 20 books and many book chapters and research studies. Dr. Goldstein serves as the Editor of the *Journal of Attention Disorders* and sits on six editorial boards. He also serves as editor of a series of books on resilience.

Cecil R. Reynolds, PhD, is Professor of Educational Psychology, Professor of Neuroscience, and Distinguished Research Scholar at Texas A&M University. He is the author of more than 300 scholarly publications and author or editor of 39 books, as well as several widely used tests of personality and behavior. Recognized for his excellence in research and his distinguished contributions to the field of neuropsychology, Dr. Reynolds serves on a number of editorial boards. He maintained a clinical practice treating trauma victims and individuals with traumatic brain injury for 25 years before retiring from clinical work in 2003.

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CONTRIBUTORS

Bonnie J. Baty, MS, Department of Pediatrics, Division of Medical Genetics, University of Utah, Salt Lake City, Utah

Erin D. Bigler, PhD, Departments of Psychology and Neuroscience, Brigham Young University, Provo, Utah

Robert T. Brown, PhD, Department of Psychology, University of North Carolina at Wilmington, Wilmington, North Carolina

Ronald T. Brown, PhD, Department of Public Health, Temple University, Philadelphia, Pennsylvania

John C. Carey, MD, Department of Genetics, University of Utah Hospital, Salt Lake City, Utah

Laura Arnstein Carpenter, PhD, Department of Pediatrics, Medical University of South Carolina, Charleston, South Carolina

Elaine Clark, PhD, Department of Educational Psychology, University of Utah, Salt Lake City, Utah

Elisabeth M. Dykens, PhD, Department of Psychology and Human Development and Kennedy Center Institute, Vanderbilt University, Nashville, Tennessee

Sam Goldstein, PhD, Neurology, Learning, and Behavior Center and University of Utah, Salt Lake City, Utah

Randi J. Hagerman, PhD, MIND Institute, University of California at Davis, Sacramento, California

Robin L. Hansen, MD, Department of Pediatrics and MIND Institute, University of California at Davis, Sacramento, California

James C. Harris, MD, Department of Psychiatry, Johns Hopkins School of Medicine, Baltimore, Maryland

Heather Cody Hazlett, PhD, Department of Psychiatry, University of North Carolina, Chapel Hill, North Carolina

Alexis Herschthal, BA, Department of Social Work, Catholic University, Washington, DC

Crystal Reneé Hill, MS, Department of Educational Psychology, College of Education, Texas A&M University, College Station, Texas

Stefan G. Hofmann, PhD, Department of Psychology, Boston University, Boston, Massachusetts

Susan Homack, MA, Department of Educational Psychology, College of Education, Texas A&M University, College Station, Texas

Arthur MacNeill Horton, Jr., EdD, Psych Associates, Bethesda, Maryland

Arthur MacNeill Horton III, BS, St. Luke's House, Inc., Falls Church, Virginia

H. A. Jinnah, MD, Department of Neurology, Johns Hopkins School of Medicine, Baltimore, Maryland

William R. Jenson, PhD, Department of Educational Psychology, University of Utah, Salt Lake City, Utah

Kordell Kennemer, PsyD, Forensic Evaluation Service, Oregon State Hospital, Salem, Oregon

Joan W. Mayfield, PhD, Our Children's House at Baylor, Dallas, Texas

William M. McMahon, MD, Department of Child and Adolescent Psychiatry, University of Utah Hospital, Salt Lake City, Utah

Kathleen K. McMillan, MEd, Summersill Elementary School, Jacksonville, North Carolina

Alicia E. Meuret, PhD, Center for Anxiety and Related Disorders, Boston University, Boston, Massachusetts

Judith N. Miller, PhD, Department of Child and Adolescent Psychiatry, University of Utah, Salt Lake City, Utah

Jacqueline Anne Noonan, MD, Department of Pediatrics, University of Kentucky Health Care, Lexington, Kentucky

M. Paige Powell, PhD, Learning Support Center for Neurobehavioral Psychology, Texas Children's Hospital, Houston, Texas

Sherri L. Provencal, PhD, Rhode Island Hospital and Department of Psychiatry and Human Behavior, Brown University Medical School, Providence, Rhode Island

Dawn H. S. Reinemann, PhD, Department of Psychology, Cardinal Stritch University, Milwaukee, Wisconsin

Cecil R. Reynolds, PhD, Department of Educational Psychology, College of Education, Texas A&M University, College Station, Texas

Richard Rider, PsyD, Neurology, Learning, and Behavior Center and University of Utah, Salt Lake City, Utah

Elizabeth Roof, MA, Department of Psychology and Human Development and Kennedy Center Institute, Vanderbilt University, Nashville, Tennessee

David J. Schretlen, PhD, Departments of Psychiatry and Radiology, Johns Hopkins School of Medicine, Baltimore, Maryland

Adam Schwebach, MS, Neurology, Learning, and Behavior Center and University of Utah, Salt Lake City, Utah

Dorothee L. Serpas, PhD, Neurology, Learning, and Behavior Center and University of Utah, Salt Lake City, Utah

Julien T. Smith, PhD, Department of Neurology, Primary Children's Medical Center, Salt Lake City, Utah

Kimberly R. Snapp, MSW, Departments of Social Work and Early Childhood Education, Lexington Community College, Paris, Kentucky

Karen Summar, MD, Department of Psychology and Human Development and Kennedy Center Institute, Vanderbilt University, Nashville, Tennessee

Susan M. Swearer, PhD, Department of Educational Psychology, University of Nebraska, Lincoln, Nebraska

Jasper E. Visser, MD, Department of Neurology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

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PREFACE

Matt Ridley (1999) beautifully described the genome when he referred to it as a book. Ridley wrote:

> There are twenty-three chapters called chromosomes. Each chapter contains several thousand stories called genes. Each story is made up of paragraphs called exons which are interrupted by advertisements called introns. Each paragraph is made up of words called codons. Each word is written in letters called bases. There are one billion words in this book. This makes it longer than 800 Bibles. (p. 2)

The human genome contains 3,164.7 million chemical nucleotide bases consisting of four chemicals—adenine, thymine, guanine, and cytosine. The average gene consists of 3,000 bases, but sizes vary greatly, with the largest known human gene being dystrophin at 2.4 million bases. The total number of genes estimated in the human genome is 30,000–35,000, much lower than previous estimates of 80,000–140,000. Of these nucleotide bases, 99.9% are exactly the same in all people. The functions of over 50% of discovered genes are still unknown. At least 50% of the human genome is made up of "junk DNA." These are repetitive sequences that we believe have no direct function, but shed light on chromosome structure and operation. These repetitive sequences reshape the genome by rearranging it, creating entirely new genes, and modifying and reshuffling existing genes. It is believed that during the past 50 million years a dramatic decrease has occurred in the rate of accumulation and repeats in the human genome. Chromosome 1, which is likely the largest, contains nearly 3,000 genes; a Y chromosome contains the fewest (231). Fewer than 2% of the genome codes are for proteins. Humans share most of the same protein families with worms, flies, and plants, but the number of gene family members has expanded in humans, especially for proteins involved in development.

Since the publication of our volume *Handbook of Neurodevelopmental and Genetic Disorders in Children* (Goldstein & Reynolds, 1999), the tug of war in people's acceptance of nurture and nature has continued. Despite increasing evidence of the power of human genes in shaping behavior, development, and life function, our society continues only reluctantly to acknowledge that there is a powerful biological basis for many behaviors. Yet our society is quick to embrace biological determinism for easily observed genetic conditions such as Down or Williams syndrome.

The present text grew out of our continued mutual interest in educating our students and fellow clinicians about the powerful role played by genetics in shaping all human behavior and achievement throughout the lifespan. We were also encouraged by the widespread adoption and acceptance of our child volume, the *Handbook of Neurodevelopmental*

and Genetic Disorders in Children (Goldstein & Reynolds, 1999). Moreover, in our own search for information to assist our patients and their families as well as to educate our students, we have found a dearth of information on adult characteristics and outcomes, as well as on the changing interventions that may be required, for those with neurodevelopmental and genetic disorders first evident in childhood. It is our hope and intent that this text will at least help to remedy this problem and serve as a ready and comprehensive companion to our previous text on children, assisting clinicians to understand, evaluate, and ultimately assist people with genetic and neurodevelopmental disorders throughout their adult years.

In many ways, this work parallels the child volume: We provide a general introduction to the key issues involved in understanding etiology, evaluation, and treatment of the disorders covered, but we also provide a foundation for understanding related disorders that are not covered herein due to space limitations. The chapters that are disorder-specific follow an essentially common format for ease of reading, for reference use of the text, and for consistency in describing the various disorders reviewed. Although the focus of the volume is primarily on the adult presentation of the disorders covered in the child volume, we have also added some disorders that are often not prominent until at least early adulthood (e.g., the various progeroid syndromes), though they are preexisting in childhood.

We both would like to express our continuing appreciation of our publisher at The Guilford Press, Seymour Weingarten, for continuing to allow us to pursue our interests through book-length works at Guilford; we also thank our current editor, Rochelle Serwator. Finally, we both wish to thank Kathy Gardner for her unfailing editorial assistance.

Sam Goldstein, PhD
Cecil R. Reynolds, PhD

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Freedom is the ability to stand up and transcend the limitations of the environment.

—Lyndon Eaves

Freedom lies in expressing your own determinism, not somebody else's. It is not the determinism that makes a difference but the ownership. If freedom is what we prefer then it is preferable to be determined by forces that originate in ourselves and not in others.

—Matt Ridley

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HANDBOOK OF NEURODEVELOPMENTAL AND GENETIC DISORDERS IN ADULTS

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PART I

Basic Principles and Applications

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1

INTRODUCTION

CECIL R. REYNOLDS
SAM GOLDSTEIN

Over the past 25 years, the study of brain–behavior relationships, or neuropsychology, has made increasing inroads into the fields of both clinical psychology and school psychology. Memberships in professional organizations devoted to neuropsychology have increased exponentially, and new organizations have appeared (e.g., the Coalition of Clinical Practitioners in Neuropsychology, or CCPN). Mental health and educational models have increasingly turned to neuropsychology to explain function and dysfunction in human learning, emotion, and behavior. Clinical neuropsychologists—those who apply knowledge in this field to diagnosis and treatment—also have increased in numbers significantly over the last 20 years. Moreover, clinical neuropsychology has taken an increasing role in forensic settings: It is not uncommon to find clinical neuropsychologists involved in competency hearings, criminal trials, and civil litigation. Though it is a new clinical discipline, neuropsychology is approaching maturity quickly. Neuropsychologists have striven to place science squarely at the center of our field.

In our introduction to the child companion to the present volume, we (Goldstein & Reynolds, 1999) reported a MEDLINE search of articles published over the period from January 1993 through November 1998, containing 6,500 peer-reviewed research studies involving chromosomal and genetic disorders in children. An additional 4,000 studies published during that same period of time were identified as specifically dealing with the neuropsychological evaluation and the treatment of children. Yet only 42 studies were found in this data base dealing with both issues. A review of these 42 studies reflected the increasing importance of a simultaneous view and understanding of these two issues for neuropsychologists, physicians, and other medical and mental health professionals. These 42 studies focused upon genetic conditions such as fragile X, Down, and Marfan syndromes, as well as conditions of unknown etiology that were suspected to have a genetic foundation.

In preparing this volume, we completed a series of new searches with a focus upon studies involving the interface of neuropsychology and, in this case, genetic disorders in both children and adults. We began with a current MEDLINE search examining the entire data base through 2004. This time we found 110 studies containing citations for neuropsychological testing and genetic disorders in children and adults. When we searched for genetic disorders and neuropsychological impairments, we found 91 studies, many of which

overlapped with those found in the initial search. When we further searched for chromosomal disorders and neuropsychological impairments, our search yielded 26 studies. However, many of these had already been located in the previous searches. Though our searches may have been limited by keywords and the data base, the lack of new research was surprising. Thus, despite the mapping of the human genome and the dramatic growth in neuropsychology from the perspective of the peer-reviewed, published literature, scientific research has not kept pace with clinical practice and interest in this arena. In fact, as far as we are aware, our 1999 *Handbook of Neurodevelopmental and Genetic Disorders in Children* was the first of its kind. We believe the current volume is the first of its kind as well.

NATURE AND NURTURE

There continue to be few topics as inflammatory, polemic, or controversial in science as the "nature–nurture controversy." Are we human beings simply automatons following predetermined blueprints of development, road maps of behavior? Or are we thinking, feeling organisms capable of shaping and changing our destinies? Or, in fact, has our evolution over millions of years occurred in concert with our environment, so that a discussion of one without the other is likely to bear little fruit? Few contemporary scientists approach this question in a simplistic way. Scientific debate now centers around the relative contributions of nature and nurture—and not in a simplistic additive algorithm (e.g., "Behavior *X* is 80% genetic and 20% environmental in its etiology"), but as existing either in a transactional relationship or, perhaps more likely, in a model of reciprocal determinism of human development and behavior.

A genotype may be considered the raw material and blueprints (genes and chromosomes) provided through the melding of the parental genotypes. Except in the cases of monozygotic twins and cloning, no two human genotypes are alike. The human organism then grows and develops in a unique environment—one that may be shared with other siblings, but is never identical to theirs—to produce the visible, accessible, acting phenotype. No single phenotype is predestined by any single genotype. Attributes that we suggest commonly were genetically determined can often be altered in the course of development or even in later life. Height, known to have a strong heritability in the human population, can be altered dramatically by the manipulation of diet. A walk through the 400-year-old parts of St. Augustine, Florida, quickly reveals that the average height at that time was much less than it is today, and so doorways were lower and furniture was smaller. Many outcomes of genetic disorders may be entirely dependent on or at least strongly determined by changes in the environment. Phenylketonuria (PKU) is an example we have written about before. When phenylalanines are eliminated from the diet of children with PKU, the outcomes for intellect, school adjustment, and other behavioral variables are all much improved. Even behaviors as complex as adult sexual activity and preference, which are strongly genetically influenced, can be altered by significant changes in the stress levels of mothers at particular times during pregnancy. Furthermore, there are critical periods during gestation when hormonal releases affect cell migration and organ development in a preprogrammed fashion. A mother under high levels of stress may alter those hormonal release patterns in ways that affect the developing fetus; in turn, these changes influence the later dyadic interaction of mother and child, which may affect the development of neurochemical systems and even certain aspects of brain development.

As Plomin, DeFries, Craig, and McGuffin (2002) note, it is important to understand the different perspectives used to investigate behavior relative to genetic issues, because of the conceptual and methodological implications of these assumptions. Research in behavioral genetics has traditionally focused on within-species interindividual differences, such as why some children have reading disabilities or attention-deficit/hyperactivity disorder (ADHD) and others do not. Yet many areas of psychology and neuroscience seldom mention individual differences and concentrate instead on normative phenomena. That is, the focus is on understanding universal qualities rather than individual differences. Single-gene mutations in human research have been the center of attention. This approach treats all members of a species as if they were genetically the same, except for a few rogue mutations that disrupt normal processes.

In contrast, the individual-difference perspective considers variations as normal. Thus the interest is in the standard deviation (i.e., how far on average each person falls on specified dimensions from the population means). Common developmental and mental health problems reflect quantitative extremes of a normal distribution. Species-universal and individual-differences perspectives form the basis of current behavioral genetic research. Species universals might include language and learning. Genes are studied as nonvarying entities. Rare, severe disorders such as Rett syndrome, which has come to be understood as a condition reflecting an abnormality in the gene coding for MECP2 protein, leads to a single-gene condition. Common, less severe conditions such as learning disabilities or ADHD may reflect multiple-gene etiologies, while specific cognitive abilities may reflect differences in quantitative trait loci. Although 99.9% of the human DNA sequence is identical for all human beings, the 0.1% that differs—3 million base pairs—is ultimately responsible for the varied genetic influence found for complex traits, including behavioral dimensions and mental health disorders (Plomin, DeFries, McClearn, & McGuffin, 2001). Genes involved in multi- or polygenetic phenomena are called "quantitative trait loci" because they are likely to result in dimensions rather than disorders. The current volume reflects conditions falling in all four of these areas.

Consider the complexity of circadian rhythms. We are well aware that the body acts with a certain rhythm and timing for activities such as sleep. When circadian rhythms are poorly modulated, some individuals develop circadian rhythm sleep disorders. An introduction of a small lipid- and water-soluble indoleamine molecule (*N*-acetyl-5-methoxytryptamine, or melatonin) has been found to modify sleep rhythm significantly, leading to improved sleep and improved daily functioning (Jan & Freeman, 2004). At the other extreme, it has been demonstrated that normal developmental processes can be affected adversely, and sometimes subtly, by exposure to certain neurotoxins. Children exposed chronically to what in the 1950s were considered normal levels of lead demonstrate less self-regulated attention, which is likely to have an adverse impact not only on their education and behavior, but on the life course they take (Davis, Chang, Burns, Robinson, & Dossett, 2004). The complexity of the interaction in potential transmission is incomprehensible. No two combinations of genotype and environment have ever been or will ever be identical. Few components of behavior are too simple to be influenced by environment or too complex to be related to genotype. Yet, as our insight into and understanding of gene–environment interactions increase, we come to appreciate the significant impact human biology has on behavior—sometimes more than we would prefer to believe.

A brief discussion of human intelligence is worth revisiting. The extremes of the various scientific arguments place the nature–nurture contributions to intelligence at 80% and 20% or at 20% and 80%, respectively (see Herrnstein & Murray, 1994; Jensen,

1980; Reynolds & Brown, 1984). One could argue cogently for a relative contribution and interaction of these two extremes, but even in the most extreme genetic view, few propositions remain escapable. First, heritability statistics only apply to groups, and the genetic influence on intelligence for an individual may be more or less than the group heritability. Second, even if 80% of an individual's intelligence is genetically determined, changes in intellectual level as a function of environmental influence can be significant; these changes in turn alter the ability of the organism to create further favorable change in the environment, which may further influence intellectual development or other aspects of brain development and function, and so on it continues (even cross-generationally).

Psychological variables such as intelligence and personality are measured with interval scales, which have no true zero point in noting the absence of a trait. With a true zero point, the actual amount of a characteristic such as height can be determined, and such statements as "A height of 6 feet is twice a height of 3 feet" are accurate. However, interval scales have no true zero point. The only point we can locate definitively is the midpoint of a characteristic. We then measure outward toward the two ends of a distribution, each of which is asymptotic to its axis. That is, we do not know where intelligence (for example) begins or ends. An IQ of 100 cannot be said accurately to reflect twice the intelligence of an IQ of 50 (indeed, it may be a third again as much, or twice, or 10 times as much; we just do not know). We believe that here lies the clinician's opportunity to intervene and create potentially meaningful results, even under the adversity of strong genetic determination. To increase an individual's intellectual level by a full 20% may mean an increase of 10, 20, 30, or even more points on a psychometric scale. The same may hold true for other human characteristics that present as complex behavioral phenomena.

As later chapters in this book describe, many genetic disorders have a high degree of variable expressivity, and this occurs for reasons that may not be well understood. We believe many of these reasons to be treatment-related, or at least associated with biological and environmental interplay in a reciprocal relationship. Early involvement (i.e., during infancy and childhood) of professionals who understand brain–behavior relationships is necessary if adults with neurodevelopmental disorders are to achieve optimal outcomes. Even in the case of a phenomenon such as elevated blood lead levels, researchers have demonstrated that enriched environments may moderate the behavioral and neurotoxic effects of lead exposure, or even the propensity to accumulate lead in the body. Schneider, Lee, Anderson, Zuch, and Lidsky (2001) demonstrated the effects of environmental stimulation promoting changes in hippocampal neurochemistry protect or stimulate repair of lead-damaged hippocampal neurons and functional circuits involved in learning and memory. Thus the caregiving environment can reset the genotype following trauma. Furthermore, cortical development is genetically preprogrammed in many ways; however, not all genetic disorders have full phenotypic impact at the same time. Environments can alter the timing of development in change—and in brain development, timing can be absolutely crucial and can have dramatic effects on the resulting phenotype.

OBJECTIVES OF THIS VOLUME

As in our previous volume, we have set out to provide readers with a stand-alone compendium covering genetic disorders and neurodevelopmental issues, but this time in adults. We have divided the present volume into three sections. Part I covers basic principles and applications, revisiting our perspective on the role of neuropsychology in the assessment, treatment, and management of adults with neurodevelopmental and genetic disorders.

Chapter 2 provides a discussion of neuropsychological assessment in adulthood. Chapter 3 provides an overview of neurodevelopmental disorders and basic concepts in medical genetics. Finally, Chapter 4 provides an overview of current knowledge about neuroimaging and genetic disorders in adulthood.

Part II provides an overview of disorders primarily affecting learning and behavior. Chapters cover learning disabilities, ADHD, Tourette syndrome, anxiety disorders, depressive disorders, autism spectrum disorders, and substance use and abuse. Many of these disorders have an accepted though not yet well-identified genetic etiology. Year by year, we gain a better understanding of the role genetics plays in these conditions' presentation, course, and response to treatment. Most of these conditions occur more frequently in the general population than those covered in Part III.

Part III, by far the lengthiest section, contains 13 chapters providing an overview of conditions that have a lower incidence in the general population, specific etiologies, and overt physical/medical manifestations. Despite the relative infrequency of these conditions, neuropsychologists can expect to see increasing numbers of adults with these problems, especially within medical settings. These conditions are also likely to be faced increasingly by other professionals, such as school psychologists, educational staff members, and primary care physicians—not just those involved in specialty care.

Quality of life has become a paramount issue in the fields of medicine and mental health. An increasing body of research has demonstrated that even those with significant genetic conditions can and do overcome adversity, and are increasingly able to live satisfying and fulfilled lives. As a field, neuropsychology has begun to ask important questions about how individuals with genetic and neurodevelopmental problems overcome many of the obstacles they face in life. How do some of them manage to succeed? What kinds of experiences do they have that may be absent in the lives of those who are not successful? How much of their survival and success can be predicted by genetics, parenting, education, mentoring, temperament, and/or mental health? In a world in which stress and adversity seem to multiply exponentially from one generation to the next, the answers to these and related questions have become increasingly important. We have come to realize that it is just as important to understand strengths and assets as it is to understand liabilities and impairments, perhaps even more so when it comes to intervention. This volume provides readers with a thorough understanding of genetic and neurodevelopmental disorders in adults; more importantly, however, it conveys an appreciation for the importance of creating a treatment model focused not just on relieving liabilities, symptoms, and deficits, but on identifying and harnessing the strengths of all individuals so that they can learn to live happy, successful, fulfilled lives.

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NEUROPSYCHOLOGICAL ASSESSMENT IN GENETICALLY LINKED NEURODEVELOPMENTAL DISORDERS

CECIL R. REYNOLDS
JOAN W. MAYFIELD

Among the common effects of neurodevelopmental and genetic disorders across the lifespan are deviations from normal development of numerous cognitive and related neuropsychological functions. Whereas some such disorders (e.g., Trisomy 21 Down syndrome) tend toward suppression of overall levels of cognitive development, especially intellect, others (e.g., certain of the muscular dystrophies) may produce more specific cognitive effects. In all instances, the range of reactions associated with the majority of known neurodevelopmental and genetic disorders is or can be substantial, particularly in disorders (e.g., phenylketonuria) where early interventions can have major benefits. It is difficult to predict the cognitive profile of a specific adult with any particular diagnosis if both level and pattern of cognitive skills are considered. Although knowledge of the adult patient's cognitive profile is clearly important to schooling and early vocational training, it is likewise important to making a host of recommendations regarding such factors as relative need for supervision in activities of daily living, placement, vocational training, and job placement. The effectiveness of any continuing treatments during the adult years also requires monitoring. Certain neurodevelopmental and genetic disorders (e.g., Down syndrome) also lead to early dementia and may create the need for changes in placement across the lifespan as well; such changes in cognitive status need to be monitored regularly and carefully. Serial neuropsychological testing in neurodevelopmental and genetic disorders serves these needs and others.

Neuropsychological testing is the application of a set of standardized procedures designed to assess and quantify brain function as expressed in overt behavior, and to facilitate additional inferences regarding the covert processes of the brain. Neuropsychological testing may include, for example, assessing the ability of the patient to solve novel problems; to learn new tasks; to execute well-defined simple and complex motor tasks; to deduce relationships via formal logic; to engage in recall, recognition, and related memory tasks; to recognize and/or interpret speech sounds, nonspeech sounds, and visual and tactile stimuli; and to develop and execute plans for behavior, among other specific cognitive

functions. Accurate neuropsychological testing requires maximum effort from the patient if valid inferences regarding brain function are to be obtained.

Neuropsychological testing remains the premier method of assessing brain–behavior relationships even as neuroimaging methods advance. Although single-photon emission computed tomography (SPECT), positron emission tomography (PET), functional magnetic resonance imaging (fMRI), quantitative electroencephalography (qEEG), and other techniques of imaging do tell us whether areas of the brain are functioning at normal levels (typically from a metabolic viewpoint), they simply cannot tell us whether a patient can still read or add numbers or learn a new job skill, or how well the patient may perform at any given cognitive task. Often after viewing a functional neuroimage, we can be reasonably certain that particular skills will be impaired, but the specific nature of the impairment and its degree are elusive to even the most advanced neuroimaging technologies. At times, behavior functions will even be normal in the face of abnormal neuroimaging studies, and vice versa. Therefore, actual neuropsychological testing and quantification of the results remain the gold standard.

The current chapter is intended to provide an overview of the applications of neuropsychological testing and assessment to adults with neurodevelopmental and genetic disorders. An introduction to basic neuropsychological tests and their underlying approaches is also offered, along with guidelines for examining and reporting on such patients. For more detailed information on specific neuropsychological tests and methods of assessment, the reader is referred especially to Lezak (1995) and to Cullum (1998).

Early neuropsychological testing is important to establish the presence of a cognitive disorder as well, since not all individuals with a neurodevelopmental or genetic disorder will have a concomitant cognitive disorder. Since neuropsychological testing is norm-referenced by chronological age, changes in cognitive status can be monitored via repeated or serial testing, and changing patterns of symptomatology can be detected; such changes are common as the central nervous system continues to develop. The effectiveness (or lack thereof) of interventions can be documented as well, and changes can be made as indicated.

These same quantitative procedures are useful throughout childhood, adolescence, and adulthood as cognitive development continues to occur and the focus changes to meeting vocational needs. Qualitative tracking of change and the detection of change through psychometric methods providing age-corrected deviation scaled scores are necessities.

MONITORING AND MANAGING SYMPTOM EXPRESSION

All of the various disorders addressed in this volume are believed to have some degree of genetic linkage, and some such linkages are stronger and more obvious than others. However, all these disorders show what is termed "variable expressivity" (i.e., the number and/or the severity of the symptoms defining the disorder vary across individuals). The interaction between the genetic basis of a disorder on the one hand, and the individual's environmental circumstances and other biological predispositions (which may or may not be affected by the genetics of the primary disorder) on the other, will also alter the severity of symptoms.

There is no cure or elimination of all symptoms for the disorders treated in this volume. Rather, most viable treatments center around symptom management. Neuropsychological and psychological assessments have two primary roles to play beyond assisting in diagnosis. The first, as noted above, is the evaluation of the severity of symptom expression; the second is the assessment of treatment effects through careful psychometric monitoring

of changes in symptom expression. As more and more individuals with neurodevelopmental and genetic disorders survive into late adulthood, this task becomes even more crucial.

Historically, neuropsychological evaluations were conducted with adults with known brain damage or injury, to determine lateralization or localization of lesion or injury. As Lezak (1995) points out, "[the] rapid evolution [of such evaluations] in recent years reflects a growing sensitivity among clinicians to the practical problems of identification, assessment, care, and treatment of brain damaged patients" (p. 7)—a comment that pertains as well to any patient with a compromised central nervous system (CNS), especially if higher cortical functions are involved. Neuropsychologists are often asked to provide information concerning prognosis for recovery, functional ability, and course of treatment. However, the practice of neuropsychology has broadened to include the need to clarify conditions where brain damage or CNS compromise has not been identified; in these cases, evaluations provide additional information for differential diagnoses, which result in more effective treatment planning. A normal neuroimaging and/or normal neurological examination does not mean an absence of disturbed brain–behavior relationships.

The remaining purposes of this chapter are to give a functional definition of neuropsychology, to provide information concerning the necessary components of a neuropsychological evaluation, and to discuss their relationship to treatment. An overview of neuropsychological assessment processes is then presented, both historically and in the context of current practices, that incorporates the basic components of evaluation and encourages integrative, comprehensive assessment of CNS compromise. Furthermore, the chapter provides information concerning why adults are referred for neuropsychological evaluations, and how the results of such evaluations are relevant to their ability to live and function in society generally and in certain settings specifically (in terms of effective remediation techniques, vocational training, and joining the work force).

WHAT IS NEUROPSYCHOLOGY?

Neuropsychology is the study of brain–behavior relationships. It requires acceptance of the idea that the brain, working as an interdependent systemic network, controls and is all-inclusively responsible for behavior. Although this premise seems simple enough now, radical behavioral psychology in the 1960s and early 1970s ignored the brain, leading some to espouse the view that the brain was irrelevant to learning and behavior. (One of us [CRR] was specifically told this in a graduate-level course in learning theory in the 1970s.) Clinical neuropsychology is the application of knowledge gleaned from neuropsychology and related sciences to patient care.

Neuropsychological assessment examines the relationship between brain functioning and behavior through tests that tap specific domains of functioning—typically much more specific domains than those that are represented on general tests of intelligence, such as attention, memory, forgetting, sensory functions, constructional praxis, and motor skills (Farmer & Peterson, 1995; Reitan & Wolfson, 1985), although a test of general intelligence is still necessary as a component of the comprehensive neuropsychological examination. Neuropsychologists examine the functioning of the brain based on behavioral expression, and are able to determine whether a brain dysfunction exists or whether atypical patterns of functional neocortical development are present.

A neurologist looks at the anatomical construction of the brain. Working in conjunction with neurologists, neuropsychologists are able to determine the functioning sequelae

of CNS dysfunction regardless of etiology. Neurologists use advanced neuroimaging techniques, including MRI, PET, and SPECT of brain regions. Working in conjunction with neurologists, neuropsychologists focus on behavior and cognition in order to offer educational help and remediation strategies to family members, vocational specialists, and counselors. Clinical neuropsychologists deal with a variety of issues as family members seek to understand the cognitive and psychological needs of adults who are coping with neurological deficits, acute or chronic. Family members frequently want to know what they can do to provide the optimal environment to help their loved ones reach the maximum level of functioning and enjoy their lives to the full extent possible. They seek to understand the specific deficits. On the basis of a person's medical, family, and developmental history, as well as the specific behavioral and vocational concerns, a neuropsychological assessment is designed and conducted.

Although this chapter discusses examples of specific neuropsychological tests and batteries of tests, neuropsychology as practiced correctly is not a set of techniques. Rather, it is a way of thinking about behavior, often expressed as test scores; in essence, it is a paradigm for understanding behavior.

COMPONENTS OF A NEUROPSYCHOLOGICAL EVALUATION

When one is designing a thorough neuropsychological assessment, just choosing a predesigned battery is typically insufficient. The most common neuropsychological batteries and approaches will need to be supplemented in specific ways, depending upon the referral questions posed. The following eight general guidelines should nevertheless prove useful and are derived from a variety of sources, including our own practices, the general teachings of Lawrence C. Hartlage, and other specific sources—in particular, Rourke, Bakker, Fisk, and Strang (1983).

1. *All (or at least a significant majority) of an adult's relevant cognitive skills or higher-order information-processing skills should be assessed*. This will often involve an assessment of general intellectual level (*g*) via an IQ test that includes both the verbal and nonverbal domains, such as a Wechsler scale or the Reynolds Intellectual Assessment Scales (Reynolds & Kamphaus, 2003). Efficiency of mental processing as assessed by strong measures of *g* are essential to provide a baseline for interpreting all other aspects of the assessment process. Assessment of basic academic skills (including reading, writing, spelling, and math) will be necessary, along with tests such as the Test of Memory and Learning–2 (TOMAL-2; Reynolds & Voress, 2006), which also have the advantage of including performance-based measures of attention and concentration. Problems with memory, attention/concentration, and new learning are the most common of all complaints following CNS compromise and are frequently associated with chronic neurodevelopmental disorders (e.g., learning disability, attention-deficit/hyperactivity disorder [ADHD]).

2. *Testing should sample the relative efficiency of the right and left hemispheres of the brain*. Asymmetries of performance are of interest on their own, but different brain systems are involved in each hemisphere, and these have differing implications for treatment. Whereas some neurodevelopmental and genetic disorders produce generalized deficits in cognitive functions, others have greater impacts on some brain systems than on others. For example, double Y syndrome often produces a pattern with greater relative suppression of left-hemisphere functions and related language skill deficits. Even in a diffuse injury such

as anoxia, it is possible to find greater impairment in one portion of an individual's brain than in another. Specific neuropsychological tests like those of the Halstead–Reitan Neuropsychological Test Battery (HRNB; see below) are useful here, along with measures of verbal and nonverbal memory processes.

3. *Testing should sample both anterior and posterior regions of cortical function*. The anterior portion of the brain is generative, expressive, and regulatory, whereas the posterior region is principally receptive. Deficits and their nature in these systems will have a great impact on treatment choices. Many common tests, such as tests of receptive (posterior) and expressive (anterior) vocabulary, may be applied here, along with a systematic and thorough sensory perceptual examination and certain specific tests of motor function. In conjunction with point 2 above, this allows for evaluation of the integrity of the four major quadrants of the neocortex: right anterior, right posterior, left anterior, and left posterior.

4. *Testing should determine the presence of specific deficits*. Any specific functional problems an adult is experiencing must be determined and assessed. In addition to such problems' being of importance in the assessment of adults with neurodevelopmental disorders, traumatic brain injury (TBI), stroke, and even some toxins can produce very specific changes in neocortical function that are addressed best by neuropsychological assessment. As they age, persons with neurodevelopmental and genetic disorders are more vulnerable to CNS insult as well; this may have more profound effects on an already compromised CNS and produce additional, specific deficits. Similarly, certain patients who have received transplants will display specific patterns of deficits. Neuropsychological tests tend to be less *g*-loaded as a group and to have greater specificity of measurement than many common psychological tests. Noting areas of specific deficits is important in both diagnosis and treatment planning.

5. *Testing should determine the acuteness versus the chronicity of any problems or weaknesses found*. The "age" of a problem is important to diagnosis and to treatment planning. When a thorough history is combined with the pattern of test results obtained, it is possible, with reasonable accuracy, to distinguish chronic neurodevelopmental disorders such as dyslexia or ADHD from new, acute problems resulting from trauma, stroke, or disease. Particular care must be taken in developing a thorough, documented history when such a determination is made. Rehabilitation and habilitation approaches take differing routes in the design of intervention and treatment strategies, depending upon the acuteness or chronicity of the problems evidenced. As people with neurodevelopmental disorders age, symptoms will wax and wane as well, and distinguishing new from old symptoms is important when treatment recommendations are being made.

6. *Testing should locate intact complex functional systems*. The brain functions as a series of interdependent, systemic networks often referred to as "complex functional systems." Multiple systems are affected by CNS problems, but some systems are almost always spared except in the most extreme cases. It is imperative in the assessment process to locate strengths and intact systems that can be used to overcome the problems the person is experiencing. Treatment following CNS compromise involves habilitation and rehabilitation, with the understanding that some organic deficits will represent permanently impaired systems. As the brain consists of complex, interdependent networks of systems that produce behavior, the ability to ascertain intact systems is crucial to enhancing the probability of designing successful treatment. Identification of intact systems also suggests the potential for a positive outcome, as opposed to fostering low expectations and fatalistic tendencies on identification of brain damage or dysfunction.

7. *Testing should assess affect, personality, and behavior*. Neuropsychologists sometimes ignore their roots in psychology and focus on assessing the neural substrates of a problem. However, CNS compromise will result in deviations from normal developmental pathways for affect, personality, and behavior. Some of these changes will be transient, and some will be permanent. Some of these changes will be direct (i.e., the results of CNS compromise at the cellular and systemic levels), and others will be indirect (i.e., reactions to loss or changes in function, or to how others respond to and interact with the individual as a genetic or neurodevelopmental disorder continues to express itself across age). A thorough history, including times of onset of problem behaviors, can assist in determination of direct versus indirect effects. Such behavioral changes will also require intervention, and intervention will be not necessarily be the same if the changes noted are direct versus indirect or if premorbid behavior problems were evident.

8. *Test results should be presented in ways that are useful in a work environment, not just to acute care or intensive rehabilitation facilities, or to physicians*. The majority of individuals with neurodevelopmental and genetic disorders will continue into higher education and/or join the adult workforce. They are assisted in such pursuits by various U.S. federal laws, such as the Americans with Disabilities Act and Section 504 of the Vocational Rehabilitation Act Amendment of 1973. It is important to establish the adult learning and vocational skills of these patients so that they may be directed toward proper education, training, and employment, and to determine any reasonable accommodations that will be required to make them successful. Neuropsychological test results are often used by vocational rehabilitation specialists to determine appropriate guidance on exactly these matters. For those individuals with more serious disorders, for whom postsecondary education and ultimate placement in a competitive work environment are not reasonable expectations, neuropsychological examinations are typically required to document the presence and extent of the disability that has resulted from the extent of their neurodevelopmental or genetic disorders. Not all disorders result in disability, and, especially given the concepts of variable expressivity and modern treatments, disability determination must be made one case at a time. Nevertheless, this determination is crucial to establishing eligibility for such life-changing programs as Supplemental Security Income and other government-funded programs (e.g., Medicaid and Medicare) for those who are permanently disabled from work.

ASSESSMENT APPROACHES AND INSTRUMENTS

There are two major conceptual approaches to neuropsychological assessment. In the first approach, a standard battery of tasks designed to identify brain impairment is used. The HRNB (Reitan & Wolfson, 1985) is the most commonly used battery, followed by the Luria–Nebraska Neuropsychological Battery (LNNB; Golden, Purisch, & Hammeke, 1991). "The second approach to neuropsychological assessment . . . favors the use of a flexible combination of traditional psychological and educational tests. The composition of this battery varies depending upon a number of . . . variables, including history, functioning level, and presenting problem . . ." (Telzrow, 1989, p. 227). The major theoretical premise of any neuropsychological battery is the proposition that behavior has an organic basis (i.e., the brain controls behavior), and thus that performance on behavioral measures can be used to assess brain functioning (Cullum, 1998; Dean, 1985; Grant & Adams, 1986). In order to infer brain functioning from behavioral measures, it is necessary to validate neuropsychological measures on adults with known brain damage.

The Halstead–Reitan Neuropsychological Test Battery

The HRNB was designed to assess the key behavioral correlates of brain function (Reitan & Wolfson, 1993). The HRNB consists of measures in six categories (1) input; (2) attention, concentration, and memory; (3) verbal abilities; (4) spatial, sequential, and manipulatory abilities; (5) abstraction, reasoning, logical analysis, and concept formation; and (6) output (Reitan & Wolfson, 1993). Right–left differences, dysphasia and related deficits (pathognomonic signs), and cutoff scores associated with absolute levels of performance that differentiate nondisabled adults from those with brain damage for each component of the battery are used to determine scores on the General Neuropsychological Deficit Scale, which is the adult's level of performance. Based on normative comparisons, raw scores are weighted as "perfectly normal" (score = 0), "normal" (score = 1), "mildly impaired" (score = 2), or "significantly impaired" (score = 3). Scores for various brain systems and right- versus left-hemisphere differences can also be derived. Table 2.1 lists the components of the HRNB most appropriate for adults. Versions for children and adolescents are available as well.

TABLE 2.1. Halstead–Reitan Neuropsychological Test Battery (HRNB)

Test administered	Functions or skills assessed	Hypothesized localization
Lateral Dominance Exam		Both hemispheres
Aphasia Screening Test	Language	Language items relate to left hemisphere; constructional items relate to right hemisphere
Finger Tapping Test	Motor	Frontal lobe
Grip Strength	Motor	Frontal lobe
Sensory-Perceptual Examination	Sensory-perceptual	
Tactile Perception Test		Contralateral parietal lobe
Auditory Perception Test		Temporal lobe
Visual Perception Test		Visual pathway; visual fields
Tactile Form Recognition		Parietal lobe
Fingertip Writing Perception Test		Peripheral nervous system; parietal lobe
Finger Localization Test		Unilateral errors implicate contralateral parietal lobe—can also occur with bilateral errors
Rhythm Test	Alertness and concentration	Global
Speech Sounds Perception Test	Alertness and concentration	Global; anterior left hemisphere
Trail Making Test		
Part A	Visual–spatial	Global
Part B	Reasoning	Global
Tactual Performance Test		
Total Time	Motor	Frontal lobe
Memory	Immediate memory	Global
Localization	Immediate memory	Global
Category Test	Reasoning	Global

Note. Data from Reitan and Wolfson (1985).

As of this writing, there simply is no set of neuropsychological assessment devices with as much clinical history and empirical support as the HRNB. Among clinicians who prefer the strong scientific base of support for a fixed-battery approach, the HRNB is the most common choice. However, the HRNB, done correctly, is quite lengthy and can require 8–10 hours for administration and scoring; this is too much for some patients and is infrequently supported by third-party payors. The HRNB, although derived initially from Halstead's (1947) biological theory of intelligence, evolved from a more purely actuarial or empirical perspective. During this time, the theoretical models of the famed Russian neuropsychologist Alexander Luria were gaining influence (e.g., Luria, 1966) in Western neuropsychology. All of these factors eventually led to the development of a second, popular fixed battery based upon Luria's model of the working brain.

The Luria–Nebraska Neuropsychological Battery

The LNNB was developed in the late 1970s and 1980s by Charles Golden and colleagues (see Golden et al., 1991) as a means of standardizing and quantifying Luria's clinical assessment procedures. The LNNB was designed to diagnose cognitive deficits that are general in their manifestation, but also to provide information on the lateralization and localization of any focal CNS deficiencies. Golden and colleagues (1991) argue that the LNNB detects very specific problems that might go unnoticed in less detailed examinations or interpretations of global scores. The LNNB is administered to individuals ages 12 and up. There are 12 clinical scales on the LNNB, and each is listed in Table 2.2, along with a listing of various other derivative scales developed for the LNNB.

As Golden (1997; Golden et al., 1991) describes, the LNNB lends itself to three levels of interpretation: scale, item, and qualitative. Each of the LNNB scales yields a *T*-score, and the resulting profile has been the subject of significant empirical work. However, the items within these scales vary in modality and other demand characteristics (i.e., they are quite heteroge-

TABLE 2.2. Scales of the Luria–Nebraska Neuropsychological Battery (LNNB)

Clinical scales	Localization scales
Motor Functions	Left Frontal
Rhythm	Left Sensorimotor
Tactile Functions	Left Parietal–Occipital
Visual Functions	Left Temporal
Receptive Speech	Right Frontal
Expressive Speech	Right Sensorimotor
Writing	Right Parietal–Occipital
Reading	Right Temporal
Arithmetic	
Memory	Summary scales
Intellectual Processes	
Intermediate Memory (Form II only)	Pathognomonic
	Left Hemisphere
Optional scales	Right Hemisphere
	Profile Elevation
Spelling	Impairment
Motor Writing	

Note. Data from Golden, Purisch, and Hammeke (1991).

neous, compared, for example, to items within subtests of the HRNB), and an analysis of item scores is also used. Finally, Luria was a renowned clinician and approached patients individually. Golden and colleagues (1991) thus designed the LNNB to allow qualitative analysis as a supplement to the typical Western psychological approach of quantitative analysis of performance on the various scales. As Table 2.2 indicates, the LNNB has some scales and items where process is the dominant feature, but others where content and learned behavior predominate. Careful review of LNNB performance at all three levels (scale, item, and qualitative) is not just possible but necessary. In a qualitative analysis, the examiner is more concerned with wrong answers than with correct ones, and analyzes the nature of the errors committed by the examinee. For example, was the inability to write to dictation caused by a visual–motor problem; a visual perceptual deficit; a failure of comprehension; or a planning, attention, or execution problem? Only through careful observation and a review of successful tasks can such questions be answered. Examiners must have extensive experience with nondisabled individuals, however, to avoid overinterpretation of such item-level performance and behavioral observations on the LNNB (or any other scale, for that matter).

The Boston Process Approach

Another, newer effort at evaluating process in neuropsychological assessment is known as the Boston Process Approach (BPA) and is described in detail in Kaplan (1988, 1990). In contrast to the use of standard batteries, the BPA uses a flexible battery of developmental and psychological tests, which permits the clinician to select tasks appropriate to the specific referral question, functioning levels, and response limitations of the adult. Client variables such as "age, gender, handedness, familial handedness, educational and occupational background, premorbid talents, patient's and family's medical, neurological, and psychiatric history, drug or alcohol abuse, use of medications (past and present), etiology of the central nervous system (CNS) dysfunction, and laterality and focus of the lesion" (Kaplan, 1990, p. 72) all provide valuable information in developing the assessment. Furthermore, this process provides an analysis of the person's neuropsychological assets, rather than focusing on a diagnosis or a specific localization of brain impairment, for which the standardized batteries have been noted. The flexible-battery approach purportedly translates more directly into educational and vocational interventions, and a major goal of conducting a neuropsychological assessment is to aid in the planning of such interventions. This model also tries to integrate quantitative and qualitative approaches to interpretation and analysis of performance on various cognitive tasks.

The BPA alters the format of items on traditional tests such as the various Wechsler scales, and BPA versions of the Wechsler Intelligence Scale for Children–IV and the Wechsler Adult Intelligence Scale–III are available. Additional, supplementary tests have been devised specifically for the BPA over many years, including the Boston Naming Test, the Boston Diagnostic Aphasia Examination, and the California Verbal Learning Test, along with others. As with other methods of assessment, examiners are advised to use BPA asssments in conjunction with history and interview data and observations of the patient. However, clinicians are also free to pick and choose among a myriad of available neuropsychological measures, some of which are listed in Table 2.3. Here, the examples of various tests that could go into a flexible-battery approach (the BPA being probably the dominant flexible battery approach at this stage) are sorted by key conceptual areas of assessment. (Kaplan might not agree with the inclusion of all of these examples or with the groupings provided, but they are common for many practitioners who mix and match tests under flexible-battery approaches similar to the BPA.)

TABLE 2.3. Examples of Common Neuropsychological Measures Appropriate for Adults

Representative measures	Functions assessed
Intellectual capacity	
Wechsler Adult Intelligence Scale–III (WAIS-III)	Intelligence
Reynolds Intellectual Assessment Scales (RIAS)	Intelligence
Draw-A-Person (DAP:IQ)	Nonverbal intelligence
National Adult Reading Test—Revised (NART-R)	Premorbid IQ estimation
Global cognitive capacity	
Dementia Rating Scale (DRS)	Presence and level of dementia
Mini-Mental State Examination (MMSE)	Gross cognitive screening
Academic achievement	
Wide Range Achievement Test–3 (WRAT-3)	Reading, spelling, math
Wechsler Individual Achievement Test–II (WIAT-II)	Basic academic skills
Woodcock–Johnson III	Basic academic skills
Executive functions and problem solving	
Wisconsin Card Sorting Test (WCST)	Cognitive flexibility/problem solving
Test of Verbal Conceptualization and Fluency (TVCF)	Cognitive flexibility/problem solving/ fluency
Category Test	Abstraction and reasoning
California Sorting Test (CST)	Cognitive flexibility/idea generation
Trail Making Test (Part B)	Mental sequencing/flexibility
Comprehensive Trail Making Test (CTMT)	Mental sequencing/flexibility/inhibition
Raven's Matrices (standard, colored, advanced)	Nonverbal reasoning
Language	
Vocabulary Tests	Word knowledge
Boston Naming Test (BNT)	Confrontation naming
Word Fluency, Controlled Oral Word Association, TVCF	Verbal fluency
Token Test	Comprehension
Boston Diagnostic Aphasia Examination (BDAE)	Overall language function
Aphasia Screening Test	Language screening
Peabody Picture Vocabulary Test–III (PPVT-III)	Receptive language
Comprehensive Receptive and Expressive Vocabulary Test (CREVT)	Receptive and expressive language
Visual–spatial abilities	
Koppitz Bender–Gestalt Test (revised and expanded)	Visual–motor integration/spatial relationships
Developmental Test of Visual Perception: Adolescent and Adult (DTVPA)	Motor enhanced and motor-free visual perception
Full Range Test of Visual–Motor Integration (FTRVMI)	Visual–motor integration/spatial relationships
Clock drawings (command and copy)	Graphomotor construction
Cross drawings (command and copy)	Graphomotor construction
Rey–Osterrieth Complex Figure (copy)	Graphomotor construction/planning
Hooper Visual Organization Test (HVOT)	Visual–spatial integration
Line bisection, visual cancellation tests	Hemispatial inattention
Ruff Figural Fluency Test	Nonverbal fluency

(*cont.*)

TABLE 2.3. (cont.)

Attention/concentration	
Digit Vigilance (number cancellation)	Sustained concentration and attention
Paced Auditory Serial Addition Test (PASAT)	Auditory concent/processing speed
Symbol Digit Modalities Test	Visual attention/psychomotor speed
Trail Making Test (Part A)	Visual tracking/psychomotor speed
Comprehensive Trail Making Test (CTMT)	Mental sequencing/flexibility/inhibition
Continuous-performance tests (various versions)	Sustained vigilance and reaction time
Visual Sustained Attention Test (VSAT)	Sustained concentration and attention
Learning and memory	
Wechsler Memory Scale–III (WMS-III)	Global memory function
Test of Memory and Learning–2 (TOMAL-2)	Global memory function
Wide Range Assessment of Memory and Learning–2 (WRAML-2)	Global memory function
California Verbal Learning Test (CVLT)	Verbal learning and memory
Rey–Osterrieth Complex Figure (recall)	Complex nonverbal memory
Hopkins Verbal Learning Test	Brief measure of verbal memory
Benton Visual Retention Test	Nonverbal memory
Warrington Recognition Memory Test	Verbal/nonverbal recognition memory
Rey Auditory Verbal Learning Test	Verbal learning and memory
Buschke Selective Reminding Test	Verbal learning and memory
Motor and sensory abilities	
Finger Tapping Test	Fine motor speed
Hand Dynamometer	Grip strength
Grooved Pegboard	Fine motor dexterity
Luria three-step hand sequence	Coordinated/integrated sequencing
Sensory-Perceptual Examination (Reitan–Kløve)	Sensory and perceptual skills

Note. Inspired by, and updated from, Table 2 in Cullum (1998).

The strength of the BPA lies in its flexibility, which enables a neuropsychologist to tailor the assessment to the referral problem. There is quite a bit of research on individual aspects of the BPA (see, e.g., White & Rose, 1997), but research on the BPA as a whole is lacking. The modifications made to well-designed, carefully standardized tests such as the Wechsler scales also have unpredictable and at times counterintuitive outcomes in examination of patients. For example, Slick and colleagues (1996) found that changes made to the BPA version of the Wechsler Adult Intelligence Scale—Revised caused a substantial number of individuals to earn lower scores on the modified items than on the corresponding standardized versions of the items, even though the intent of the modification was in part to make the items easier. This could easily draw a clinician into overinterpretation and overdiagnosis of pathology. Slick and colleagues correctly conclude that whenever changes are made to standardized instruments, comprehensive norms are required under the new testing conditions. They also conclude that clinical interpretation of such modified procedures prior to the development and purveyance of the norms is questionable from an ethical standpoint.

The lack of good normative or reference data has been a long-term problem for neuropsychological assessment (see, e.g., Reynolds, 1997). This causes a variety of problems related to test interpretation, not the least of which is understanding the relationship of such variables as gender, ethnicity, and socioeconomic status to test performance. The BPA, because of its principal strengths, also makes inordinate cognitive demands on the examiner.

Another major concern about the BPA is the difficulty in establishing validity for the innumerable versions of batteries used, as interpretations may not be uniform or reliable. This issue has been addressed inadequately thus far. Until the normative and data integration problems of the BPA are solved, it is recommended here primarily only as a research approach (albeit a most promising one). It may be useful now, but only to a small group of clinicians with extensive, supervised training in its use from one of its progenitors.

REASONS FOR REFERRAL

Adults are initially referred to neuropsychologists for a variety of reasons. Adults may benefit from neuropsychological assessments if they have experienced learning difficulties or congenital brain defects, especially as they prepare for their vocation. Functioning adults who have sustained TBI, stroke, or other neurological injury or illness will benefit from an evaluation to help determine appropriate vocational adjustments and provide information to facilitate rehabilitation or habilitation. Earlier in this chapter, we have reviewed a variety of reasons for neuropsychological assessment of adults with neurodevelopmental and genetic disorders. Understanding the current referral questions and the particular patient's history are critical to performing an appropriate evaluation.

No two brain dysfunctions or injuries are the same. Two adults can experience the same type of injury or developmental neuropathology, and can even have identical neuroimaging studies, yet still may require different types of remediation. The information gained from a neuropsychological evaluation enables the neuropsychologist to make recommendations concerning attention, learning and memory, intellectual functioning, cognitive strengths and weaknesses, problem-solving abilities, and so forth to the patient and his or her family members.

TEACHING/HABILITATING ON THE BASIS OF STRENGTHS

One of the primary reasons for conducting a neuropsychological evaluation is not to determine "what has been impaired," but rather to determine "what has been spared." Family members supply numerous examples of what a person is unable to do: "He cannot follow instructions," "She can't remember anything." Very seldom does a referral source approach an evaluation with a list of the activities or skills that the person is able to accomplish with ease and proficiency. But whether or not the source realizes it at the time of the referral, such a list contains the very information that is urgently needed for the person to reach his or her maximal level of functioning. It is essential that we optimize a person's strengths instead of his or her weaknesses. Teaching to a person's weaknesses focuses on brain areas that are damaged or dysfunctional. When teaching and therapeutic methods focus on cortical areas that are not intact, the potential for failure is increased, which is harmful. Reynolds (1981b) also points out that research on these remedial practices (referred to as "deficit-centered models" of remediation) has found them to be ineffective.

In contrast, teaching to a person's strengths has a number of advantages. This method may be especially helpful for people who are resistant to focused remediation of weaknesses. When self-confidence is low or when a failure syndrome emerges as a result of frustration, a strength-centered approach should be adopted. Moreover, Luria (1966) suggested that recovery of function following cortical damage can be achieved "by the replacement

of the lost cerebral link by another which is still intact" (p. 55). This fundamental principle works for chronic CNS problems evident in neurodevelopmental and genetic disorders as well. Intact complex functional systems can be used to develop compensatory behaviors to accomplish a variety of behavioral goals.

OTHER INFORMATION NEEDED FOR ASSESSMENT

When a person is initially referred to a neuropsychologist, his or her history is the first critical set of information. This history should include prenatal, perinatal, developmental, and medical history. It is also important to include familial information about educational or learning problems, vocation, and family structure. If the person has had a TBI or illness, age of onset, duration of illness of injury, and time since illness or trauma all provide important information, in addition to a full medical history of the extant genetic or neurodevelopmental disorder.

Educational records provide invaluable information as well. School transcripts may be helpful in evaluating individual motivational factors, study habits, and daily classroom performance. IQ tests or other standardized academic tests (e.g., the Woodcock–Johnson III, the Wide Range Achievement Test–3, the Wechsler Individual Achievement Test–II) provide standardized scores, which give further information about a person's previous cognitive and academic strengths and weaknesses. This information will allow us to track changes throughout adulthood, as well as to ascertain the extent of previously acquired academic skills and any regression in development that may be evident since the person has left school.

HABILITATION AND REHABILITATION CONSIDERATIONS

When one is making recommendations for habilitation of a person with a chronic developmental disorder, several additional considerations are evident. It is important to determine what types of functional systems are impaired. Impaired systems may, for example, be modality-specific or process-specific. The nature or characteristics of such impairments must be elucidated before an intelligent remedial plan can be devised.

The number of systems impaired should be determined. In addition, because a person with a disability may not be able to work on everything at once, a system of priorities should be devised so that the impairments with the most important impact on overall quality of living are the first and most intensely addressed. The degree of impairment, a normative question, will be important to consider in this regard as well. At times, this will require the neuropsychologist to reflect on the indirect effects of the disorder, as an impaired or dysfunctional system may adversely affect other systems that are without true direct organic compromise (i.e., an organic problem in one part of the brain may, through faulty communication systems, interfere with otherwise normal brain systems).

As noted earlier, the quality of the neuropsychological strengths that exist will also be important; this tends to be more of an ipsative than a normative determination. Certain strengths are more useful than others, as well. Preserved language and speech are of great importance, for example, whereas an intact sense of smell (an ability often impaired in TBI) is of less importance in designing treatment plans and outcome research. Even more important to long-term planning for individuals with disabilities are intact planning and

concept formation skills. The executive functioning skills of the frontal lobes take on greater and greater importance with age, and strengths in these areas are crucial to long-term planning (as are weaknesses).

MEMORY AND LEARNING

In cases of TBI, including closed head injury, problems with memory and attention are the most common, frequent complaints at all age levels. However, memory and learning problems seem to characterize nearly any CNS disorders in which higher cortical systems are involved (e.g., see Gillberg, 1995; Knight, 1992; Reynolds & Bigler, 1997).

The approach to assessment proffered herein would seem to require an assessment of a person's memory and immediate learning skills. The neuropsychological batteries primarily in use with adults, even when accompanied by a thorough assessment of intellect (as they should be), provide only a brief screening of memory and learning skills.

Basic Neurobiology of Memory

"Attention" leaves tracks or traces within the brain that become memory. "Memory," as commonly conceptualized, is the ability to recall some event or information of various types and forms. Biologically, memory functions at two broad levels: the level of the individual cell, and a systemic level. With the creation of memories, changes occur in individual cells (see, e.g., Cohen, 1993; Diamond, 1990; Scheibel, 1990), including alterations in cell membranes and synaptic physiology.

At the systems level, there exists a division of sorts in the formation of memory and memory storage. There is considerable evidence for distributed storage of associative memory throughout the cortex, which may even occur in a statistical function (Cohen, 1993). At the same time, evidence indicates more localized storage of certain memories and localized centers for memory formation and for classical and operant conditioning.

The medial aspect of the temporal lobe—particularly the hippocampus and its connecting fibers within the other limbic and paralimbic structures—is particularly important in the development of associative memory. The limbic system (with emphasis on the posterior hippocampal regions) also mediates the development of conditioned responses, and some patients with posterior hippocampal lesions may not respond to operant paradigms in the absence of one-to-one reinforcement schedules. Damage to or anomalous development of either the medial temporal lobe and its connecting fibers, or the midline structures of the diencephalon, typically results in the difficulties in formation of new memories (anterograde amnesia); however, it may also disrupt recently formed memories preceding the time of injury (retrograde amnesia) when acute insult is involved. Various regions within the limbic and paralimbic structures have stronger roles in formation of certain types of memory, and simple conditioned memories may occur at a subcortical level. Through all the interactions of these systems, related mechanisms of attention, particularly in the brain stem and the frontal lobes, are brought to bear and will influence memory formation directly and indirectly. Memory is a complex function of the interaction of brain systems (with unequal contributions), and damage to or abnormal neurodevelopment of one or more of many structures may impair the ability to form new memories.

In right-handed individuals, there is a tendency for damage or abnormal developmental patterns within the left temporal lobe and adjacent structures to affect verbal and se-

quential memory more strongly. Damage to the cognate areas of the right hemisphere affects visual and spatial memory more adversely.

Through distributive storage of memory, the entire brain participates in memory functioning. The recall of well-established memories tends to be one of the most robust of neural functions, whereas the formation of new memories, sustained attention, and concentration tend to be the most fragile of neural functions. Neurological dysfunction of most types is associated with a nonspecific lessening of memory performance, along with disruptions of attention and concentration; this is of greater consequence when temporolimbic, brain stem, or frontal lobe involvement occurs. However, a variety of psychiatric disturbances, especially depression, may also suppress fragile anterograde memory systems. A careful analysis of memory, forgetting, affective states, history, and comprehensive neuropsychological test results may be necessary before one can conclude that memory disturbances are organic in origin, especially in the complex case of neurodevelopmental disorders.

Assessing Memory

There are three major memory batteries available for use with adults that provide reasonably comprehensive assessment of memory functions: the TOMAL-2, mentioned earlier (Reynolds & Voress, 2006); the Wide Range Assessment of Memory and Learning–2 (WRAML-2; Adams & Sheslow, 2003); and the Wechsler Memory Scale–III (WMS-III; Wechsler, 1997). Of these, the TOMAL-2 is the most comprehensive, while the WMS-III has the most extensive history of research and clinical application in the evaluation of CNS disturbances of all types. All three batteries include measures of attention, verbal and nonverbal memory, learning, and forgetting, all of which are central to a thorough evaluation of memory and learning function.

As noted above, memory may behave in unusual ways in an impaired brain, and traditional content approaches to memory may not be as effective as more comprehensive assessment strategies. In this regard, the TOMAL-2 provides alternative groupings of the subtests into five supplementary indexes: Sequential Recall, Free Recall, Associative Recall, Learning, and Attention and Concentration. These supplementary indexes were derived by having a group of "expert" neuropsychologists sort the 14 TOMAL-2 subtests into logical categories (Reynolds & Voress, 2006). To provide greater flexibility to the clinician, a set of four purely empirically derived factor indexes—Complex Memory, Sequential Recall, Backward Recall, and Spatial Memory—has been made available as well (e.g., see earlier factor analyses by Reynolds & Bigler, 1996).

The TOMAL-2 subtests systematically vary the format of both presentation and response, so as to sample verbal, visual, and motoric modalities and combinations of these. Multiple trials to a criterion are provided on several subtests, including the Selective Reminding subtests, so that learning or acquisition curves may be derived. Multiple trials (at least five are necessary, according to Kaplan [1996], and the TOMAL-2 provides up to six) are provided on the Selective Reminding subtests to allow an analysis of the depth of processing. In the Selective Reminding format (wherein examinees are reminded only of stimuli "forgotten" or unrecalled), when items once recalled are unrecalled by an examinee on later trials, problems are revealed in the transference of stimuli from working memory and immediate memory to more long-term storage. Cueing is also provided at the end of certain subtests, to add to the examiner's ability to probe depth of processing.

Subtests are included that sample sequential recall (which tends strongly to be mediated by the left hemisphere, especially temporal regions; see, e.g., Lezak, 1995) and free

recall in both verbal and visual formats to allow localization. To assess more purely right-hemisphere functions, tests of pure spatial memory are included; these are very difficult to confound via verbal mediation.

Well-established memory tasks (e.g., recalling stories) that correlate well with school learning are also included, along with tasks more common to experimental neuropsychology that have high (e.g., Facial Memory) and low (e.g., Visual Selective Reminding) ecological salience. Some TOMAL-2 subtests employ highly meaningful material (e.g., Memory for Stories), whereas others use highly abstract stimuli (e.g., Abstract Visual Memory).

Aside from allowing a comprehensive review of memory function, the purpose of such a factorial array of tasks across multiple dimensions is to allow a thorough, detailed analysis of memory function and of the sources of any memory deficits that may be discovered. The task of the neuropsychologist demands subtests that have great specificity and variability of presentation and response, and that sample all relevant brain functions, in order to solve the complex puzzle of dysfunctional brain–behavior relationships. Kaufman (1979) first presented a detailed model for analyzing test data in a comprehensive format (later elaborated; Kaufman, 1994), which likens the task of the clinician to that of a detective. The thoroughness, breadth, and variability of the TOMAL-2 subtests, coupled with their excellent psychometric properties, make the TOMAL-2 ideal for use in a model of "intelligent testing" and particularly in the analysis of brain–behavior relationships associated with memory function.

ASSESSMENT OF BRAIN–BEHAVIOR RELATIONSHIPS THROUGH LURIAN PROCESSING MODELS

The previously reviewed approaches to assessing brain–behavior relationships focus on specificity of aptitudes or mental skills (i.e., their relative distinctiveness from one another) as a model for their assessment. Processing models of brain function focus more heavily on the manipulative demands of a mental task than on the content demands. Cognitive tasks can thus be grouped according to these processing demands for more reliable and detailed assessment, leading to conclusions about brain function with direct implications for intervention (e.g., see Hartlage & Reynolds, 1981; Kamphaus & Reynolds, 1987; Reynolds, 1981a, 1981b).

From a clinical perspective, the neuropsychological models of information processing as posed by Luria are of the greatest utility. "Alexander R. Luria's theory of higher cortical function has received international acclaim. His conceptual schemes of the functional organization of the brain are probably the most comprehensive currently available" (Adams, 1985, p. 878). Much of Luria's work elaborated and extended the earlier work of Sechenov (1863/1965) and Vygotsky (1978).

Luria defined mental processes in terms of two sharply delineated groups, "simultaneous" and "successive," following Sechenov's suggestions. The first process involves the integration of elements into simultaneous groups. Luria further qualified Sechenov's original meaning, indicating that simultaneous processing means the synthesis of successive elements (arriving one after the other) into simultaneous spatial schemes, whereas successive processing means the synthesis of separate elements into successive series.

Luria (1966) divided the brain into three blocks. Block One consists of the brain stem and reticular system and is responsible principally for regulating level of consciousness, arousal, and the overall tone of the cortex. Block Two consists of the parietal, occipital, and temporal lobes of the brain (the lobes posterior to the central sulcus) and is respon-

sible for receiving and encoding sensory input. Block Three consists of those regions of the brain anterior to the central sulcus (the frontal lobes and the prefrontal regions) and is responsible for the self-regulation of behavior, including such variables as attention, planning and execution of behavior, and other tasks generally referred to as "executive functions." In Luria's model, various zones and regions of the brain interact in a transactional manner to produce complex behavior; thus the functional localization of complex mental tasks is seen as dynamic, defying efforts at highly specific anatomical localization. Luria's approach lends itself to strength-centered intervention models, wherein the clinician actively seeks intact complex functional systems within the brain that can be used to habilitate and facilitate learning, rather than to models focusing on remediating dysfunctional or damaged brain systems (e.g., see Reynolds, 1981b, 1997; Riccio & Reynolds, 1998).

It has been proposed that sequential processing and simultaneous processing are lateralized to the left and right hemispheres, respectively (e.g., Reynolds, 1981b). Many other dichotomies have been suggested. Some find the research on cerebral specialization difficult to coalesce. Indeed, the many seeming contradictions in the results of cerebral specialization studies have prompted at least one pair of leading researchers to remark: "[To] say that the field of hemispheric specialization is in a state of disarray and that the results are difficult to interpret is an understatement. The field can best be characterized as chaotic" (Tomlinson-Keasey & Clarkson-Smith, 1980, p. 1). On the other hand, reviews by Dean (1984) and Reynolds (1981a) have noted some consistencies, especially when one focuses on process specificity and not the content of the task stimulus.

For the vast majority of individuals, the left cerebral hemisphere appears to be specialized for linguistic, propositional, serial, and analytic tasks, and the right hemisphere for more nonverbal, oppositional, synthetic, and holistic tasks. The literature includes numerous studies of hemispheric specialization that have attempted to provide anatomical localization of performance on specific, yet higher-order, complex tasks. Much of the confusion in the literature stems from the apparently conflicting data of many of these studies. However, Luria's principle of dynamic functional localization, and the knowledge that any specific task can potentially be performed through any of the brain's processing modes, should give some insight into the conflicting results that appear in the literature. In this regard, it is most important to remember that cerebral hemispheric asymmetries of function are process-specific and not stimulus-specific. Shure and Halstead (1959) noted early in this line of research that manipulation of stimuli is at the root of hemispheric differences—a notion that is well supported by later empirical research (e.g., Ornstein, Johnstone, Herron, & Swencionis, 1980) and thought (e.g., Reynolds, 1981a, 1981b). The confusion of the content and sensory modality through which stimuli are presented with the process by which they are manipulated, particularly in the secondary and tertiary regions of each lobe of the neocortex, seems to be at the root of the chaos. How information is manipulated while in the brain is not dependent on its modality of presentation and not necessarily dependent on its content, though the latter may certainly be influential.

We think that a process-oriented explanation provides a better organizing principle than does a focus on content. The "content-driven" attempts at explaining hemispheric differences fail to recognize the possibilities for processing any given set of stimuli or particular content in a variety of processing modes. Bever (1975) emphasized this point and elaborated on two modes of information processing that are of interest here because of their similarity to simultaneous and sequential cognitive processes. Assessments interpreted with this model in mind can elaborate cognitive strengths as well as weaknesses in brain systems in addition to detecting specific functional deficits. When evaluations include assessments of each block of the brain and the primary, secondary, and tertiary

zones of each block with carefully constructed, psychometrically sound batteries (whether the HRNB, the LNNB, or some variant of the flexible-battery approach), truly functional maps of CNS function can be derived for individual patients that have sound theoretical and empirical bases.

CONCLUDING REMARKS

There are many methods and models of neuropsychological assessment. The field of neuropsychology is young as clinical disciplines go. Controversies continue over the training and credentialing of neuropsychologists as well. However, the field has proven itself to be of value in contributing to patient care, and thereby it will continue to grow and even thrive. Clinicians must recognize that patient care is the ultimate goal and must provide carefully integrated, treatment-relevant data. A clinician writing a report on an adult's neuropsychological examination should pay particular attention to the following suggestions:

1. *Write reports that go beyond a simple descriptive presentation of test data and findings*. A clinician should integrate data across the history and across data sources. Data should be interpreted for the reader.
2. *Write professionally*. A clinician should use proper grammar and formal language structures in presenting reports.
3. *Use language that is easily understood*. Reports on adults will be used in many arenas, and writing a neuropsychological report in such a way as to be interpretable only by a physician or another neuropsychologist does not facilitate treatment. The report of the neuropsychologist is of no value if it cannot be understood. Reports should be cognitively accessible to family members (including parents and spouse or partner), rehabilitation staff (e.g., occupational therapists, speech therapists, physical therapists, vocational counselors), and the patient, in addition to the referring physicians.
4. *Write reports about people, not about tests*. Too often the neuropsychological evaluation of an adult reads like a test recital (i.e., test after test is presented, and the person's performance is noted). No data integration is attempted, and it is common to find contradictory statements in such rote reports. Adults and/or their family members often interpret such impersonal reports as lacking in concern or interest for the adults as individuals.
5. *Draw diagnostic conclusions*. Whenever possible, the examining clinician should proffer a diagnostic summary for consideration of other sources. Diagnosis is treatment-relevant and should be noted.
6. *Describe treatment implications of neuropsychological findings*. Although no one clinician can reasonably be expected to know all treatment implications of a set of findings, clinicians should note, to the extent of their knowledge, treatment implications of the findings of their own examinations. Neuropsychological results may indicate a need for specific interventions (e.g., neurocognitive therapy, speech therapy) or for specific methods of intervention within a known vocation (e.g., organizational strategies, etc.).

Neuropsychologists have much of value to offer in the care of people with neurodevelopmental disorders. Data and recommendations related to symptom expressivity, new problems, effectiveness of treatment, and possible behavioral interventions are some of their most valuable offerings. In this age of cost containment, it is crucial to provide useful, scientifically supported conclusions that contribute to treatment and other facets of patient care, and to maximize the benefit of the neuropsychological examination.

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3

NEURODEVELOPMENTAL DISORDERS AND MEDICAL GENETICS

An Overview

BONNIE J. BATY
JOHN C. CAREY
WILLIAM M. McMAHON

The entrance of the discipline of medical genetics into the care of persons with neurodevelopmental disorders is a relatively recent but highly significant event. The application of the principles of genetics to medicine in general is crucial, because of the important role of genes in the causation of human developmental disorders. In addition, a precise diagnosis of a genetic condition or syndrome is of importance to the person diagnosed, his or her family, and the practitioner caring for the individual. Individuals with disabilities and differences of any sort frequently ask questions about the risk of their disorders' occurring in future pregnancies.

Medical genetics has only recently emerged as a bona fide specialty in medicine. In the 1960s, the fields of biochemical genetics, clinical cytogenetics, and dysmorphology developed and paved the way for the delineation of this discipline. Now, with the recently publicized advances in the mapping and cloning of human disease genes, interest in genetics and its roles in human disorders is commonplace; indeed, these have become topics of everyday conversations. The purpose of this chapter is to summarize the body of knowledge and principles of medical genetics needed for the discussion of the neurodevelopmental disorders presented in this book. The first section of the chapter provides an overview of basic concepts in human genetics. The second section is a primer of the principles of medical genetics. The chapter closes with a brief discussion of the concept of behavioral phenotypes in dysmorphic syndromes and genetic conditions.

BASIC CONCEPTS IN HUMAN GENETICS

Genomic Structure

The influence of genetics as we know it today is primarily the result of research accomplished during the past century. The basic foundation of the field of genetics is the understanding of

genomic structure. The "genome" is the term applied to the total complement of deoxyribonucleic acid (DNA). DNA molecules are organized into approximately 30,000 units ("genes"). Alterations in these genes, either alone or in combination with alterations in other genes, can produce the diseases that we call "genetic disorders." Genes are strips of DNA that are the functional and physical units of heredity, passed from parent to offspring. Most genes contain the information for making a specific protein product. They are organized in a microscopically visible set of structures called "chromosomes." The basic biology of DNA and chromosomes was established in the 1950s and 1960s. Thus most of our knowledge of the molecular, chromosomal, and even biochemical basis of human disease has been acquired in just the latter half of the 20th century.

Each human cell—with the exception of a few cell types, notably the "gametes" (i.e., sperm or egg cells)—contains 23 pairs of different chromosomes for a total of 46 chromosomes. One member of each pair ("allele") is derived from an individual's father, while the other is derived from the mother. One pair of chromosomes is designated as sex chromosomes, consisting of XX in a female and XY in a male. XX indicates that females have two sex chromosomes with the same sequence of genes, while XY indicates that males have two sex chromosomes with a different sequence of genes, forming the basis for the unique features of X-linked inheritance. The remaining 22 pairs of chromosomes are called "autosomes" and are numbered from 1 to 22. A gamete or germ cell is different from a somatic cell, in that it contains only one chromosome from each pair. The reader is referred to basic texts of biology and genetics that discuss cell division and meiosis in more detail (e.g., Jorde, Carey, Bamshad, & White, 2003).

Types of Genetic Disorders

Genetic disorders in humans are classified into four major groups:

1. *Chromosome disorders*. In these conditions, the entire chromosome or segments of a chromosome are missing or duplicated ("aneuploidy"). They are divided into conditions of abnormal number and conditions of abnormal structure. Human chromosome disorders are diagnosed by performing a "karyotype" (chromosome study) of a body tissue—usually blood, but almost any tissue in which cells can grow can be utilized. A number of disorders, such as Down and Klinefelter syndromes, have their biological basis as a disorder of human chromosomes. Some of the important concepts that relate to chromosome syndromes are discussed below.

2. *Monogenic* (*mendelian*) *conditions*. These are disorders in which a single gene or pair of genes contains a "mutation" (alteration of DNA structure) that is the primary cause of the disease. They are divided into "autosomal dominant," "autosomal recessive," and "X-linked" conditions. The term "mendelian" refers to Gregor Mendel, the 19th-century scientist who established the basic laws of heredity in his studies of pea plants.

3. *Multifactorial or polygenic disorders*. These are conditions caused by a combination of multiple effects, either multiple genes (hence the term "polygenic") or gene–environment interactions. Epidemiological and family studies indicate that there is a genetic basis for these conditions, but the conditions do not follow the simple, regular rules of inheritance established for single-gene disorders (Mendel's laws). Many human diseases fall into this less well-defined category. These include neurodevelopmental disorders such as attention-deficit/hyperactivity disorder (Acosta, Arcos-Burgos, & Muenke, 2004; Faraone, 2004) and learning disabilities (Chapman, Raskind, Thomson, Berninger, & Wijsman, 2003; Francks, MacPhie,

& Monaco, 2002; Plomin & Walker, 2003), as well as psychiatric disorders such as schizophrenia and bipolar disorders (Sherman et al., 1997; Smalley, 1997).

4. *Mitochondrial disorders*. This group of disorders includes a relatively small number of diseases caused by alterations of the small cytoplasmic mitochondrial chromosome.

The chromosome, monogenic, and multifactorial disorders, as well as their principles, are reviewed in some detail in this chapter. Although a discussion of mitochondrial disorders is important in any review of genetic diseases, these conditions are not covered in detail here. The reader is referred to recent texts on medical genetics for more detail on mitochondrial disorders (Jorde et al., 2003; Gehlerter, Collins, & Ginsberg, 1998; Thompson, McInnes, & Willard, 2001).

Table 3.1 summarizes the various types of human genetic disorders defined above, with examples in each category. This table also lists three other features of inheritance—"mosaicism," "genomic imprinting," and "anticipation," which are defined and discussed later in this chapter. All of the concepts in the table are also discussed in the chapters on individual conditions.

Population Prevalence of Human Genetic Disorders

Although genetic disorders are often thought of as rare and exotic, these conditions constitute an important cause of human mortality and morbidity. About 30–50% of postnatal deaths in the United States from 1979–1992 were due to birth defects and genetic diseases (Yang, Khoury, & Mannino, 1997). In a population-based study, Yoon and colleagues (1997) found that 12% of pediatric hospitalizations were due to birth defects and genetic diseases. A genetic etiology has been found for 30–40% of severe mental retardation and 10% of mild mental retardation (Bundey, 2001). Before 25 years of age, at lease 5% of individuals can be expected to have a disease with an important genetic component (Baird, Anderson, Newcombe, & Lowry, 1988); 12% of adult hospital admissions are for genetic causes (Rimoin, Connor, Pyeritz, & Korf, 2001); and 10% of the chronic diseases (heart conditions, diabetes, arthritis) that occur in adult populations have a significant genetic component (Weatherall, 1985).

The calculation of incidence and prevalence figures for genetic disorders is very complex. Difficulties in establishing disease registries, and lack of standardization in diagnosis

TABLE 3.1. Types of Human Genetic Disorders

Inheritance	Exemplary disorders
Traditional	
Chromosome	Down syndrome, Klinefelter syndrome
Monogenic/mendelian	Neurofibromatosis type 1, fragile X syndrome
Multifactorial/polygenic	Learning disabilities, schizophrenia
Nontraditional	
Mitochondrial	Kearns–Sayre syndrome, MELAS
Mosaicism	Turner syndrome, fragile X syndrome
Genomic imprinting	Prader–Willi and Angelman syndromes
Anticipation	Fragile X syndrome, Huntington disease

and recording practices, make estimates difficult at best. Various investigations that have attempted to estimate the frequency of monogenic disorders, chromosome disorders, and congenital malformations derive figures of about 3–7% for the likelihood that an individual will develop one of these well-established genetic disorders during his or her lifetime. These figures, however, do not include cases of common adult diseases such as schizophrenia, diabetes mellitus, and cancer, all of which have some genetic basis (Jorde et al., 2003). Moreover, most epidemiologists would not classify human disease as purely environmental/acquired or purely genetic. Rather, causation of human disease represents a continuum. At one end of the spectrum are those disorders that are strongly determined by genes, especially monogenic and chromosome disorders; at the other end are those that are strongly determined by environment. However, there is now increasing evidence that many infectious diseases (or resistance to infectious diseases—e.g., resistance to HIV) have a genetic basis (Cheung, Wynhoven, & Harrigan, 2004; Quirk, McLeod, & Powderly, 2004). Thus most diseases are multifactorial in the strict sense of the word.

Types of Genetic Services

With the development of medical genetics as a specialty in mainstream medicine, clinical genetic services have become an integral part of the health care delivery system in North America and Europe, where most university medical centers have a program or clinic in genetics. In addition, medical genetics services are becoming more common in other countries. The percentage of clinical genetics posters presented at the American Society of Human Genetics meetings from countries outside North America and Europe increased from 9% to 23% between 1993 and 2003. The major objective of clinical genetics programs is to provide genetic diagnosis and counseling services for the referred patient population.

The cornerstone of medical genetics is the art and science of genetic counseling. Although the term "counseling" implies that this service is in the domain of mental health or psychotherapy, genetic counseling in fact is a marriage of human genetics and behavioral science. In 1975, the American Society of Human Genetics adopted a definition that was proposed by an assigned working group:

> Genetic counseling is a communication process which deals with the human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in a family. This process involves an attempt by one or more appropriately trained persons to help the individual or family to: (1) comprehend the medical facts including the diagnosis, probable cause of the disorder, and available management; (2) appreciate the way heredity contributes to the disorder and the risk of occurrence in specified relatives; (3) understand alternatives for dealing with the risk of reoccurrence; (4) choose a course of action which seems to them appropriate in the view of their risk, their family goals, and their ethical and religious standards and act in accordance with that decision, and (5) to make the best possible adjustment to the disorder in the affected family member and/or to the risk of recurrence of that disorder. (Ad Hoc Committee on Genetic Counseling: Report to the American Society of Human Genetics, 1975)

This well-established definition illustrates the complex tasks presented to the practitioner of medical genetics. The first task involves establishing the diagnosis and discussing the natural history and management of the disorder in question. The second task requires an understanding of the basic tenets of medical genetics. The third and fourth objectives of the genetic counseling process underlie the primary differentiation between the genetic model suggested here and the traditional biomedical approach. Here the tasks involve a discussion

of reproductive options and a facilitation of decision making, respectively. Implicit in the definition is the notion of respect for the family members' autonomy and for their perception of the risk. This approach is often different from the traditional medical approach, which often has recommendations as its basic theme. The final task of the genetic counseling process involves helping the family cope with the condition, its impact, and its potential heritability. All of the tasks require strong communication skills to enable the family to understand and process complicated medical and personal information and to utilize the information in a way that enhances their health and quality of life. Recently, Biesecker and Peters (2001) have proposed a new definition of genetic counseling—one that focuses on genetic counseling as a psychodynamic process, and emphasizes a therapeutic relationship that helps clients to "personalize technical and probabilistic genetic information, to promote self-determination and to enhance their ability to adapt over time" (p. 194).

The practice of clinical genetics involves a diverse array of services. A genetics program or clinic provides diagnosis, management, genetic counseling, and consultation. These occur in a variety of settings, including university outpatient clinics, community clinics, hospital wards, and specialty clinics, often with a multidisciplinary team approach. For example, medical geneticists are often involved in organizing or coordinating team clinics for such disorders as Turner syndrome, neurofibromatosis, and sickle cell disease. Multidisciplinary clinics have improved medical care for individuals with genetic disorders and birth defects by providing better access to services; greater likelihood of multidisciplinary consensus in medical decision making; concentrated expertise among a group of practitioners; less redundancy of services; and ability to offer unusual services, such as direct access to research protocols, support groups, and emergency coverage. Genetic services also include prenatal screening, which is presently done in conjunction with obstetricians and perinatologists. Moreover, genetic practitioners are closely involved with the development, orchestration, and delivery of genetic screening programs, which serve prenatal, neonatal, and general populations. Genetic practitioners also provide presymptomatic or predictive genetic testing, which enables individuals to learn whether or not they have a gene mutation that will predict or predispose them to genetic disease. Traditionally, genetic conditions have few treatment options available. However, this is gradually changing with the advent of therapies involving enzyme replacement (e.g., for mucopolysaccharidoses) and gene therapy (e.g., for ornithine transcarbamyline deficiency), in addition to more traditional therapies, such as pharmacological treatment (e.g., growth hormone for Turner syndrome) and nutritional management (e.g., for Prader–Willi syndrome). Genetic services are beginning to include treatment centers. The various types of clinical genetic services are discussed in detail elsewhere (Donnai, 2002; Rimoin et al., 2001).

One of the hallmarks of evaluation in a clinical genetic setting is the documentation of family history. It is now considered standard for practitioners evaluating a person with a potential genetic disorder to construct an accurate family history ("pedigree") and place it in the patient's chart. The National Society of Genetic Counselors has developed recommended standards for symbols used in the construction of a pedigree to document this important data set (Bennett, 1999; Bennett et al., 1995; for family-friendly instructions, see www.nsgc.org/consumer/familytree/family_history.pdf).

PRINCIPLES OF MEDICAL GENETICS: A PRIMER

In this section, the basic principles of medical genetics required to understand the biological basis of the syndromes described in this book are summarized. Our goal here is not to

provide a comprehensive summary of the science, but rather to highlight the important points. The key terms important in clinical discussion of these genetic disorders are emphasized throughout the discussion (see also Jorde et al., 2003; Rimoin et al., 2001).

Chromosome Disorders

Figure 3.1 is a standard karyogram, showing the chromosome arrangement of a normal male. Note that the chromosomes are paired, and that the pairs (except for the sex chromosomes) are numbered from 1 to 22. There are dark and light areas ("bands") on each chromosome. Each chromosome is lined up in a standard way, with the "centromere" (central constriction) representing a landmark. The shorter of the two longitudinal chromosome segments is called the "p arm," and the longer one is called the "q arm." The chromosomes are grouped according to the size and location of the centromere. Chromosomes 1 through 3 have a centrally placed centromere ("metacentric"), while chromosomes 4 and 5 have a "submetacentric" construction. Details of the standard banding/numbering system are available in many genetic texts. Figure 3.2 shows two chromosome diagrams ("idiograms") and their designated bands.

Most chromosome studies done in a clinical setting utilize a "Giemsa-banding" ("G-banding") technique, which averages about 550 bands on all 23 pairs of chromosomes. A

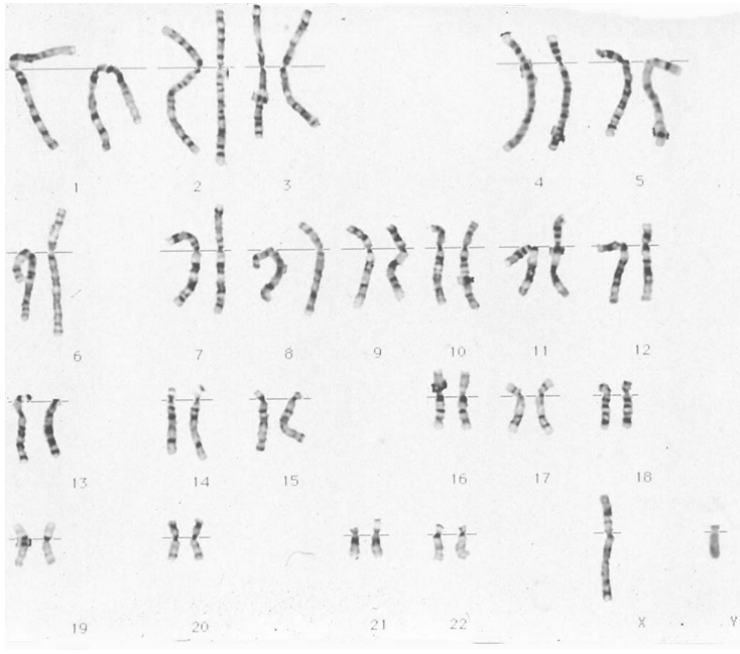

FIGURE 3.1. G-banded karyogram from a normal male. Note that there are 23 pairs of chromosomes arranged in a specific, orderly array. The autosomes are numbered from 1 through 22, and the sex chromosomes are conventionally placed at the bottom right-hand portion of the karyogram. The individual pattern of G-bands determines the chromosome. (Courtesy of Dr. Art Brothman, University of Utah Health Sciences Center.)

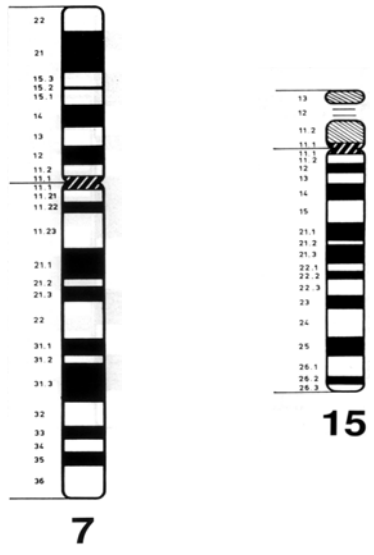

FIGURE 3.2. Idiograms at the 550-band resolution for chromosomes 7 and 15, two important chromosomes for neurobehavioral disorders. Chromosome 7 is a typical "submetacentric" chromosome (i.e., the centromere is off center). The part of the chromosome on the shorter side is called the "short arm" or "p arm"; the part on the longer side is called the "long arm" or "q arm." Chromosome 15 is called an "acrocentric" chromosome; the centromere is near one end, and the short arm contains the "satellite material." Note that the band numbers move consecutively away from the centromere, and the chromosome arms are divided broadly into segments and then into individual bands. Chromosomes are numbered by segment and then by band. The region that is deleted in the Prader–Willi syndrome is the 15q11–q13 region. The region that is deleted in Williams syndrome is the 7q11.2 region. (Courtesy of Dr. Art Brothman, University of Utah Health Sciences Center.)

more recently developed technique called "high-resolution banding" (HRB) stops the cell in an early part of the cell cycle and allows for more extended chromosomes, and thus for more bands (average about 650). HRB techniques allow for the recognition of more subtle chromosome disorders. When an HRB technique was used in the early 1980s, some patients with Prader–Willi syndrome were recognized to have a subtle but definite missing piece (deletion) of the uppermost band on the long arm of chromosome 15. However, HRB was not sensitive enough to pick up the deletion seen in individuals with Williams syndrome. In this situation, the diagnosis of the characteristic deletion of Williams syndrome requires a newer technique using DNA fluorescent probes combined with HRB of chromosomes, called "fluorescent *in situ* hybridization" (FISH). This technique is of significance because it is now the technique of choice for detecting the subtle deletions of Prader–Willi, Angelman, Williams, and 22q11.2 deletion syndromes. Also, it is sometimes utilized to pick up more subtle submicroscopic deletions in relatively well-known deletion syndromes, such as 5p or 4p deletion syndrome. Figure 3.3 is a black-and-white photograph of FISH in a patient with the 22q11.2 deletion syndrome. This important condition is a common autosomal disorder in humans.

A special application of the FISH technique is called "subtelomeric FISH analysis." The tips of chromosomes are called "telomeres." It has recently been shown (de Vries, Winter, Schinzel, & van Ravenswaaij-Arts, 2003; Flint & Knight, 2003) that about 5–10%

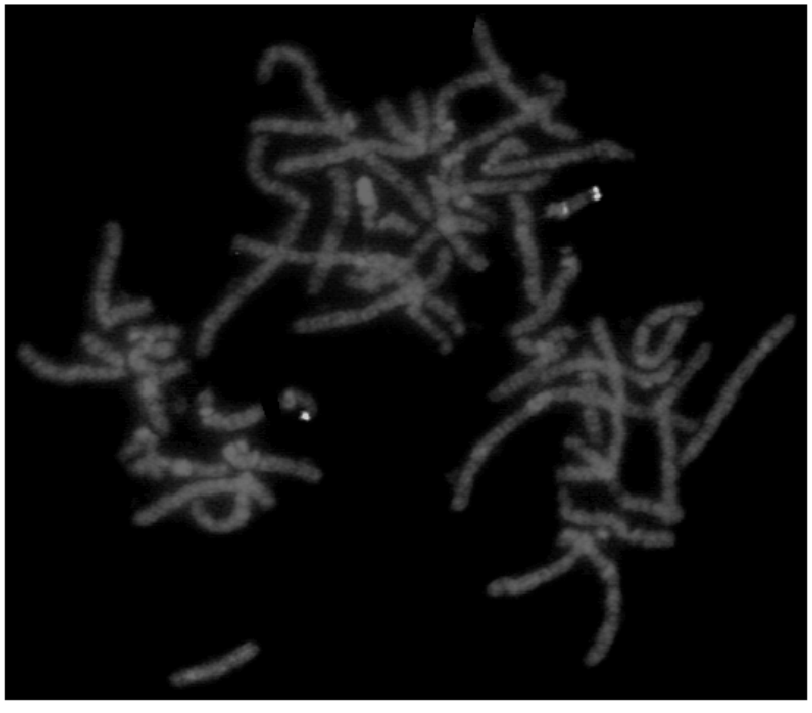

FIGURE 3.3. An abnormal FISH study of an individual with a 22q11.2 deletion. The normal chromosome 22 shows two signals, while the other chromosome 22 (lower left) is missing a signal. Thus there is a missing piece of DNA in the critical region consistent with this syndrome. (Courtesy of Dr. Art Brothman, University of Utah Health Sciences Center.)

of undiagnosed individuals with mental retardation and other signs of multisystem involvement have a deletion close to the tip of a chromosome (the subtelomeric region). Some of these deletions coincide with known deletion syndromes (e.g., 4p deletion syndrome), and others are in regions without previously described syndrome associations. An even newer technique called "microarray analysis" detects small deletions and duplications (but not rearrangements) throughout the genome. The technique uses an array of small, regular-spaced, cloned segments of DNA from all the chromosomes. Figure 3.4 is a black-and-white photograph of a microarray analysis. Laboratory tests have just become clinically available that combine a microarray assay with a conventional karyotype, followed by confirmation of abnormal results with FISH probes. Because the deletions and duplications detected with these powerful new tools are usually smaller than previously described imbalances, genotype–phenotype data are needed to provide clinical prediction. These techniques have enabled practitioners to diagnose a higher percentage of individuals with clinical symptoms suggesting a chromosome disorder, including many individuals whose tests were negative by previous techniques.

As mentioned above, chromosome disorders can be divided into disorders of chromosome number and structure. Disorders of chromosome number are those conditions in which there is either an entire extra chromosome or a missing chromosome. Down syndrome (trisomy 21) involves the presence of an extra chromosome 21 (usually the entire chromosome) and represents the prototypical chromosome condition of abnormal number (see

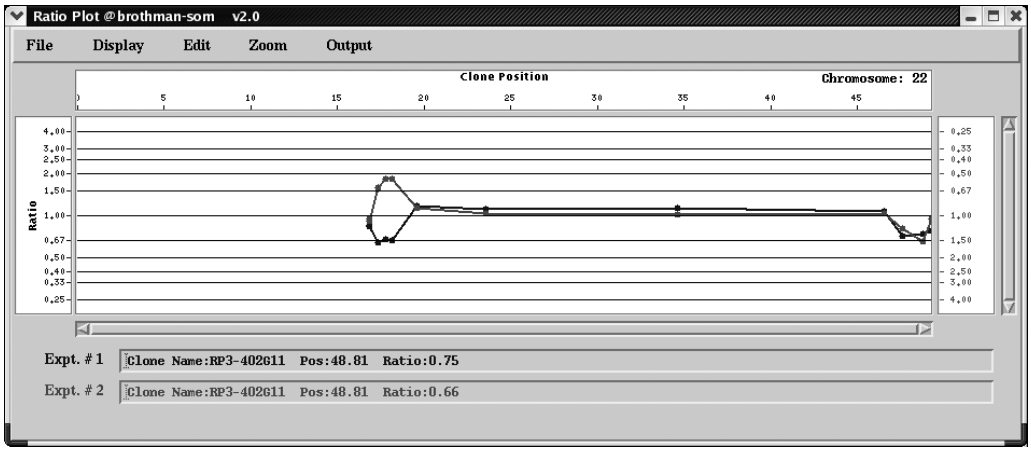

FIGURE 3.4. Ratio plot of chromosome 22, showing deletion at the DiGeorge locus (22q11.2) on the left of the plot where the two lines separate. Each clone is shown by a dot along the line and signifies that the clone is deleted. (Courtesy of Dr. Art Brothman, University of Utah Health Sciences Center.)

Hazlett, Chapter 18, this volume). Turner syndrome (monosomy X) and Klinefelter syndrome (47,XXY) represent other disorders of abnormal chromosome number (see Powell & Snapp, Chapter 12, and Hazlett, Chapter 19, this volume).

Disorders of abnormal structure involve conditions where a segment of a chromosome is either missing ("deletion") or extra ("duplication"). The terms "partial monosomy" and "partial trisomy," respectively, are also utilized. The most common deletion syndromes include 5p deletion (also known as *cri du chat* syndrome), 4p deletion (Wolf–Hirschhorn syndrome), and 18q deletion. Although the letter p or q refers to the particular chromosomal arm, that designation does not tell one where the actual deletion is; the banding number is also needed. A more comprehensive discussion of chromosome biology is available in most textbooks of human and medical genetics.

In the 1980s, as noted above, a number of chromosome deletion syndromes involving very subtle deletions were described. These have come to be known as the "microdeletion syndromes." Prader–Willi, Angelman, and Williams syndromes all fall into this category. Because the deletions are subtle and are thought to affect a potentially definable cluster of neighboring genes, the microdeletion syndromes are sometimes referred to as "contiguous gene syndromes." Prader–Willi and Angelman syndromes are discussed further in the section below on nontraditional inheritance.

From a clinical point of view, chromosome disorders are associated with characteristic syndromes. In each of these conditions there is a recognizable and relatively reproducible pattern of physical manifestations, minor anomalies, and sometimes major congenital malformations, often consistent enough to be recognized by the experienced clinician. The syndrome thus represents the manifestations that we actually observe physically or clinically ("phenotype"). The concept of phenotype is contrasted with the term "genotype," which refers to the individual's genetic constitution. For example, the phenotype in Down syndrome is the constellation of physical findings first described by J. Langdon Down; the genotype is the chromosomal constitution of 47,XY +21. (About 90–95% of persons with Down syndrome have the chromosomal finding of trisomy 21, while the remaining 5–10% have other structural changes; see Hazlett, Chapter 18, this volume.)

One of the clinical decisions that often confronts the practitioner is when to order a chromosome study. The most common reason for such a study is to confirm the presence of a well-established chromosome syndrome, such as Down or Turner syndrome. Since autosomal chromosome disorders produce syndromal patterns of multiple anomalies, usually with psychomotor retardation, a karyotype is indicated in a person who has this type of clinical picture. Thus, in the evaluation of an individual with developmental delay or mental retardation, a chromosome study is obviously indicated when a person has multiple major and minor anomalies or features different from those of his or her family background. The question of doing a karyotype in a person who has mental retardation or developmental delay without dysmorphic signs or minor anomalies is somewhat more controversial. However, since the dysmorphic features can often be quite subtle even in established syndromes (e.g., 5p deletion/*cri du chat* syndrome and 17p deletion/Smith–Magenis syndrome), most geneticists seriously consider doing a karyotype for any individual with developmental delay or mental retardation (Curry et al., 1997). In more recent years, many clinicians in the field have also considered doing a karyotype for any individual with autism who has no associated medical diagnosis. This is because of the recognition of the inverted duplication 15 syndrome, where the clinical signs are quite subtle (Battaglia et al., 1997). The yield of chromosome studies looking for this finding or for other chromosome disorders in large populations of individuals with autism with no medical diagnosis is not available, but this testing can be pursued on a case-by-case basis. It is important to order both an HRB karyotype and FISH when one is considering one of the specific microdeletion syndromes (i.e., Prader–Willi, Angelman, Williams, or Shprintzen syndrome).

Another reason for a chromosome study is to study a parent when a child has a disorder of chromosome structure. Here one is looking for a chromosome rearrangement (e.g., translocation). There are a number of other indications for performing chromosome studies that are not as relevant to the neurodevelopmental arena and are not discussed in detail here; these include recurrent miscarriages, an undiagnosed stillborn infant, concern about one of the chromosomal instability syndromes, and diagnosis of certain malignancies. Comprehensive discussions of these indications are available in the texts cited earlier in the chapter.

Monogenic Disorders

Monogenic disorders are those conditions resulting from a "mutation" (change in a gene), either in a single allele or in both alleles of a gene. Prior to the 1980s, the notion of a monogenic disorder was one that involved an assumption. Now that the genes for over 1,600 human disorders have been mapped to a chromosomal location, or in many cases identified ("cloned"), the notion of the gene is no longer a theoretical construct.

Monogenic disorders, also known as mendelian conditions, can be divided into autosomal dominant, autosomal recessive, and X-linked conditions (as noted earlier). The determination of the inheritance pattern was known long before the new DNA technology became available; it was based on interpretation of pedigree structure. Thus, when a condition was recognized to occur through generations in a vertical fashion, the assumption was usually made that the condition was an autosomal dominant disorder. This was the logic that permitted the recognition of neurofibromatosis type 1 (NF1) as an autosomal dominant condition long before the gene was identified in 1990. (NF1 is utilized in this section to illustrate principles.)

The concept of an "autosomal dominant" gene means that one allele in each gene pair possesses a mutation, while the other is a normal ("wild-type") allele. In recent years, many of these mutations have been determined at the molecular level for many conditions. When a person has an autosomal dominant mutation, the chance of transmitting the mutation to offspring is one in two (or 50%) with each pregnancy. The pedigree structure will often be multigenerational, because inheriting the trait from one parent is sufficient to cause the condition. Figure 3.5 shows a typical autosomal dominant pedigree in a family with NF1. Note that there is transmission in this particular family history from a father to a son (i.e., male-to-male transmission), confirming that this is an autosomal trait and not an X-linked trait. (In an X-linked trait, a male cannot transmit the trait to a male offspring, because the father transmits his Y to a son and his X to a daughter.) In many autosomal dominant traits, a condition starts off with a person called the "progenitor." In that situation it is assumed that there is a "de novo" (new) mutation for the gene. Thus, in many autosomal dominant conditions there will be no family history, because the particular person in question is the progenitor for the disorder. This is often the case in NF1, where in the clinical setting about 50% of all patients who present to a medical genetics clinic have their disorder due to a de novo mutation. (The other 50% inherit the gene from one of their parents.) This illustrates the point that the absence of any family history of a condition by no means excludes genetic causation. In fact, in X-linked and autosomal recessive conditions (where there is often no family history) as well, the belief that the lack of family history mitigates against a genetic disorder is inaccurate.

An "autosomal recessive" disorder is one in which both alleles in a gene pair have a mutation. In an autosomal recessive pedigree, each parent is assumed to have a mutant copy of the gene, and thus the parents are referred to as "carrying" or "heterozygous for" the mutation. The term "homozygous" is used when a person has two mutant alleles or two normal alleles. Because of the "segregation pattern" (the genotypes inherited by the offspring) that occurs in recessive situations, the chance that a family in which both parents carry the mutation will have a child with the recessive condition is one in four (25%) with each pregnancy. Most inborn errors of metabolism are inherited in an autosomal recessive fashion. These biochemical conditions represent disorders of intermediary

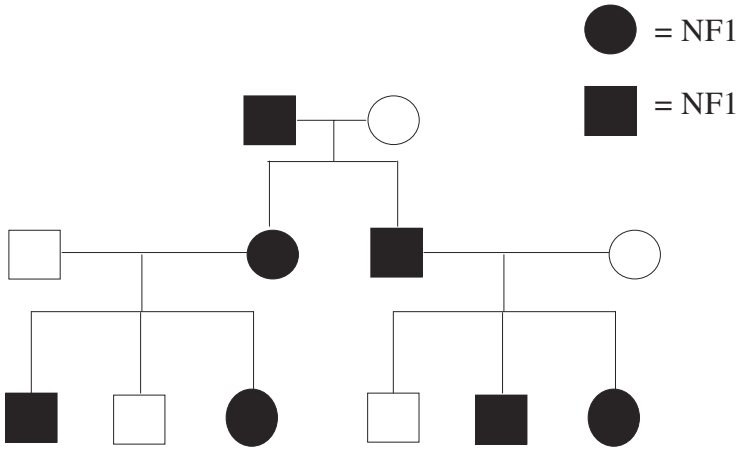

FIGURE 3.5. This family pedigree illustrates the typical inheritance pattern of an autosomal dominant trait, NF1. Note the transmissions from a father to son.

metabolism, and a homozygous deficiency of an enzyme accounts for each such disorder. The hemoglobinopathies, including sickle cell anemia (see Smith, Chapter 17, this volume), are also inherited in an autosomal recessive fashion. A comprehensive discussion of the principles of population genetics that are important in any discussion of autosomal recessive diseases can be found in the textbooks cited earlier.

The third type of disorder transmitted in a mendelian fashion is an "X-linked" disorder. The X-linked disorders are conditions that from pedigree structures (and now DNA technology) are known to be mutations on the X chromosome. In this situation, a female (who typically has two X chromosomes) will "carry" the gene for the condition and may or may not express it, while the male (who only has a single X) will almost invariably express the condition. Again, just as in autosomal dominant disorders, some individuals who have an X-linked disorder may have it because of a new mutation of the gene on the X chromosome. Figure 3.6 shows a typical X-linked pedigree of a family with fragile X syndrome seen in a clinical setting (see Hansen & Hagerman, Chapter 13, this volume). Other conditions of significance in the neurodevelopmental arena with X-linked inheritance include Hunter syndrome, Lesch–Nyhan syndrome (see Visser, Schretlen, Harris, & Jinnah, Chapter 21, this volume), and X-linked aqueductal stenosis/hydrocephalus.

Decisions about patterns of inheritance are complex and often controversial in the field of medical genetics. Knowledge of the genetic basis for many conditions is now being acquired through recent developments in DNA technology. Detailed discussions of the evidence for inheritance patterns of human diseases and phenotypes are available in the classic multivolume text *Mendelian Inheritance in Man*. V. A. McKusick, the author, is often considered the father of medical genetics, and has produced 12 editions of this semi-

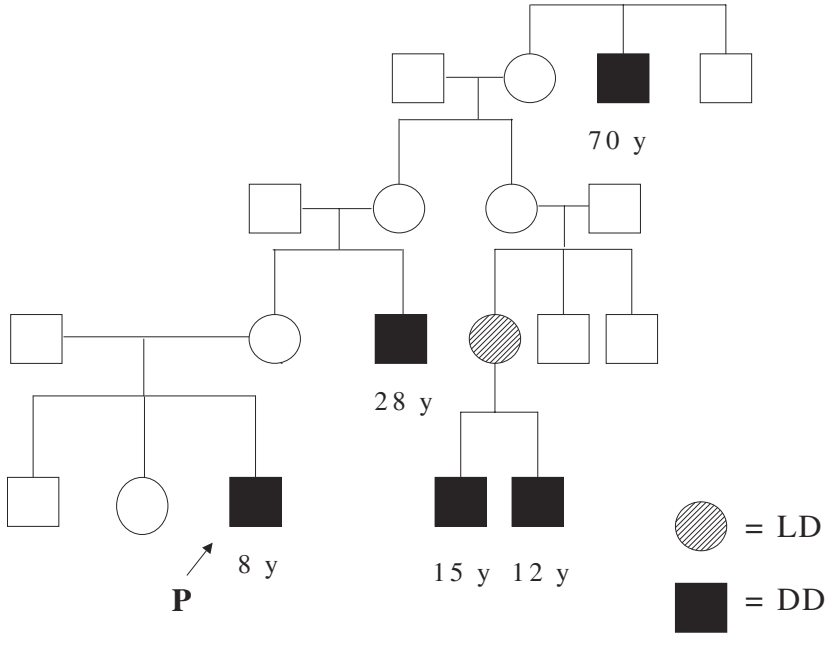

FIGURE 3.6. A typical family pedigree of an X-linked condition, fragile X syndrome. Note that one female is mildly affected, and that there is no male-to-male transmission. LD, learning disability; DD, developmental delay.

nal work. One is now able to look up conditions or phenotypes and discover key and recent citations on clinical and genetic aspects as well as molecular biology (McKusick, 1998). This work is also currently available online at the website of the National Center for Biotechnology Information (www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM), free of charge. This is an incomparable and invaluable resource for current knowledge about the genetic and molecular basis of almost any condition. The 12th edition of the text (McKusick, 1998) includes 8,587 entries. In September 2004, the online version (*Online Mendelian Inheritance in Man*) listed 9,098 loci. Another online resource that is especially useful for clinical information—including differential diagnosis, diagnostic tests, detailed genetic information, management, and family support groups—is the GeneTests website (www. genetests.org).

Genotype–Phenotype Relationships: Basic Tenets

Although the discussion thus far seems to be relatively straightforward, the actual evaluation of a patient with a potential genetic condition is not so clear-cut. As mentioned above, an abnormality of chromosome structure or a gene mutation produces a phenotype that is recognizable and often discrete. However, the relationship between the gene alteration and the disease state is complex, as there is marked variability in the clinical picture, regardless of the genotype. Various conditions seem to have their own intrinsic degree of variability. For these reasons, geneticists over the past century have developed concepts that explain the often fuzzy relationship between genotype and phenotype, discussed in the following paragraphs.

"Expressivity" is a term utilized in genetics to refer to the variability in clinical severity seen in a given condition. Various members of the same family with a certain genetic trait have exactly the same mutation, yet the degree of involvement can range from minimal to severe. The study of the clinical aspects of NF1 illustrates this point (see Serpas, Chapter 16, this volume). About 50–70% of patients with NF1 only have *café au lait* spots or dermal neurofibromas, and their disorder is of mild significance. Approximately 30–50% of patients have one of the many listed serious manifestations of NF1, including optic pathway tumors, neurofibrosarcomas, or scoliosis. Even within the same multigenerational kindred, there will be marked variability. This discussion also applies to Noonan syndrome (see Noonan, Chapter 15, this volume). Again, even within the same pedigree, there will be marked variability in the clinical signs (short stature, pulmonic stenosis, etc.), even though all patients will have at least the facial features.

"Penetrance" is the frequency of expression of a genotype. Some individuals who carry a gene mutation in a mendelian disorder will have no observed clinical signs of the condition, while others with the same mutation will have clinical signs. Penetrance is usually expressed as the ratio of individuals with the mutation and symptoms to all individuals with the mutation. The absence of any signs of such a disorder will give the impression that the gene in question has skipped a generation. The concept of "incomplete penetrance" or "lack of penetrance" is an attempt to explain the clinical picture in cases where the genotype and phenotype do not match, as one would expect. All of the monogenic conditions described in this book essentially have 100% penetrance. For example, in NF1, individuals who have the trait have some cutaneous or eye signs of NF1—usually by the age of 5, but certainly by the age of 20 years. Sometimes it may be difficult to exclude the presence of the gene in a young child, but usually by adulthood, the *café au lait* spots, dermal neurofibromas, and Lisch nodules of the iris have made their appearance. In examination

of NF1 pedigrees, one does not see examples of three-generation pedigrees where the gene mutation has skipped. On the other hand, in tuberous sclerosis, there have been cases reported in which there are two affected offspring of normal, unaffected parents. This particular pedigree structure could be described as incomplete penetrance; however, one does not see three generations of people with tuberous sclerosis where the person in the middle generation lacks any signs. Most geneticists currently think that families with siblings affected with tuberous sclerosis and unaffected parents represent "germ-line mosaicism" (i.e., mutation occurring in multiple gametes and not in somatic cells, putting the parents at increased risk for recurrence). Mosaicism is now thought to occur more often than was previously recognized in the field. In Table 3.1 it is listed as one of the nontraditionalmodes of inheritance, and it is discussed further below.

The concepts of expressivity and penetrance are critical in the evaluation of family histories of complex diseases, such as depressive disorders and learning disabilities. In such kindreds, it is typical to have multiple affected family members with intervening relatives who do not express the condition (nonpenetrance) or express it partially (variable expressivity). In this case, we are dealing not only with variable expression of a single gene, but often with multiple genes and/or environmental factors. We often think of these genes as conferring a "susceptibility" to the condition.

Age is an important factor in the concepts of both expressivity and penetrance. For many conditions, symptoms are age-specific. This means that the phenotype changes with age and may be harder to recognize at some ages than others. Examples are coarsening of facial features in mucopolysaccharidoses as storage material accumulates in the body; the development of ataxia in older individuals carrying the fragile X mutation; and the chorea, psychosis, and dementia of Huntington disease, which usually do not occur until well into adulthood. Thus symptoms vary not only between family members, but within individuals throughout the life cycle. It also means that penetrance is sometimes calculated as an age-specific curve.

The concept of "heterogeneity" presently has a number of usages in medical genetics. The traditional concept is "genetic heterogeneity," in which a certain phenotype (e.g., retinitis pigmentosa or cataracts) is known to be caused by different genetic alterations (i.e., autosomal dominant, autosomal recessive, or X-linked). With the recent advances in DNA technology, the existence of genetic heterogeneity has been proven. For example, in tuberous sclerosis, some families with this autosomal dominant gene map to chromosome 16 and have a mutation of a certain tumor suppressor gene, whereas other families map to chromosome 9 and have the disorder because of mutations of a different gene. This can be referred to as either "locus heterogeneity" or genetic heterogeneity. The term is also used to refer to a mixture of phenotypes as well. For example, when it was recognized in the 1980s that bilateral acoustic neuromas were not seen in classical neurofibromatosis, the notion of phenotypic heterogeneity of the neurofibromatoses was proposed. Even before the two separate genes were mapped and cloned, clinicians and scientists were referring to multiple forms of neurofibromatosis. Now the terms NF1 and NF2 are used for the classic condition (NF1) and for bilateral acoustic neuromas (NF2).

The concept of "pleiotropy" refers to the idea that diverse manifestations in different organs and systems can have a single-gene cause. Again, NF1 illustrates this concept nicely. In this syndrome, one sees manifestations that at first glance do not seem to be tied together pathogenically (i.e., *café au lait* spots, neurofibromas, optic pathway tumors, learning disabilities, skeletal findings, etc.). The notion here is that a single gene has multiple roles in development and cell biology, and thus that a mutation in this gene

has multiple effects. In the case of NF1, the common denominator is presumably in the control of cells derived from the developing neural crest of the embryo. To give another example, the pleiotropic manifestations of Noonan syndrome include the characteristic face, short stature, pectus excavatum, and pulmonic stenosis. Again, this diverse array of effects appears to be due to the single mutation. The concept of pleiotropy is important in understanding how a gene produces the phenotype (i.e., its pathogenesis), and how it relates to the idea of a syndrome.

As mentioned in various places in the chapter, "mutation" refers to the specific alteration of the DNA molecule in a particular condition. In recent years, with the advances in DNA technology, the specific mutations that cause many disorders have been detected. For example, after the gene for NF1 was identified in 1990, about 10% of individuals with NF1 had a detectable mutation. In the other 90%, scientists were not technically able to find the gene alteration, presumably because of the size of the NF1 gene. Since 1990, because of new techniques, laboratory scientists have become able to detect the disease-causing mutations in 95% of patients with NF1 (Messiaen et al., 2000). Of note is the fact that about 80% of the mutations are ones in which the gene is basically inactivated (i.e., there is simply one operating gene, while the other is not operating). In some cases the entire gene is deleted, while in others a small deletion of only a few nucleotides is present. Most cases are caused by a single nucleotide change that either results in a shortened protein or affects function of the protein. In other conditions, the specific type and location of gene mutations affect the phenotype. For example, Apert syndrome is due to relatively specific mutations of a gene that encodes a protein called fibroblast growth factor receptor 2 (Webster & Donoghue, 1997). This is a cell receptor protein that sits on the outside of a cell and, when signaled by a growth factor, sends a message to the nucleus of the cell. It is now known that Apert syndrome is due to mutations of the gene that alter the extracellular portion of this growth factor receptor. Mutations of other parts of this same gene produce different phenotypes and are the cause of recognized syndromes that have manifestations overlapping with those of Apert syndrome, but are considered different and distinct clinical syndromes (Reardon et al., 1994; Wilkie et al., 1995). These other syndromes, which include Crouzon and Pfeiffer syndromes, are not discussed here in detal.

In summary, the area of genotype–phenotype correlation is a timely topic. Ideally, better understanding of how mutations in specific genes produce specific phenotypes will clarify the pathogenesis of human diseases of this nature.

Recently Delineated Concepts: Nontraditional Inheritance

As mentioned above, the concepts of variability, pleiotropy, and heterogeneity were created to explain observed relationships between genotypes and phenotypes. From the 1980s onward, a number of newer, nontraditional categories of inheritance have been recognized. One of these, "mosaicism," has been mentioned above. In mosaicism, there are two cell lines—either one that is normal and one that contains a gene or chromosome mutation, or two that are abnormal. More rarely, mosaic individuals have more than two cell lines. In many cases, a normal cell line makes the phenotype milder. Other concepts that have been proposed in recent decades include "genomic imprinting" and "anticipation." These concepts have altered thinking about the clinical and genetic aspects of a number of important conditions. These concepts are discussed below as they relate to two of the conditions

described in this text (i.e., the Prader–Willi and fragile X syndromes), as well as to Angelman syndrome.

The principle of "genomic imprinting" challenged the central dogma of genetics that arose from Mendel's experiments with peas. Originally it was thought that a trait was inherited from a mother or a father, and that the parent of origin made no difference. However, it has become increasingly apparent that in some genes the parent of origin does make a difference and has an effect on phenotype and disease manifestation. In imprinting, the expression of a gene is influenced by the parental origin of the gene, and the activity level depends on this origin. The concept of genomic imprinting in humans is best illustrated by the Prader–Willi and Angelman syndromes. As mentioned earlier, it has been known since the early 1980s that a microdeletion on chromosome 15 in the upper portion of the long arm could produce Prader–Willi syndrome (see Dykens, Summar, & Roof, Chapter 22, this volume). A similar deletion was recognized in some patients with Angelman syndrome. (Angelman syndrome is a condition of profound developmental disability, seizure disorder, muscle tone abnormalities, small head size, and a characteristic face.) If a deletion arises on the paternal chromosome 15, the offspring will develop Prader–Willi syndrome; if the deletion arises on the maternal chromosome 15, the offspring will develop Angelman syndrome. Thus there is a definite parent-of-origin effect. It is now clear that a gene (or genes) within the crucial segment of chromosome 15 is normally only active on the paternal chromosome and not the maternal one (the maternal copy is said to be "imprinted"). In a case when the critical gene (or genes) is deleted on the paternal chromosome and thus inactivated, this deletion results in Prader–Willi syndrome. Conversely, the gene for Angelman syndrome has also been identified, and the logic is the reverse. Although most cases of Prader–Willi syndrome and Angelman syndrome are sporadic (i.e., without a family history), this parent-of-origin effect results in some unusual pedigrees that would not at first glance fit any of the simple rules of single-gene disorders discussed above (see Jorde et al., 2003).

Another concept that is classified as nontraditional is that of "anticipation." Since the early part of the 20th century, it has been observed that some genetic diseases display an earlier age of onset and have more severe expression in later generations of the family tree. Such disorders are said to exhibit anticipation. Until recently, most investigators felt that this was probably a bias of ascertainment and not a real biological phenomenon. In the early 1990s, the genes for a number of conditions were identified through the positional cloning approach. These included fragile X syndrome (see Hansen & Hagerman, Chapter 13, this volume), myotonic dystrophy, and Huntington disease. These conditions share a unique mutation mechanism, that of the expanded DNA repeat; they have thus been labeled the "trinucleotide repeat-expansion disorders." There are repeat sequences of DNA nucleotides that are normally present in all individuals; persons with repeat-expansion disorders have an increased number of these nucleotide repeat sequences. Such an expansion affects the way the DNA works or the way the protein functions, and therefore it produces the disease. There is also a correlation with repeat size and phenotype; larger repeat sizes are associated with more severe symptoms and/or earlier onset. Repeats in the expanded range are unstable and tend to get larger in offspring. For example, in fragile X syndrome, expanded cytosine–guanine–guanine repeats are associated with methylation of a cytosine–phospho–guanine island, which appears to "turn off" the gene. Thus, for these conditions, triplet repeat expansions explain the phenomenon of anticipation and give it a biological basis. Like genomic imprinting, this phenomenon provides the biological and molecular basis for observations in family histories that are discrepant with the known rules of mendelian inheritance.

DNA Technology and Linkage

The tools and strategies to localize a particular gene for a mendelian disorder to its particular chromosome (or chromosomes) arose in the late 1970s and early 1980s. The combination of the development of DNA probes, complicated computer programs, and restriction endonucleases laid the groundwork for the application of this technology. Before this, for the overwhelming majority of genetic disorders (except the biochemical disorders), the biological bases were almost entirely unknown. One could speculate that a condition like NF1 was due to some disorder of neural crest biology, or that Apert syndrome was due to a developmental disorder of the skeleton, but the real basis of the pleiotropy in each case was unclear. For this reason, the concept that one can map a gene by utilizing the incredible and well-known variation in DNA structure arose. The concept of "linkage analysis" is based on the idea that an individual's normal DNA variations cosegregate with the disease genes in question. By using complicated computer programs and previously linked DNA probes, one can map a gene. Once a disease gene is mapped, the first step toward being able to isolate the causative gene is accomplished. The isolation of the gene for a condition is referred to as "gene identification" or "cloning." If the basic structure of the DNA is known, one can then derive the amino acid sequence and the peptide structure. The strategy, once called "reverse genetics" and now referred to as "positional cloning," has been highly successful since the 1980s in identifying important disease genes. The first gene mapped by this approach was the gene for Huntington disease. In the late 1980s, the genes for cystic fibrosis, Duchenne muscular dystrophy, and NF1 were mapped and then cloned. Another important refinement of linkage analysis introduced in the 1990s is the use of single-nucleotide polymorphisms (SNPs). This type of DNA variation is ubiquitous in the genome and enables mapping at much smaller intervas of DNA, thus enabling more rapid localization of genes. The process of identifying human genes has been aided by the Human Genome Project, a massive, government-funded biological project that succeeded in mapping the entire human genome between 1990 and 2003 (see the National Human Genome Research Institute website at www.nhgri.nih.gov). Correlation of the detected mutations with specific phenotypes is now ongoing for all conditions in which there has been gene identification.

Figure 3.7 illustrates this paradigm. First, families with a particular dominant or recessive condition are collected. If, by chance, some patients have an associated chromosomal rearrangement that suggests a gene location, the success rate in mapping the gene is improved. Once a gene is mapped, linkage testing in the clinical arena is available. For example, in familial cases of NF1, the families that are interested in prenatal diagnosis or early-infancy diagnosis (often before any *café au lait* spots have developed) now have this option. Once a gene has been mapped or localized, perusal of the existing gene map may show "candidate genes" in the same region that may be the basis for the disorder in question. This approach was used to clone the gene responsible for Apert syndrome. Once the gene for a related but different condition called Crouzon syndrome (referred to above) was mapped to chromosome 10, and a candidate gene on chromosome 10 was discovered that encodes fibroblast growth factor receptor 2, mutations were detected in patients with Crouzon syndrome. The logical hypothesis was that perhaps different mutations of the same gene cause related disorders, including Apert syndrome. This turned out to be the case, and it is now known that the gene for fibroblast growth factor receptor 2 is the causative gene in Apert syndrome (Webster & Donoghue, 1997). As mentioned above, this paradigm was also successful in mapping and cloning the important gene in fragile X syndrome. At present if a person is recognized to have fragile X syndrome and this is con-

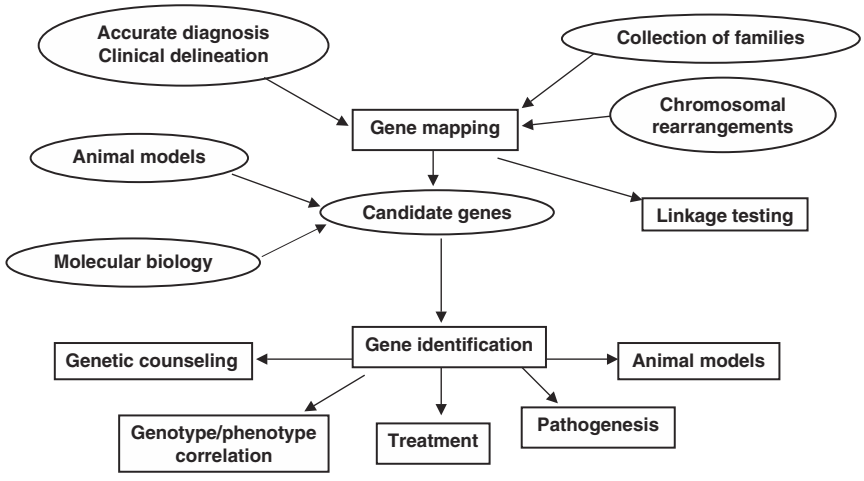

FIGURE 3.7. The gene-cloning paradigm: The chronology of the mapping and identifying of a disease gene, with its resulting consequences. Note that after a gene is mapped, the possibility that linkage testing can be used in the clinical arena occurs. Cloning a gene creates the potential for understanding pathogenesis and perhaps orchestrating strategies for treatment and prevention.

firmed on a molecular basis, DNA testing can be offered to other members of the family who are at risk. Direct mutation testing for the expanded repeat of fragile X syndrome is currently available in most clinical molecular laboratories in North America (see Hansen & Hagerman, Chapter 13, this volume). With the increased use of faster technology that shortens the time between mapping and cloning a gene, direct mutation testing is quickly becoming the norm for clinical testing. Interestingly, although new techniques have revolutionized the availability of clinical tests once biological samples are available, the process is still just as dependent on astute clinicians who report and collect blood samples from families affected with genetic disorders.

The ultimate aim of this strategy is to understand the molecular pathogenesis of these single-gene conditions. If the protein is detected and its role in cell biology is sorted out, then one can begin to propose treatments that can alter or modify the sequence of events in the cell pathway in question. For example, the gene for NF1 is a tumor suppressor gene that is involved in signal transduction within the cell. The encoded protein neurofibromin is known to slow down growth within the cell. Thus, if a mutation occurs, the expected brakes on cell growth will not be present and will predispose a person to develop benign or malignant tumors. If one could figure out how to alter some of the elements of the pathway, then perhaps one could prevent the occurrence of benign or malignant tumors in NF1.

Multifactorial Inheritance

"Multifactorial inheritance" refers to the important group of disorders that have an inherited component involving more than one gene and/or gene–environment interactions. These include important neurodevelopmental disorders such as learning disabilities, Tourette syndrome, depressive disorders, and autism (see Goldstein & Kennemer, Chapter 5; Carpenter & Brown, Chapter 7; Reinemann & Swearer, Chapter 9; and Clark, Jenson, & Miller,

Chapter 10, this volume). It has been challenging to delineate the genetic components of these conditions because of the difficulty in describing discrete phenotypes, unraveling the effects of multiple genes and environmental factors, and genetic heterogeneity. Genes influencing these conditions may operate by any of the mechanisms described for mendelian (single-gene) conditions, and a given condition may involve genes with different modes of inheritance. Because of the complexity of these conditions, geneticists have developed mathematical models to study genetic effects in these disorders. Some of the important concepts related to multifactorial inheritance are discussed in the following paragraphs.

Multifactorial conditions are often thought of in the context of a normal curve of "susceptibility," with both genes and environment capable of contributing susceptibility. There may be a "threshold" above which symptoms are expressed ("penetrance" of the condition is the percentage above the threshold). This threshold may be different for males and females. Figure 3.8 shows a liability distribution for a multifactorial disease in a population. These conditions are usually common, and often are a mixture of multiple conditions with similar or identical phenotypes ("genetic heterogeneity"). In many cases, mendelian conditions have been identified and "pulled out" of the more general category (e.g., fragile X and Rett syndromes are subsets of autism; fragile X, Turner, Tourette, Noonan, and Williams syndromes, as well as NF1 and sickle cell anemia, are subsets of attention-deficit/hyperactivity disorder). (See the chapters devoted to these conditions in this volume.)

The analytical tools that have been most useful in the analysis of multifactorial conditions are "twin concordance studies" (measuring the frequency of the condition in identical and fraternal twins), large-scale family studies with "linkage analysis" (matching disease status to known DNA markers), and "segregation analysis" (observation of proportion of affected offspring). In all these studies, computer models are used to compute "heritability" (estimate of the proportion of cases attributed to genetic factors) and the likelihood of major-gene and other models. For most multifactorial conditions, we have not delineated models that provide risk figures for families; therefore, recurrence risks are generally derived from empirical data from family studies, taking into account gender of the proband and degree of relationship. Since most of these conditions also have environmental triggers, it will be important to study these factors as well.

PRINCIPLES OF MEDICAL GENETICS

Diagnostic Principles

For many of the genetic disorders described in this chapter and in this text, clinicians and investigators have set forth criteria that allow a practitioner to arrive at a secure diagnosis. The idea of developing these criteria arose in the 1980s as gene linkage studies progressed. It became clear to both clinicians and scientists that in order for one to attempt to map a gene, there had to be a consensus on who was affected and who was not. The diagnostic criteria for NF1 illustrate this principle. In 1987, at a National Institutes of Health (NIH) conference on NF1 and NF2, criteria were proposed for making the diagnosis of NF1. Table 3.2 presents these criteria. The basic premise is that if a patient's manifestations fulfill the required items, the clinician can settle upon a highly secure diagnosis of the condition (NIH Consensus Development Conference, 1988). Diagnostic criteria are not widely available or established for many other genetic conditions. However, in certain circumstances (e.g., Apert syndrome), diagnostic criteria are not really necessary, since the

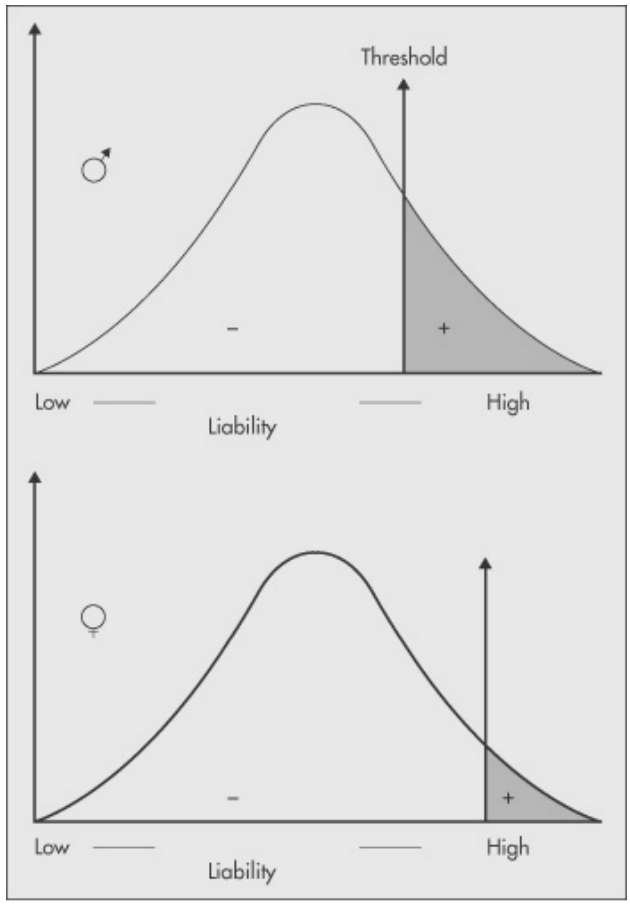

FIGURE 3.8. A liability distribution for a multifactorial disease in a population. To be affected with the disease, an individual must exceed the threshold on the liability distribution. This figure shows two thresholds, a lower one for males and a higher one for females. From Jorde, Carey, Bamshad, and White (2003). Copyright 2003 by Mosby, Inc. Reprinted by permission.

distinctiveness of the pattern is clear-cut. For conditions in which the diagnosis can be made on a molecular basis (e.g., Prader–Willi syndrome), diagnostic checklists or criteria are not needed as much for diagnosis, but are still useful to help a clinician decide who needs to be evaluated. The concept of diagnostic criteria is emphasized here simply to underscore the subjective nature and occasional difficulty of arriving at the diagnosis of a genetic disorder or syndrome. This concept is further discussed below in regard to syndromes (and, later, to behavioral phenotypes). Diagnosis is often considerably more difficult for multifactorial conditions (e.g., see the discussion in Goldstein & Schwebach, Chapter 6, this volume).

Syndrome Diagnosis

The term "syndrome" is utilized in a specific way in the field of medical genetics. It refers to a recognizable and consistent pattern of multiple manifestations known to have a spe-

TABLE 3.2. NIH Consensus Statement: Diagnostic Criteria for NF1

The diagnostic criteria for NF1 are met in an individual if two or more of the following are found:

- Six or more *café au lait* macules of over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals.
- Two or more neurofibromas of any type or one plexiform neurofibroma.
- Freckling in the axillary or inguinal regions.
- Optic glioma.
- Two or more Lisch nodules (iris hamartomas).
- A distinctive osseous lesion such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudoarthrosis.
- A first-degree relative (parent, sibling or offspring) with NF1 by the above criteria.

Note. From NIH Consensus Development Conference (1988).

cific etiology. The cause is usually a mutation of a single gene, a chromosome alteration, or an environmental agent. In other words, a syndrome is a specific complex phenotype that has a single cause. The notion of syndrome is related closely to the concept of pleiotropy, described earlier. The diagnosis of malformation or developmental syndromes in general is a challenge, as over 1,000 syndromes involving multiple congenital anomalies are listed in catalogs and diagnostic computer programs (see Gorlin, Cohen, & Hennekam, 2001; Jones, 1997).

In addition to knowledge of the more common disorders, the clinician who approaches the area of syndromology needs knowledge and skill in the recognition of minor anomalies of structure, which often provide phenotypic clues for a diagnosis. Thus, for example, diagnosing Williams syndrome can be difficult in early childhood or infancy unless one is familiar with the physical characteristics of the face in the context of the developmental condition. Even such signs as curly hair and characteristic voice are among the component manifestations that are helpful in diagnosis. Since no individual feature or manifestation is obligatory in almost any syndrome, one has to be familiar with the clinical variability in order to secure the diagnosis. The diagnosis of chromosome syndromes can often be straightforward if the clinician has the appropriate index of suspicion; ordering the chromosome study confirms the diagnosis. As mentioned earlier, if one is considering a microdeletion syndrome, the appropriate chromosome study (including FISH) needs to be performed. By contrast, if the condition in question possesses relatively consistent features (e.g., the multiple *café au lait* spots of NF1), and diagnostic criteria are available to establish the diagnosis, the diagnostic reasoning process can be fairly straightforward. Conditions familiar in childhood may be harder to recognize in adulthood, as the typical features may change with age; thus it is important to obtain information about how phenotype changes with age.

One of the important points in this discussion is that the concept of a syndrome encompasses a multiplicity of manifestations, most of which are variable within the constellation. In chromosome syndromes in general and in the syndromes discussed in this book, some disorder of development is invariably present. In that sense, mental retardation is accepted widely as a component manifestation of many of these syndromes. In the same sense, alterations in cognition, personality, and behavior can be variable manifestations in many of these syndromes, just like the more clearly defined manifestation of mental retardation. This point is the essence of the concept of "behavioral phenotype," which is discussed below.

Environmental Syndromes

In addition to syndromes of single-gene or chromosome etiology, there exist several syndromes caused by teratogenic agents. A "teratogen" is an agent external to the fetus that induces structural malformations, growth deficiency, or functional alterations during prenatal development. Although teratogens cause only a small percentage of developmental disabilities and birth defects, they are an important group because of the potential for prevention. In the neurobehavioral arena, the most important and common condition is fetal alcohol syndrome (FAS). This condition has a recognizable pattern of malformation consisting of prenatal growth deficiency (low birth weight and length), postnatal growth deficiency (short stature, failure to thrive), microcephaly, and a characteristic pattern of minor facial anomalies (Streissguth, Clarren, & Jones, 1985; Thackray & Tifft, 2001). Although at first glance the facial anomalies may seem nonspecific, together they are diagnostic of FAS. These facial alterations include short palpebral fissures (small eyelids on horizontal measurement), short upturned nose, long philtrum (distance from nasal septum to upper lip), and relatively thin upper lip. The facial gestalt of older children with FAS is quite characteristic, and a clinician who has experience with the disorder can make a secure clinical diagnosis in the context of maternal alcohol abuse. The full syndrome occurs in 10–40% (depending on the study) of children whose mothers drink excessively and abuse alcohol during their pregnancies (Stratton, Howe, & Battaglia, 1996). Although the issue of whether moderate or less frequently used amounts of alcohol cause adverse effects is controversial and not clear-cut, there is no question that maternal alcoholism is a significant risk factor for this recognizable syndrome.

One of the component manifestations of FAS is neurodevelopmental difficulty. A majority of children with FAS have learning disabilities, but some have enough developmental disability to be diagnosed as having mental retardation. In addition to this, a behavioral phenotype has been suggested but not well documented in the literature (Mattson & Riley, 1998; Stratton et al., 1996). This particular behavioral profile includes attention deficits, hyperactivity, an unusual degree of memory loss, and conduct problems (a deficiency in a person's awareness of the consequences of his or her actions). Although none of these components of the behavioral profile are specific, they appear to represent a consistent manifestation of the overall pattern when taken together in the context of full FAS.

Some of the other teratogenic syndromes are known to involve developmental difficulties, but all require additional investigation before any firm conclusions can be drawn. For instance, some children with the fetal valproate syndrome have been said to have autism (Christianson, Chesler, & Kromberg, 1994), but this requires further investigation. Children with fetal hydantoin and isotretinoin syndromes have also been recognized to have developmental disabilities, but further study on the learning profile is also needed. Little is known about the adult phenotypes in the teratogenic syndromes.

Benefits of Diagnosis

Often the diagnosis of a neurodevelopmental disorder or dysmorphic syndrome is relegated to the area of the exotic. However, as has been emphasized throughout this chapter, diagnosis is important for the individual, the family, and the family's medical practitioners. Table 3.3 summarizes the benefits of making the diagnosis of a genetic condition or syndrome. These can be illustrated in the diagnosis of Williams syndrome. Once a diagnosis

TABLE 3.3. Benefits of Diagnosis in a Genetic Condition or Syndrome

- *Recurrence risk in genetic counseling*. The recognition of an established disorder of known etiology provides information on causal and genetic aspects of the condition, including risk of recurrence, reproductive options, and identification of at-risk relatives.
- *Prediction of prognosis*. Each disorder has its own particular natural history and outcome. Knowledge of the degree of disability that occurs on average is often helpful to families.
- *Appropriate laboratory testing and screening*. Precise diagnosis can eliminate the need for many tests frequently considered in the evaluation of an individual with a developmental disorder. Appropriate screening can be planned according to natural history.
- *Guidelines for management*. Knowledge of the natural history of a syndrome allows for the establishment of guidelines for routine care, including suggestions for educational and vocational interventions.
- *Family support*. In some families, the knowledge of a condition helps in dealing with the uncertainty of the situation. A diagnosis provides a biological basis for a condition, and provides an entrée to support groups, specialty clinics, and other services.

has been established, and the deletion of the elastin gene has been confirmed with FISH, recurrence risk counseling can occur; if a parent does not have Williams syndrome (which is usually the case), the deletion is certainly de novo, and the recurrence risk approaches that of the background. Prenatal diagnosis with the FISH technique is possible in future pregnancies but is probably not necessary, given the low recurrence risk in sporadic cases. An individual with Williams syndrome has a 50% risk of having a child with Williams syndrome with each pregnancy and can consider a range of reproductive options, including prenatal diagnosis. Depending on the developmental status of the individual, parenting skills must also be considered. When other relatives are at increased risk for the condition, it is also important to recommend genetic counseling for other at-risk family members to preserve their reproductive choices. The diagnosis helps the clinician in stating some predictions about prognosis, especially the neurodevelopmental outcome, but also the natural history of the condition. Individuals with Williams syndrome will need a cardiac evaluation, due to a 60% occurrence of heart defects (especially supravalvular aortic stenosis). In addition, a higher index of suspicion for hearing loss, visual difficulties, urinary tract infections, and hypertension should occur, and this should further modify the primary care practitioner's health supervision plan.

Clinicians have developed management guidelines, also referred to as "anticipatory guidance," for common genetic conditions (e.g., Cassidy & Allanson, 2005). These guidelines are usually organized by age of the individual. A diagnosis makes it possible to avoid unnecessary laboratory testing. A person with Williams syndrome who has developmental delay should not require any metabolic testing or neuroimaging—tests that are frequently done in the diagnostic evaluation of a individual with this presentation. Moreover, knowledge of the natural history of the developmental profile in Williams syndrome at least allows for some initial steps in planning educational and vocational intervention in school and work settings. Although it is certainly true that a "cookbook"-type plan cannot be laid out, there is a profile of strengths and weaknesses in individuals with Williams syndrome that can help the educator or therapist (see Rider, Chapter 14, this volume). Finally, making a diagnosis of a specific condition often helps a family with the experience of uncertainty, as often a general diagnosis of a developmental disability conveys a sense

of meaninglessness and confusion. A diagnosis of a particular syndrome, even an uncommon one, gives a biological basis and often credibility to the individual's difficulties. For many families, the diagnosis is the entrée to a support group and specialty clinics with concentrated expertise (e.g., for Williams syndrome, the support group website is www.williams-syndrome.org). When families participate in support groups and specialty clinics, this provides pools of patients who often volunteer for studies of genotype–phenotype correlations, which in turn improves patient care. Also, although it seems self-evident that an individual with special needs should be able to obtain services based on those needs, in practice a diagnosis often entitles the person and his or her caregivers to services previously denied without a diagnosis.

One important new area of diagnosis is predictive or presymptomatic diagnosis. "Presymptomatic diagnosis" is a diagnosis based on DNA testing before symptoms are present. "Predictive diagnosis" is similar, but in this case the test predicts a susceptibility rather than certainty of symptoms. An example of presymptomatic diagnosis is testing for Huntington disease (HD). The genetic test is fairly straightforward, using a polymerase chain reaction (PCR) assay to determine the number of cytosine–adenine–guanine (CAG) repeats in the IT15 gene. Individuals with 40 or more CAG repeats develop the symptoms of HD. The disease typically manifests itself in the 30s or 40s, and includes progressive chorea and dementia, with death typically occurring 10–15 years after diagnosis. It is an autosomal dominant condition, so children of a parent carrying the gene mutation have a 50% risk of developing the condition, with age-specific penetrance that reaches 100% by late adulthood. Testing is generally only done in centers offering a protocol that includes genetic counseling, neurological examination, and psychiatric evaluation and support. There are complex psychosocial and ethical issues involved in presymptomatic testing for HD. Psychosocial issues include the availability of life-altering testing for a disease with no currently effective treatments, complex family issues (including survivor guilt), and the risk of adverse psychological reactions in both counselees who test positive and those who test negative. Ethical issues include the nonavailability of testing without counseling, the possibility of insurance discrimination, testing in minors, and testing in situations where one family member's results reveal those of another family member.

BEHAVIORAL PHENOTYPES IN MEDICAL GENETICS

The term "behavioral phenotype" has been used for the last few decades in the fields of child psychiatry and medical genetics. There is no consensus on its definition, and it is used by different people to mean different things. Turk and Hill (1995) provide an excellent summary of the issues in their review. They assert that "a number of conditions, recognizable by a common physical phenotype, single gene defect or chromosomal abnormality, seem also to have a constellation of behaviors or cognitive anomalies which are characteristic" (p. 105). Flint and Yule (1994) take a stricter view of this concept and require that before the term is used, there must be a distinctive behavior that occurs in almost every case and rarely in other conditions. However, we agree with Turk and Hill that this more restrictive view is not applied in the inclusion of nonbehavioral manifestations in the definition of syndromes. For example, the atrioventricular canal defect seen in 20–30% of individuals with Down syndrome is relatively characteristic, as almost two-thirds of individuals with this defect have Down syndrome. However, there are clearly other causes of this defect other than trisomy 21, and not all patients with Down syndrome have it. Simi-

larly, only about 20% of individuals with Turner syndrome have a left-sided obstructive lesion of the heart, and the overwhelming majority of persons who have this heart lesion do not have Turner syndrome. Thus, as illustrated here, most clinicians would not require the physical defects of the heart to occur completely consistently and specifically before including them as part of the syndrome. The same concept then, we believe, should hold true for behavioral components.

In the literature, the term "behavioral phenotype" is used without its users' necessarily clarifying whether it refers to a psychological/cognitive profile, a behavioral disorder, or a personality trait (Turk & Hill, 1995). In this context, we propose a modification of the definition of the term suggested by Turk and Hill. As we see it, a behavioral phenotype is a profile of behavior, cognition, or personality that represents a component of the overall pattern seen in many or most individuals with a particular condition or syndrome. Although the profile may not be specific, it is consistent in the syndromal pattern. The challenge for the next decade (as stated in many of the chapters in this book) is continued documentation of these parameters with state-of-the-art tools. The diagnosis of a dysmorphic syndrome needs to be rigorous and clear-cut, and the documentation of the neurodevelopmental and neuropsychological profile demands the best current strategies. At present, a glance through review papers, like those of Turk and Hill (1995) and Flint and Yule (1994), gives one the impression that there is not much specificity to the behavioral patterns described in the literature reviewed. However, this perusal is not very different from one's first glance through a catalog of listed facial features and minor anomalies in chromosome syndromes. Yet the consistency in the facial features of individuals of the same age with chromosome disorders illustrates the reproducibility of these syndromes. Recognition of facial features and documentation of their pattern are often difficult without tools for quantification. These same kinds of issues apply to documentation in the neurobehavioral realm, especially in the profiles of behavioral disorders and personality traits. The principles are the same: Just as the facial features differ from those of the family background in such conditions as Williams syndrome and Down syndrome, there is an alteration of the biological basis of behavior and personality beyond the family background in these conditions. Shalev and Hall (2004) have recently proposed a behavioral pattern profile. This tool consists of 12 categories of behavioral features and is intended to facilitate a standardized collection of behavioral data in a clinical setting.

Table 3.4 lists dysmorphic syndromes that have been found to have a relatively specific or characteristic behavioral profile. The chromosomal location or identified gene is listed as well. The reader is referred to the above-mentioned review papers. Moreover, the chapters in this text summarize the behavioral profiles of several of these syndromes.

A behavioral phenotype is generally defined by beginning with a sample of subjects with a specific dysmorphic syndrome and then studying specific cognitive, affective, or behavioral characteristics, as compared to those of a relevant control group. Some syndromes, such as Williams and Prader–Willi syndromes, have been associated with chromosomal regions as well as with behavioral patterns. A complementary approach has made use of several large affected families, extensive cognitive testing, and DNA markers to find linkages for components of a complex cognitive phenotype—developmental dyslexia. In six large families containing 94 adults affected with reading disability (documented in childhood), defective phonological awareness was linked to markers on chromosome 6, and defective single-word reading was linked to chromosome 15 (Grigorenko et al., 1997). Success in using genetics to dissect this complex phenotype first required careful study of the reading disability phenotype through state-of-the-art cognitive

TABLE 3.4. Dysmorphic Syndromes Thought to Have a Characteristic Behavioral Phenotype

Syndrome	Cause
Chromosome	
Williams syndrome	7q microdeletion
Velocardiofacial/DiGeorge syndrome	22q11 deletion
Prader–Willi syndrome	15q11–q13 microdeletion[a]
Angelman syndrome	15q11–q13 microdeletion[a]
Smith–Magenis syndrome	17p11 microdeletion
Down syndrome	Trisomy 21
Klinefelter syndrome	XXY
Monogenic	
Neurofibromatosis type 1 (NF1)	Mutation in NF1 gene at 17 q11.2
Noonan syndrome	Mutation in PTPN11 gene at 12q24.1
Fragile X syndrome	Mutation in FMR1 gene at Xq27.3
Rett syndrome	Mutation in MECP2 gene on Xq28
de Lange syndrome	Mutation in NIPBL gene on 5p13.1
Environmental	
Fetal alcohol syndrome	Maternal alcohol abuse
Fetal valproate syndrome	Maternal use of valproate

[a]Imprintable genes; see text. (See also Dykens et al., Chapter 22, this volume.)

science (Pennington, 1997). Future progress in understanding genotype–phenotype relationships in neurobehavioral disorders, such as autism or Tourette syndrome, is likely to rely on an interplay of approaches from psychology, genetics, neuroimaging, and other disciplines.

CONCLUSION

The field of medical and molecular genetics has blossomed since the 1980s, with a concomitant interest in genetics among primary care practitioners and specialists in other fields. The basic paradigm provides the potential for a newer understanding of human disease pathogenesis, similar to the advances in infectious diseases and immunology earlier in the 20th century. The principles necessary to apply this approach in the clinical setting can be mastered with some effort and are valuable in the care of patients with neurodevelopmental disorders. The diagnosis of genetic disorders and syndromes is of vital importance to patients, their families, and care providers. The relatively recently proposed concept of behavioral phenotype fits quite well into the paradigm of medical genetics. Ongoing work utilizing current techniques in phenotype analysis, medical genetics, and neuropsychology will be necessary to delineate the behavioral profiles (specific or nonspecific) of various syndromes. An understanding of the biological basis of the neurodevelopmental aspects in these genetic conditions can provide fresh insight into well-known and common symptomatic disorders, such as learning disabilities and autism.

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4

NEUROIMAGING AND GENETIC DISORDERS

SHERRI L. PROVENCAL
ERIN D. BIGLER

Contemporary imaging methods, including computerized tomography (CT) and magnetic resonance imaging (MRI), provide exquisite visualization of gross brain anatomy. For example, the images provided in Figure 4.1 compare the levels of detail in surface, cortical, and subcortical brain structures provided by a postmortem brain and by magnetic resonance (MR) images.

The interpretation of such images is based on two simple principles that characterize the brains of normal individuals: "symmetry" and "similarity." In the normal brain, what is present in one hemisphere is duplicated in the other. This first principle, symmetry, is readily apparent in Figure 4.2, which shows coronal and axial views of the normal brain scanned with MRI. The three-dimensional rendering of the image slices allows for further visual inspection of the brain, as well as detailed volumetric analysis of symmetry of particular brain regions and structures.

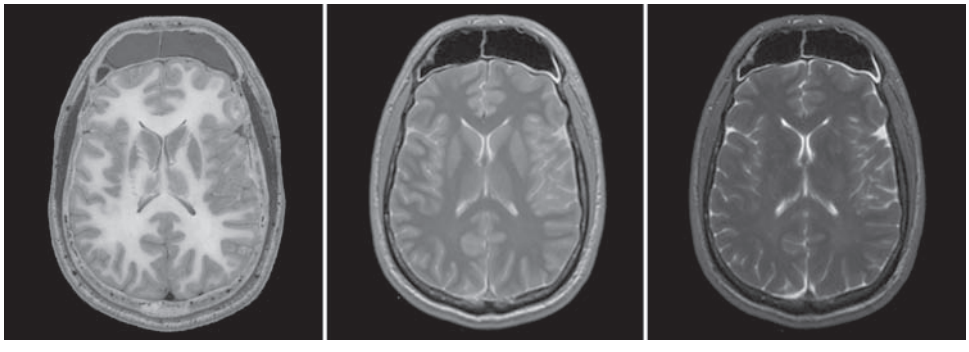

FIGURE 4.1. The left horizontal section is from a postmortem brain. Note the anatomical detail provided by MRI at the same level via two different acquisition techniques, each with different properties in displaying underlying anatomy. The middle image is a proton-density axial image in which differentiation of white and gray matter can be visualized. The right image is a T2-weighted axial image in which cerebrospinal fluid is readily identified.

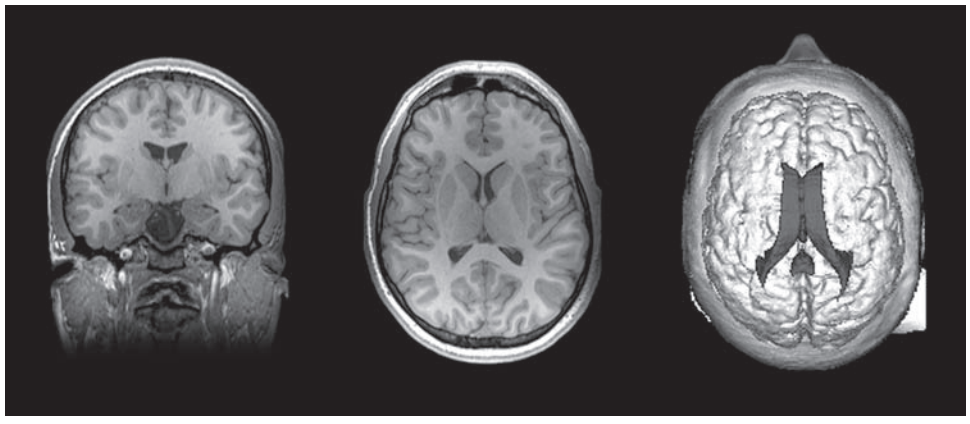

FIGURE 4.2. MRI is depicted in the coronal plane (left), axial plane (middle), and top view of a three-dimensionally rendered brain highlighting the ventricles (right). Regardless of the view, note the general symmetry of the brain when one side is compared to its counterpart in the opposite hemisphere. Because of the closeness with which one hemisphere mirrors the other, features that show up in one hemisphere and not the other can be signs of underlying pathology.

The second principle, similarity, is the consistent reproducibility of basic brain structures across individuals. For example, Figure 4.3 compares MR images of three normal subjects, all at the thalamus–basal ganglia level. An image at a given level in one normal subject parallels that seen in all other subjects at similar levels.

These two principles provide the basis for clinical interpretation of brain imaging findings when one is examining any clinical case (Bigler, 2005). Neuroimaging can provide valuable information when the clinical history and behavioral presentation of a patient

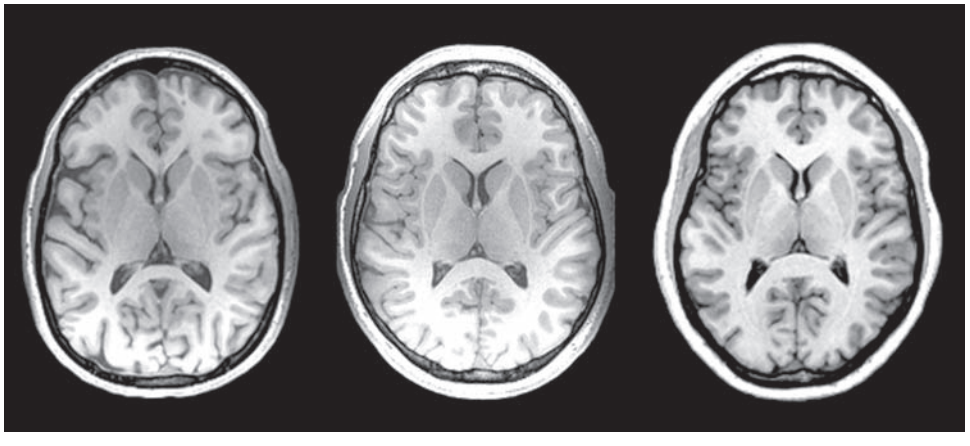

FIGURE 4.3. This figure demonstrates the principle of similarity across the brains of three individuals all scanned at approximately the same level (thalamus–caudate nucleus). Note the almost identical appearance of the anterior horns across the three scans. The anatomical similarity in the normal brain provides a comparison measure for pathological changes related to various neurological disorders.

suggest neurological involvement. The images at the top of Figure 4.4, for example, depict the case of a 2-month-old with an arachnoid cyst in the right frontal region and hydrocephalus, subsequently shunted.

When the midsagittal and axial sections of the CT scan are compared to those of a typically developing child (Figure 4.4, bottom left), the extent of the excess cerebrospinal fluid filling the void created by the absence of brain tissue is obvious. The CT images demonstrate moderate dilation of the lateral ventricles, with agenesis of the corpus callosum and colpocephaly. In cases of hydrocephalus, periodic imaging is conducted to assess functioning of the shunt that manages cerebrospinal fluid flow. In a scan of the affected child at age 12 years, the significant impact on brain development as a result of the hydrocepha-

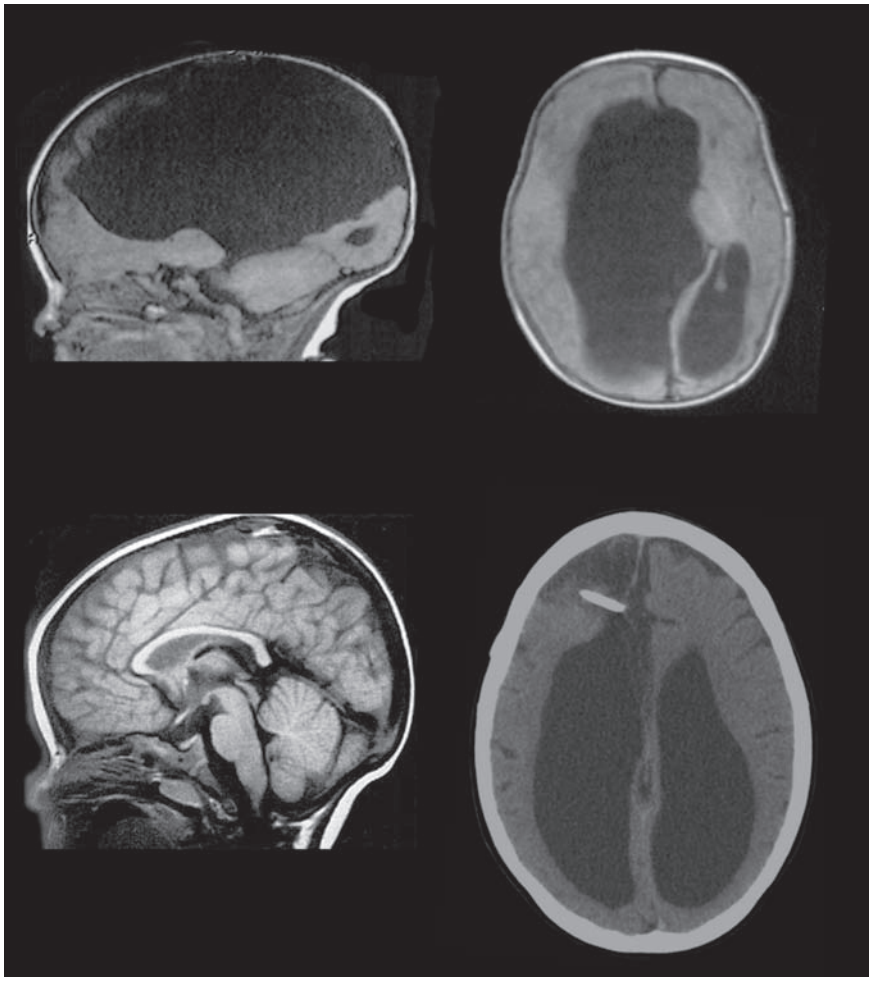

FIGURE 4.4. The CT images on the top are of a 2-month-old with an arachnoid cyst in the right frontal region and shunted hydrocephalus. Note the extent of the excess cerebrospinal fluid when compared to an MRI scan of a normal 6-month-old on the bottom left (from Barkovich, 2000; copyright 2000 by Lippincott Williams & Wilkins; reprinted by permission). The bottom right CT scan is from the same patient as in the top row, taken during a routine checkup of shunt functioning when he was 12 years old. Moderate dilation of the lateral ventricles is still apparent.

lus is still apparent (Figure 4.4, bottom right). Applying the rules of symmetry and similarity in this manner to the interpretation of scans from individuals being assessed for genetic disorders provides important clinical information about the structural integrity of the brain. Further details on clinical interpretation of scan findings and contemporary research can be found elsewhere (Bigler, 1996a, 1996b; Osborn, 1994; Wolpert & Barnes, 1992).

The interpretive principles reviewed above also apply to neuroradiological interpretations in some of the common genetic disorders. Often in genetic disorders, associated morphological brain abnormalities coexist with skeletal, skin, or other organ abnormalities. Brain embryogenesis often relates to other organ abnormalities, in that some early parent cells or cellular mechanisms share a common origin that may simultaneously influence brain, skin, muscles, bone, or other organs. For many neurogenetic diseases and neurodevelopmental disorders, there are no evident signature MRI findings. Clinical scans are often interpreted as normal or as having some nonspecific abnormality that does not aid in the diagnosis of a neurogenetic disorder (Gropman, 2004). There are exceptions, however: Some disorders result in significant brain malformations, and some individuals may have nonidiopathic types of a disorder, in which there is some underlying brain abnormality accounting for phenotypic expression of the disorder. Figure 4.5 is a scan from an adult with Jaubert syndrome, a rare brain malformation characterized by the absence

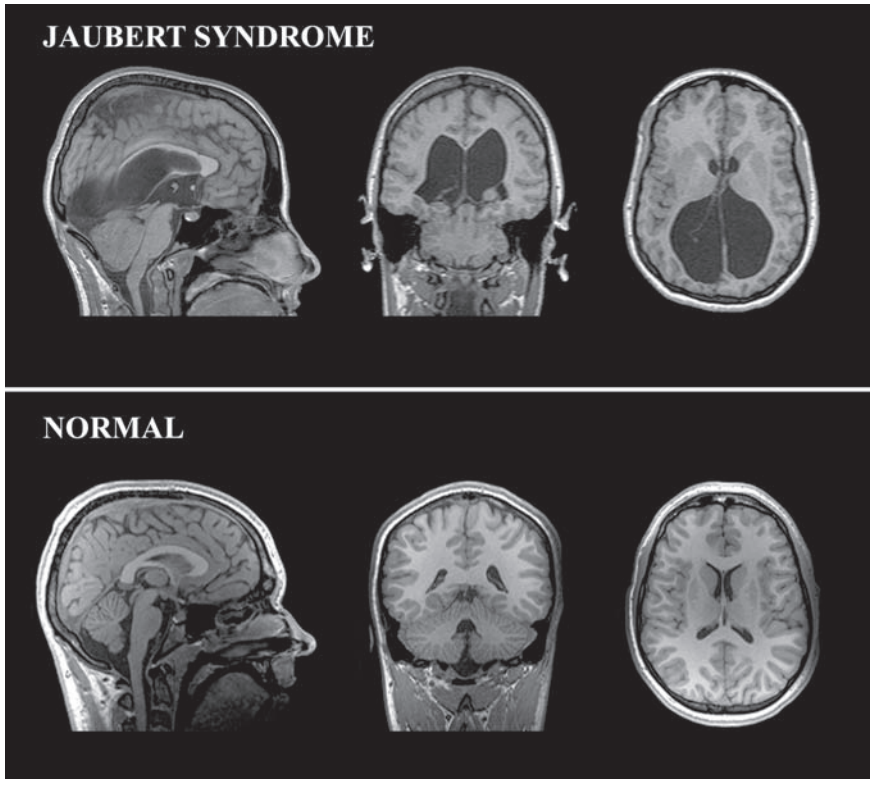

FIGURE 4.5. T2-weighted image of a young female with Jaubert syndrome resulting in the development of an occipital encephalocele, which was surgically removed at birth (top). Compared to the image from a typically developing young adult (bottom), note the enlarged ventricles, thinning of the corpus callosum, and underdeveloped cerebellar vermis.

or underdevelopment of the cerebellar vermis. In this case, also note the enlarged ventricles and thinning of the corpus callosum. The posterior abnormalities in this individual were the result of an occipital encephalcele, probably another genetic anomaly associated with cell migration.

Neuroimaging is a relatively new development in radiology. Clinical application of CT was introduced circa 1974, followed by the introduction of MRI about a decade later (see Bigler, Yeo, & Turkheimer, 1989). With the fast-moving changes in computer technology, both CT and MRI have rapidly improved from the mid-1980s to the present. Because the early technology was relatively crude, few systematic studies involving genetic disorders were performed in the early days of imaging. Furthermore, because of the rapid changes in technology, some of the early studies (i.e., those performed before 1985) may not represent contemporary findings. Thus the field has seen dramatic transformations since its emergence. Review of the clinical and research literature in this area indicates that only the most common genetic disorders have received any systematic research attention; most reports that deal with less common genetic disorders tend to be single-case, anecdotal finds.

This chapter focuses primarily on MRI findings in neurogenetic disorders, because MRI is the most widely used imaging method and provides excellent anatomical detail. Since gross anatomical abnormalities of the brain are not apparent in the majority of genetic or neuropsychiatric disorders (e.g., schizophrenia), researchers frequently aim to quantify brain structure to evaluate more subtle differences in brain size or symmetry. Subcortical nuclei of the basal ganglia, for example, are of particular interest in many of the disorders to be discussed below. Figure 4.6 shows MR images of the components of the basal ganglia in the three planes; it illustrates how the separate nuclei can be traced to investigate morphology of these regions, which play a role in motor planning and higher-order cognitive functions (e.g., emotion motivation, attention, implicit learning).

Diffusion tensor imaging (DTI) is a type of structural MRI that may be clinically useful for diagnosing and monitoring genetic disorders with white matter tract abnormalities, although recent reports applying this technique to the study of genetic disorders will not be covered in this chapter. Because DTI-MRI allows investigation of the tissue at a microscopic scale, white matter integrity can be assessed before any anatomical changes may be evident with traditional MRI (Wieshmann et al., 1999). This approach to investigating white matter integrity in the brain is clearly promising.

Undoubtedly, the number of neuroimaging studies in genetic disorders is rapidly growing. It is important to remember that structural MRI techniques offer information regarding brain *structure*; these techniques alone do not provide important information about brain *function*. Several imaging techniques in use today directly measure brain activity or function. There is a surge of interest in studying brain function in genetic and neuropsychiatric disorders via functional magnetic resonance imaging (fMRI), single-photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance spectroscopy (MRS). Other methods that are not imaging techniques per se—electroencephalography (EEG), particularly quantitatively analyzed EEG, and magnetoencephalography (MEG)—provide real-time, direct assessment of brain electrophysiology. When combined with CT or MRI, functional imaging techniques provide a valuable picture of what is happening in the brain and where it is happening. Although these other imaging methods are sometimes used to assess adults with genetic disorders, the primary imaging tool for this purpose is still MRI. As such, this chapter summarizes the most recent structural neuroimaging findings for a select few of the most common genetic disorders. The chapter also briefly discusses neuroimaging findings in neuropsychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD), learning disabilities, pervasive

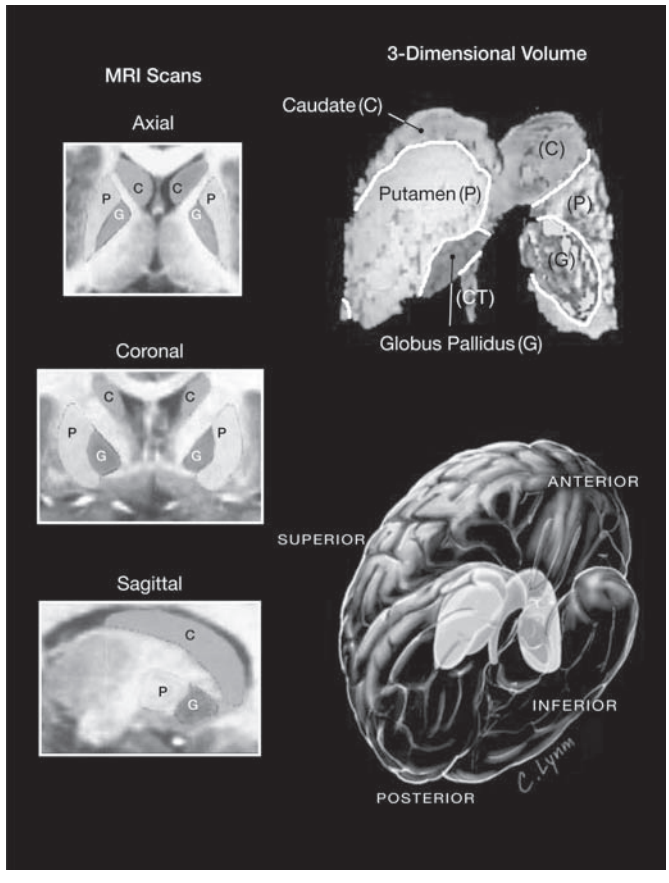

FIGURE 4.6. Neuroimaging techniques such as MRI are used to quantity brain structures and regions. The basal ganglia, consisting of the caudate, putamen, and globus pallidus, are particular regions of interests for many neurodevelopmental disorders. These subcortical structures can be isolated and measured via MR quantitative analysis techniques. C, caudate; CT, caudate tail; G, globus pallidus; P, putamen. From Peterson et al. (2003). Copyright 2003 by the American Medical Association. Reprinted by permission.

developmental disorders (PDDs), and schizophrenia, which may all have some genetic underpinnings. Some of the earlier neuroimaging findings in various disorders have been summarized by Peterson (1995) and are presented in Table 4.1.

ANGELMAN SYNDROME

Both CT and MRI studies have indicated generalized cerebral atrophy in Angelman syndrome (Boyd, Harden, & Patton, 1988; Dorries, Spohr, & Kunze, 1988; Ganji & Duncan, 1989; Robb, Pohl, Baraitser, Wilson, & Brett, 1989; Williams & Frias, 1982; Yamada & Volpe, 1990). MRI studies of Angelman syndrome often compare patients to those with Prader–Willi syndrome, since both disorders are related to a deletion error on the long arm of chromosome 15. One study, for example, found that 75% of children with Angelman but only 12% of children with Prader–Willi demonstrated sylvian fissure anomalies (Leonard

TABLE 4.1. Summary of Major Neuroimaging Findings in Various Developmental Disorders

Condition	Ventricles	Cortex	Subcortex	Other
Autism	Possibly increased cortical and ventricular CSF	High frequency of regional structural abnormalities that include localized parietal and frontal volume loss, localized pachygyria, and micro- and macrogyria, suggestive of neuronal migration abnormalities Diffuse regional abnormalities in rCBF and metabolism may correspond to the presence of regional structural abnormalities MRS studies suggest hyper-metabolism and abnormal cell membrane metabolism in prefrontal cortex Possibly increased cortical CSF	None described	Possibly altered size of vermian lobules VI and VII; hypo- and hyperplastic subtypes may exist No alterations in cerebellar blood flow have been seen Possibly reduced size of midbrain and medulla
Fragile X syndrome	Increased fourth-ventricle size	Bilaterally increased hippocampal volumes Bilaterally decreased size of the superior temporal gyrus Hippocampal and superior temporal gyrus volume changes may be correlated with increasing age	None described	Size reductions of vermian lobules VI and VII that may correlate with sex-specific differences in the degree of genetic loading
Down syndrome	None described	Decreased whole-brain and gray matter volumes, with a disproportionately large reduction in frontal gray matter volume Abnormal regional intercorrelations of frontal and parietal cortices	Relative sparing of lenticular nucleus and diencephalon	Reduced size of the anterior regions of the corpus callosum Reduced cerebellar volumes and reduced size of all vermian lobules

Schizophrenia	Increased VBR Increased size of temporal horn of left lateral ventricle Ventricular size in at-risk individuals appears to be determined by the interaction of genetic and environmental risk factor exposure	Decreased metabolism and rCBF in frontal cortex Probably reduced frontal cortex volumes Reduced volumes of anterior superior temporal gyrus (auditory association cortex), and possibly increased rCBF during auditory hallucinations Possibly reduced amygdala and hippocampus (esp. gray matter) volumes Possibly reduced asymmetries of temporal lobe and cortical surface Increased cortical CSF	Variable volumetric changes in basal ganglia, possibly increased Decreased metabolism and rCBF in basal ganglia that may normalize with treatment Reduced basal ganglia volumetric and metabolic asymmetries Increased right-sided basal ganglia metabolism with neuroleptics Inconsistent findings of increased striatal dopamine receptor density Thalamic lesions, esp. on the right	Inconsistent reports of increased size of all cerebellar vermian lobules
TS	Possibly enlarged ventricles with abnormal asymmetries	Possibly reduced metabolism in frontal, cingulate, and insular cortices Abnormal T2 asymmetries in frontal white matter	Left-sided lenticular nucleus volume reductions and absence of asymmetry in children and adults Reduced basal ganglia metabolism, possibly more pronounced in ventral portions Abnormal T2 asymmetries in basal ganglia Possibly increased level of presynaptic dopamine transporter sites	Reduced midsagittal cross-sectional area of the corpus callosum in adults Possibly abnormal T2 times in red nucleus and amygdala

(*cont.*)

TABLE 4.1. (cont.)

Condition	Ventricles	Cortex	Subcortex	Other
ADHD	No obvious ventricular size abnormalities	Possibly sulcal widening Variable functional findings, including reduced metabolic rates in sensory–motor, auditory, and occipital regions in adolescents; reductions in global rates and regional normalized rates in premotor and sensory–motor regions in adults	Possibly reduced left lenticular nucleus volumes in subjects with ADHD and comorbid TS Possibly reduced striatal metabolism in adolescents Possibly absence of normal caudate nucleus asymmetry	Reduced cross-sectional area of corpus callosum subregions, variably seen in anterior (genu, rostrum) and posterior (rostral body, isthmus, splenium) portions
Dyslexia	None described	Varying reports of abnormal asymmetries in the planum temporale Tissue may be distributed differently between the temporal and parietal banks of the planum in subjects with dyslexia Multiple Heschl gyri often seen on either side in the planum temporale Metabolic activation of the left posterior planum may be reduced, and activation of medial portions may be increased bilaterally during phonological processing tasks	None described	None

Note. See the corresponding portions of the text for a more complete discussion of these summary findings and citations of the studies reporting them. CSF, cerebrospinal fluid; rCBF, regional cerebral blood flow; MRS, magnetic resonance spectroscopy; VBR, ventricle–brain ratio; ADHD, attention-deficit/hyperactivity disorder; TS, Tourette syndrome. From Peterson (1995).

et al., 1993). In Prader–Willi syndrome, because of the characteristics of insatiable appetite and corresponding obesity, MRI studies have focused on the hypothalamic–pituitary axis, where some (but not all) subjects display abnormalities (Swaiman, 1994).

APERT SYNDROME

Central nervous system (CNS) malformations and intracranial hypertension are commonly observed in patients with Apert syndrome. The syndrome is associated with skull abnormalities (in particular, cramosynostosis), which is commonly treated surgically to increase the intracranial volume and decrease structural abnormalities in the brain (Kragskov, Sindet-Pedersen, Gyldensted, & Jensen, 1996). A recent study reported the incidence of various brain malformations observed in 18 patients with Apert syndrome several years following surgical intervention (Yacubian-Fernandes et al., 2004). No brain alterations were noted in 44% of the cases upon visual inspection of MRI scans. Common abnormalities in brain development seen in the remaining cases included ventricular enlargement, corpus callosum hypoplasia, septum pellucidum hypoplasia, cavum vergae, and arachnoid cysts in the posterior fossa.

DOWN SYNDROME

The most commonly reported abnormalities in patients with Down syndrome (DS) compared to age-matched normal controls have been smaller overall brain volumes (Figure 4.7) and reduced volume of various cortical and subcortical structures, particularly the cerebellum, hippocampus, brain stem, and frontal lobe (Aylward, Habbak, et al., 1997; Aylward, Li, et al., 1999; Jernigan & Bellugi, 1990; Jernigan, Bellugi, Sowell, Doherty, & Hesselink, 1993; Kesslak, Nagata, Lott, & Nalcioglu, 1994; Peterson, 1995; Raz et al., 1995; Wang, Doherty, Hesselink, & Bellugi, 1992; Weis, 1991; Weis, Weber, Neuhold, & Rett, 1991). Interestingly, despite overall smaller brain volume, there is preservation of particular subcortical structures (i.e., basal ganglia) and tissue composition in certain brain regions (i.e., temporal and parietal lobes) (Aylward, Habbak, et al., 1997; Pinter, Eliez, Schmitt, Capone, & Reiss, 2001; Raz et al., 1995).

Adults with DS older than 40 years of age begin to show cognitive decline (starting with memory functions) that mirrors the dementing process seen in Alzheimer disease. Neuroanatomical evidence of premature aging is detectable on MRI scans of adults with DS (Emerson et al., 1994; Emerson, Kesslak, Chen, & Lott, 1995; Pinter et al., 2001; Prasher, Barber, West, & Glenholmes, 1996; Roth, Sun, Greensite, Lott, & Dietrich, 1996). Generalized atrophy of the brain is not present prior to the cognitive and behavioral signs of dementia (Schapiro et al., 1989), although age-related reductions in the mesial–temporal lobe structures (hippocampus and amygdala) and corpus callosum have been reported in nondemented adults with DS (see Figure 4.8) (Krasuski, Alexander, Horwitz, Rapoport, & Schapiro, 2002; Teipel et al., 2003). In addition, Aylward, Habbak, and colleagues (1997) have shown that while cerebellar volumes are smaller in DS, they do not diminish significantly with age. Comparison of the changing status of cerebral structures to that of the more age-resistant cerebellar structures may aid in detecting deterioration. Recent studies using MRI with voxel-based morphometry techniques support findings using traditional volumetric analyses, and add to our understanding of changes in tissue composition in the brains of patients with DS in the predementia stage (Teipel et al., 2004; White, Alkire, & Haier, 2003).

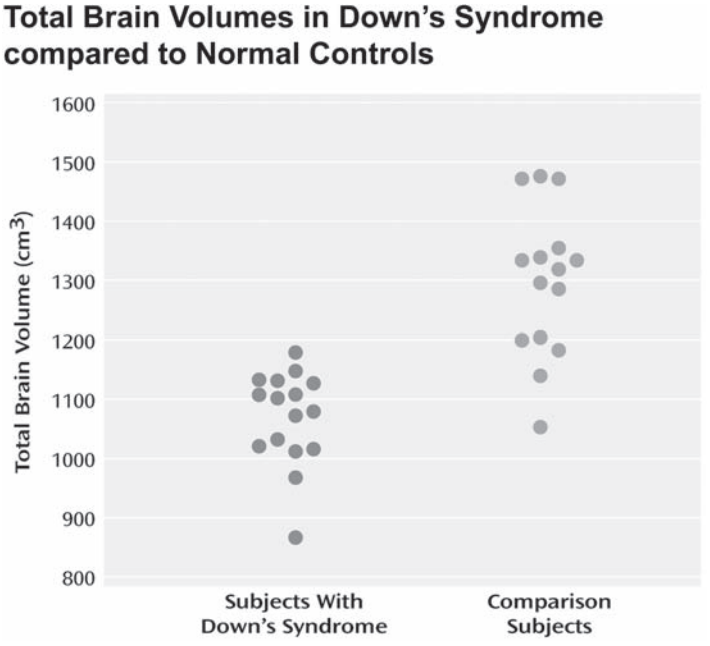

FIGURE 4.7. This graph shows results from a quantitative MRI study finding an 18% decrease in total brain volume in subjects with Down syndrome (DS) compared to normal controls. From Pinter et al. (2001). Copyright 2001 by the American Psychiatric Association. Reprinted by permission.

FRAGILE X SYNDROME

Using quantitative CT procedures to investigate brain structure in fragile X syndrome (FXS), Schapiro and colleagues (1995) found a 12% greater intracranial volume in patients with FXS as compared to controls. This increased brain size is not accompanied by generalized cerebral atrophy or hypoplasia, as suggested in previous studies using qualitative CT procedures (Rhoads, 1982; Wisniewski et al., 1985). Rather, megalencephaly in FXS may indicate anatomical abnormalities of development, such as increased neuronal production, large neurons, excessive synaptic contacts, and/or a failure of programmed cell death. More localized differences of brain regions in FXS have been reported and may reflect regional abnormalities of brain development. Refer to Reiss and Dant (2003) for a comprehensive review of neurobiological findings in FXS. Quantitative analyses of MRI scans from subjects with FXS most consistently reveal structural anomalies in the temporal lobe regions, the caudate nucleus, and the cerebellum. Reiss and colleagues (1994) reported age-related decreases in superior temporal gyrus volume in FXS. The hippocampus, a temporal lobe structure involved in memory functions, is reportedly increased in volume in patients with FXS as compared to neurologically normal controls and developmentally delayed controls (Kates, Abrams, Kaufmann, Breiter, & Reiss, 1997; Reiss, Freund, Tseng, & Joshi, 1991b; Reiss, Lee, & Freund, 1994). Consistent findings of increased caudate nucleus volume in males and females with FXS have also been reported (Reiss, Abrams, Greenlaw, Freund, & Denckla, 1995; Reiss, Freund, Baumgardner, Abrams, & Denckla, 1995). Another structural anomaly of interest in FXS is the cerebellum, a posterior structure important in sensory processing (Rao, Mayer, & Harrington, 2001) as well as in processing of higher-order

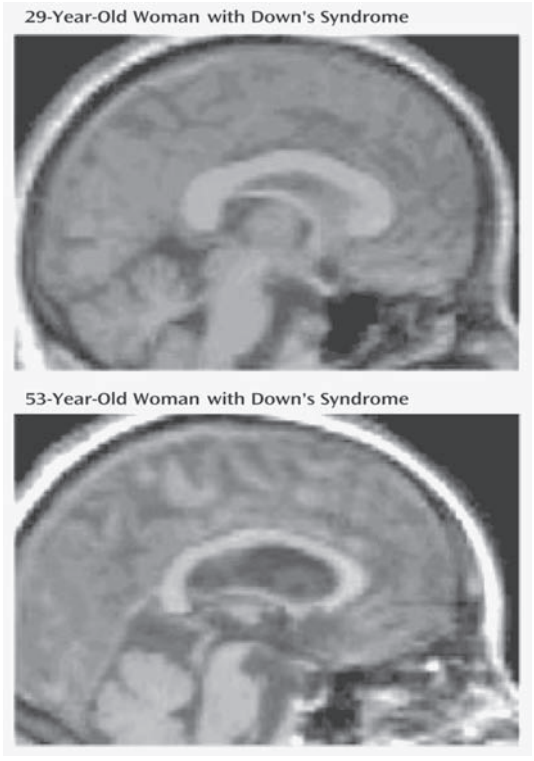

FIGURE 4.8. Both scans are T1-weighted images from patients with DS. Significant differences in brain morphology were found between younger and older subjects with DS not yet showing clinical features of dementia. Most notable were bilateral reductions in hippocampal volume and a reduction in corpus callosum area, which was most prominent in the posterior portion. From Teipel et al. (2003). Copyright 2003 by the American Psychiatric Association. Reprinted by permission.

cognitive functions (Calarge, Andreasen, & O'Leary, 2003; Corina, San Jose-Robertson, Guillemin, High, & Braun, 2003; Fabbro et al., 2004; Levisohn, Cronin-Golomb, & Schmahmann, 2000; Voroyev et al., 2004). Findings of decreased cerebellar vermis size and increased fourth-ventricle volume have been found in males with FXS (Guerreiro et al., 1998; Reiss, Aylward, Freund, Joshi, & Bryan, 1991; Reiss, Freund, et al., 1991; Reiss, Patel, Kumar, & Freund, 1988). One recent study using DTI-MRI to investigate the integrity of white matter connectivity in FXS found lower fractional anisotropy values, mostly in frontal–striatal and parietal sensory–motor tracts, in subjects with FXS (Barnea-Goraly et al., 2003). Reiss and Dant (2003) postulate that a disruption of prefrontal–striatal (caudate) pathways occurs during development and results in particular behavioral and cognitive deficits and FXS. Etiological theories based on neuroimaging findings are interesting to consider in light of those found in autism spectrum disorders, given the overlap in behavioral expression between the two disorders.

FRIEDREICH ATAXIA

Although individuals with Friedreich ataxia demonstrate motor disturbances and slowness of processing speed, no specific CNS abnormalities were noted from early MRI stud-

ies of subjects with early- or late-onset Friedreich ataxia (Ormerod et al., 1994). More recent studies, however, consistently find cerebellar hemisphere atrophy and particularly vermal atrophy in Friedreich ataxia (Wollmann, Barroso, Monton, & Nieto, 2002; Wollmann, Nieto-Barco, Monton-Alvarez, & Barroso-Ribal, 2004).

HUNTINGTON DISEASE

Several neuroimaging studies have documented a caudate atrophy that correlates with progression of the disease and severity of symptoms in Huntington disease (Aylward, Li, et al., 1997; Aylward et al., 2000; Harris et al., 1992). Some researchers have recently suggested that caudate volume may serve as a useful outcome measure to monitor effectiveness of available treatments for Huntington disease (Aylward et al., 2003).

INBORN ERRORS OF METABOLISM

Patients with inborn errors of metabolism have numerous structural and metabolic abnormalities of the brain. One of the most common of these disorders is X-linked adrenoleukodystrophy (X-LALD), in which extensive white matter degeneration occurs (see Figure 4.5 and Patel et al., 1995; Vanhanen, Raininko, Autti, & Santavuori, 1995; Vanhanen, Raininko, Santavuori, Autti, & Haltia, 1995). This X-linked neurodegenerative disorder involves primarily white matter tracts; demyelination typically begins in the parietal–occipital regions and extends across the corpus callosum before progressing anteriorly (Moser et al., 2000). A recent review of the literature by Moser, Dubey, and Fatemi (2004) discusses the role of MRI in determining cerebral involvement in patients with X-LALD, as well as in determining treatment options such as bone marrow transplant. For patients with adrenomyeloneuropathy, a phenotype of X-LALD more common in adults, repeat MRI scans may be useful tool for following the progression of demyelination of white matter or general brain atrophy (Mo, Chen, & Liu, 2004). Metabolic disorders with dystrophy have devastating neurological effects, often resulting in early death. Imaging the progression of these disorders may provide a better understanding of the developmental progression, and hence may suggest possible genetic or biological interventions for persons suffering from neurodegenerative metabolic diseases. Recent work with DTI-MRI and MRS shows promise in the investigation and treatment of X-LALD (Eichler, Barker, et al., 2002; Eichler, Itoh, et al., 2002). The same is true for phenylketonuria (PKU), another inborn error of metabolism discussed separately below.

KLINEFELTER SYNDROME

Individuals with Klinefelter syndrome (KS) typically present with cognitive and learning difficulties that present similarly to dyslexia. As such, there is speculation about aberrant brain growth and tissue maturation in KS. One of the few studies investigating brain morphology in patients with KS reported a reduction in left temporal lobe gray matter compared to controls (Patwardhan, Eliez, Bender, Linden, & Reiss, 2000). Testosterone supplementation effects were also investigated in this study. Although the sample size was small, patients with KS and a history of testosterone supplementation since puberty ($n = 5$) demonstrated preserved gray matter in the left temporal regions as well as in-

creased verbal fluency scores, compared to patients with KS but without a history of testosterone supplementation ($n = 5$).

NEUROPSYCHIATRIC DISORDERS

Considerable genetic loading is present in many of the major neuropsychiatric disorders. From a neuroimaging perspective, schizophrenia and ADHD are probably the most widely studied of the neuropsychiatric disorders. The consensus of this work is that these disorders are associated with underlying structural aberrations, none of which are diagnostic. In addition, there are considerable inconsistencies regarding morphological MRI findings in neurodevelopmental disorders. Many variables account for the diversity in findings within each of the neurodevelopmental disorders: differences in sample selection due to the heterogeneity of the disorders and comorbid diagnoses; differences in MRI acquisition; differences in methods of parceling and measuring particular brain structures or regions; and differences in methods in statistical adjustment for total brain size or other variables (e.g., intellectual ability). Nevertheless, subtle structural brain differences within and between disorders provide important information for understanding the gene–brain–behavior link underlying neurodevelopmental disorders.

Attention-Deficit/Hyperactivity Disorder

As a potential marker for development gone awry, total brain volume is of particular interest in neuroimaging studies of developmental disabilities. Several studies have reported 3–5% smaller brain volumes in children with ADHD compared to comparison groups (Berquin et al., 1998; Castellanos et al., 1994, 1996; Filipek et al., 1997; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002). There is some evidence that this reduction in overall volume throughout the brain is most marked in the white matter of patients without a history of stimulant drug therapy (Castellanos et al., 2002). MRI studies have also focused on specific brain regions with reductions in volume or abnormalities in asymmetry—typically the frontal, caudate, and parietal regions (Castellanos et al., 1994, 1996, 2003; Filipek et al., 1997; Mostofsky et al., 2002). Such findings support theoretical models of abnormal right-sided frontal–striatal and parietal function in ADHD. There is also evidence that poor behavioral performance on response inhibition tasks correlates with reduced anatomical measures of the right-sided prefrontal cortex, caudate, and globus pallidus (Casey et al., 1997; Semrud-Clikeman et al., 2000). These studies provide further support for aberrant right-hemisphere prefrontal–striatal circuitry in ADHD. Other regions of the brain have also been investigated in MRI studies of ADHD. The corpus callosum, for example, is a sensitive indicator of cortical anatomy and connectivity and is important in the transmission of information from one hemisphere to the other (Witelson & McCulloch, 1991). As such, the morphology of the corpus callosum is a region of interest in ADHD. Several studies report significantly smaller area of the rostral/anterior body of the corpus callosum in patients with ADHD as compared to various control groups, consistent with the hypothesis of aberrant frontal anatomy in ADHD (Baumgardner et al., 1996; Giedd et al., 1994; Hynd et al., 1991). Another study found no regionaldifferences in the anterior areas of the corpus callosum, but found a decrease in posterior regions, particularly the splenium (Semrud-Clikeman et al., 1994). Abnormalities in the cerebellar vermis, which may play a role in higher-order cognitive functions such as attention, have also been reported

(Berquin et al., 1998; Castellanos et al., 1996, 2001; Mostofsky, Reiss, Lockhart, & Denckla, 1998).

Learning Disabilities

Because reading disorder is the most common type of learning disability, the majority of MRIs studies have focused on morphometric brain findings in dyslexia. Normal reading ability requires a complex interaction of both non-language-based (e.g., visual perception, memory) and language-based (e.g., phonological awareness, reading comprehension) information-processing systems. Disruption of any underlying brain mechanism, therefore, may result in poor reading skills. A robust finding across many neurobiological studies of dyslexia involves aberrant structure and function of temporo–parieto–occipital region of the left hemisphere. Several reviews of neuroimaging studies in learning disabilities are available (Bigler, 1992; Collins & Rourke, 2003; Frank & Pavlakis, 2001; Vellutino, Fletcher, Snowling, & Scanlon, 2004). Subtle differences in brain morphometry—most notably in the temporal lobe, planum temporale, and corpus callosum—have been reported in reading-disordered individuals compared to nonimpaired individuals. Many studies report aberrant asymmetry or size differences in these regions, although there are many discrepancies in the literature. Several reviews are devoted to neuroimaging findings in the planum temporale, which plays an important role in auditory comprehension and language processing (Hynd & Semrud-Clikeman, 1989; Morgan & Hynd, 1998; Schultz et al., 1994). Functional studies have supported the hypothesis of deviant information processing in the left-hemisphere language regions for children and adults with dyslexia (Breier et al., 2003; Horwitz, Rumsey, & Donohue, 1998; Pugh et al., 2001; Rumsey et al., 1997; B. A. Shaywitz et al., 2002; S. E. Shaywitz et al., 1998).

Pervasive Developmental Disorders

Over the last decade, a number of neuroimaging studies have been conducted on children with various PDDs. The majority of neuroimaging studies are those of patients with high-functioning autism. There is converging evidence of widespread abnormalities of the brain in autism involving total and regional brain growth and volumetric differences of specific brain structures in autism. Findings from developmental studies indicate that brain volume is increased in 2- to 5-year-old children, only slightly larger than normal by late childhood, and average-sized by adolescence and adulthood (Aylward, Minshew, et al., 1999; Courchesne, Carper, & Akshoomoff, 2003; Courchesne et al., 2001; Lainhart et al., 1997; Sparks et al., 2002). Interestingly, cortical white matter volumes (and not gray matter volumes) are increased in children ages 7–12 years with autism (Herbert et al., 2003). MRI evaluations performed on children diagnosed with autism reveal a high percentage of some degree of ventricular enlargement, a nonspecific indication of possible injury or maldevelopment (Piven, Arndt, Bailey, & Andreasen, 1996; Piven et al., 1995). Specific brain anomalies have also been reported in autism. The most replicated findings include abnormalities of the parietal–occipital region (Piven et al., 1996), limbic structures (Aylward, Minshew, et al., 1999; Sparks et al., 2002), corpus callosum (Egaas, Courchesne, & Saitoh, 1995; Hardan, Minshew, & Keshavan, 2000; Piven, Bailey, Ranson, & Arndt, 1997), and cerebellar lobules (Courchesne, Saitoh, et al., 1994; Courchesne, Townsend, & Saitoh, 1994; Hashimoto et al., 1995).

Neuroimaging findings in Rett syndrome (RS), another of the PDDs, are summarized later in the chapter. It should be noted that studies of patients with autism suggest no specific structural abnormality that appears to encompass the spectrum of PDDs (Atlas, 1996; Filipek, 1996a, 1996b).

Schizophrenia

There is converging evidence that brain development is disrupted in schizophrenia. A recent MRI meta-analysis of neuroimaging studies in schizophrenia reported smaller brain volumes, decreased gray matter volume, and increased ventricular volumes in patients with schizophrenia compared to healthy controls (Wright et al., 2000). A recent study by Bartzokis and colleagues (2003) provided further evidence of aberrant tissue composition growth—most notably, a lack of normal myelination with age in the frontal and temporal lobes—in schizophrenia. Although attempts to identify structural abnormalities in specific brain regions in schizophrenia often yield inconsistent findings (see Shenton, Dickey, Frumin, & McCarley, 2001, for a review), MRI studies find volume or asymmetry differences in frontal brain regions (McCarley et al., 1999), temporal lobe structures and gyri (Barta et al., 1997; Joyal et al., 2003; Shenton et al., 1993; Velakoulis et al., 2001), insula (Crespo-Facorro et al., 2000; Kim et al., 2003; Wright et al., 1999), cerebellar vermis (Ichimiya, Okubo, Suhara, & Sudo, 2001; Loeber, Cintron, & Yurgelun-Todd, 2001; Okugawa, Sedvall, & Agartz, 2003), and corpus callosum (Bachmann et al., 2003; Woodruff, McManus, & David, 1995).

The appearance of brain anomalies early in development, such as the high incidence of cavum septum pellucidum (Galarza, Merlo, Ingratta, Albanese, & Albanese, 2004; Nopoulos, Giedd, Andreasen, & Rapoport, 1998; Rajarethinam et al., 2001), has led to the characterization of schizophrenia as a neurodevelopmental disorder. The relationship between gross and subtle brain anomalies and the clinical presentation of schizophrenia, however, are complex and speculative at best. Efforts to predict functional and behavioral outcome based on morphological MRI findings are also mixed (Davis et al., 1998; Galderisi et al., 2000; Rossi et al., 2000; Staal et al., 2001; van Haren et al., 2003). Regarding lifespan development, there is some evidence that the decrease in total brain volume is progressive, whereas abnormal findings in temporal lobe structures are stable features of the disorder (Wood et al., 2001). Cognitive decline/dementia is common in patients with schizophrenia. Unlike Alzheimer disease, where the presence of gliosis is a hallmark of the neurodegenerative process, no specific underlying brain abnormality accounts for the cognitive decline in schizophrenia (Falke, Han, & Arnold, 2000; Harrison, 1995). Longitudinal studies investigating the neuroanatomical and cognitive courses in elderly patients with schizophrenia are warranted.

NEUROFIBROMATOSIS

Neurofibromatosis (NF) is one of the genetic disorders most frequently studied with CT and MRI, because of the characteristic MRI abnormalities that represent the CNS extensions of the classic cutaneous lesions associated with this disorder. Most neuroimaging studies have demonstrated lesions, ranging from focal areas of signal intensity to glial tumors, in the basal ganglia, thalamus, cerebellum, and subcortical white matter of the brain (Boardman, Anslow, & Renowden, 1996; Castillo et al., 1995; DiMario, Ramsby,

Greenstein, Langshur, & Dunham, 1993; Es, North, McHugh, & Silva, 1996; Ferner, Chaudhuri, Bingham, Cox, & Hughes, 1993; Hofman, Harris, Bryan, & Denckla, 1994; Itoh et al., 1994; Menor & Marti-Bonmati, 1992; Menor, Marti-Bonmati, Mulas, Cortina, & Olague, 1991; Moore, Ater, Needle, Slopis, & Copeland, 1994; North et al., 1994; Pont & Elster, 1992; Terada, Barkovich, Edwards, & Ciricillo, 1996). A number of studies have attempted to relate the number of central NF lesions to cognitive and/or behavioral deficits, but no clearly systematic relationships have been characterized (Denckla et al., 1996; DiMario et al., 1993; Ferner et al., 1993; Hofman et al., 1994; Moore, Slopis, Schomer, Jackson, & Levy, 1996). In the first *in vivo* study of brain volume in NF1, Said and colleagues (1996) found larger brain volumes in children and adolescents with NF1 than in controls. This increase in brain size was related to an increase in white matter volume in the patient group. Unlike studies finding no relationship between brain lesions and cognitive functioning in NF1, this study reported a significant relationship between right-hemisphere gray matter and visual–spatial abilities.

PHENYLKETONURIA

MRI studies consistently demonstrate diffuse white matter hyperintensities in PKU, particularly in the periventricular parietal and occipital regions, although the white matter abnormalities may extend to more anterior and subcortical regions in more severe cases (Cleary et al., 1994; Leuzzi, Trasimeni, Gualdi, & Antonozzi, 1995; Phillips, McGraw, Lowe, Mathews, & Hainline, 2001; Pietz, Kreis, et al., 1996; Thompson et al., 1993). Figure 4.9 depicts typical periventricular white matter lesions in PKU (Dezortova, Hajek, Tintera, Hejcmanova, & Sykova, 2001).

Partial reversal of the periventricular white matter abnormalities has been observed in patients maintaining a strict low-phenylalanine diet (Cleary et al., 1995; Thompson et al., 1993). The extent of the white matter abnormalities has been correlated with length of dietary treatment and with levels of serum phenylalanine, but not with cognitive or neuropsychological performance (Cleary et al., 1994; Koch et al., 2002; Pietz, Meyding-Lamade, & Schmidt, 1996). One recent study of children with early-treated PKU, however, suggested that patients with white matter abnormalities extending beyond the posterior periventricular regions to include subcortical/frontal regions demonstrated more significant neuropsychological impairments than those with white matter abnormalities restricted to the posterior regions (Anderson et al., 2004). PET imaging and MRS studies show promise in understanding the nature and significance of the white matter abnormalities seen in patients with PKU (Dezortova et al., 2001; Koch et al., 2002; Moller et al., 2003).

RETT SYNDROME

RS is a progressive, X-linked neurodevelopmental disorder that occurs primarily in young females and is classified as a PDD. Given the acquired microcephaly in RS, it is not surprising that MRI studies find global volume reductions in both white and gray matter (Subramaniam, Naidu, & Reiss, 1997). Whereas the white matter reductions appear globally distributed throughout the brain, gray matter reductions are more prominent in frontal and anterior temporal regions. This generalized reduction in tissue composition, together with findings of reduced volumes of certain brain structures (i.e., caudate nucleus), is in-

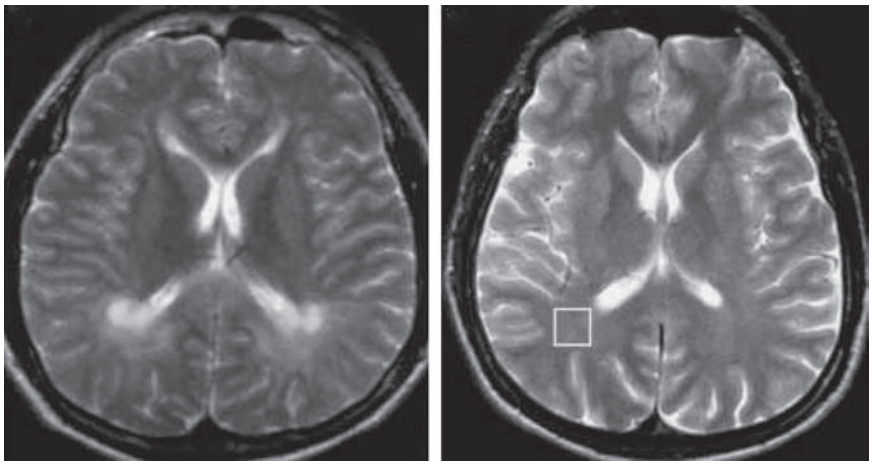

FIGURE 4.9. In patients with phenylketonuria (PKU), lesions are visibly most prominent in the periventricular white matter. In these T2-weighted transversal MR images, white matter appears dark. Note the pathological lesions (bright white) in the posterior parts of the lateral ventricles in the patient with PKU (left) when compared to a healthy volunteer (right). From Dezortova et al. (2001). Copyright 2001 by Taylor & Francis. Reprinted by permission.

terpreted as a global hypoplasia of the brain in RS—perhaps with progressive cerebellar atrophy, as depicted in Figure 4.10 (Gotoh et al., 2001; Murakami, Courchesne, Haas, Press, & Yeung-Courchesne, 1992).

SICKLE CELL DISEASE

Neuroimaging abnormalities associated with sickle cell disease (SCD) are often related to the greater likelihood of vascular strokes in this disorder. Ischemic stroke is more common in children with SCD, whereas hemorrhagic stroke is more common in adults (Powars, Wilson, Imbus, Pegelow, & Allen, 1978). Kugler and colleagues (1993) compared children with SCD to age-matched normal children and found that over 90% of the children with SCD followed over time had vascular lesions and white matter hyperintensities. "Silent strokes" (the presence of positive neuroimaging findings in the absence of any clinical symptoms of stroke) are also reported in children with SCD (Armstrong et al., 1996; Craft, Schatz, Glauser, Lee, & DeBaun, 1993; Moser et al., 1996; Pegelow et al., 2002; Wang et al., 2001). In children with SCD, a relationship was found between structural abnormities (including those from silent strokes) and cogntive/neuropsychological performance (Grueneich et al., 2004; Steen et al., 2003).

TOURETTE SYNDROME

Despite a growing consensus that the etiology of Gilles de la Tourette syndrome (TS) is biologically based, few studies describing morphometric findings in TS have been reported. In addition, structural MRI findings in TS are complicated by developmental factors and the presence of co-occurring psychiatric disorders in patients with TS (see Gerard & Peterson, 2003, for a review). Because of their role in behavioral inhibition, the frontal

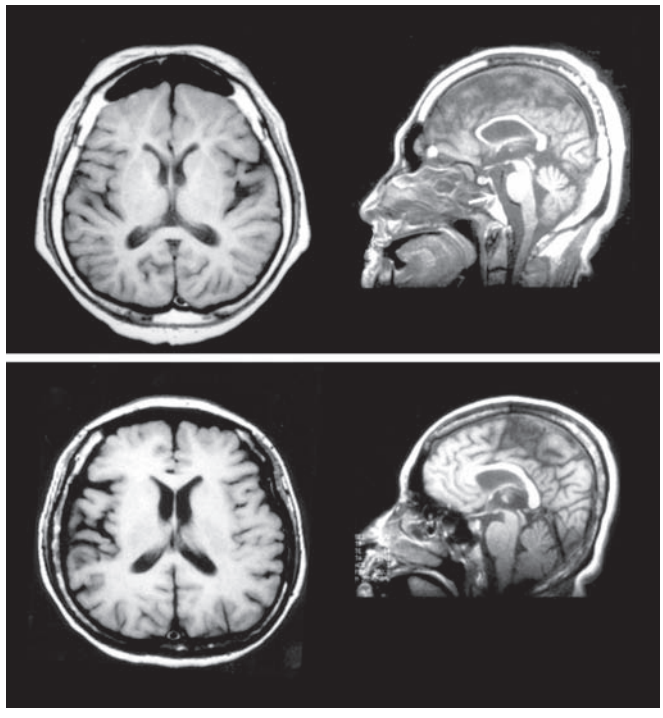

FIGURE 4.10. In Rett syndrome (RS), there is progressive reduction in white matter (throughout the brain) and in gray matter (most notably in the frontal and anterior temporal regions). The MR images in the top row are from a 46-year-old patient with RS. Visible pathological findings include narrowing of the corpus callosum, widening of the prepontine cistern, narrowing of the brain stem, cerebellar atrophy, frontal and temporal lobe atrophy, and dilation of the sylvian fissures. The images in the bottom row are from a 35-year-old female patient with RS. Similar pathology is visible, including dilation of the sylvian fissures and ventricle and atrophy of the frontal and temporal lobes. The cerebellum and brain stem also demonstrate some mild atrophy. From Gotoh et al. (2001). Copyright 2001 by Elsevier. Reprinted by permission.

lobes and basal ganglia are the brain regions of interest in TS. Abnormalities of basal ganglia size or symmetry in children and adults with TS have been repeatedly reported, especially in the caudate nucleus (Hyde et al., 1995; Peterson et al., 2003; Singer et al., 1993). Because TS is more prevalent in boys than in girls, few studies have investigated potential gender differences in TS and brain morphology. There is some evidence, however, that the association between TS and caudate asymmetry is different for girls with TS (Zimmerman, Abrams, Giuliano, Denckla, & Singer, 2000). Volume and tissue composition in TS is abnormal for frontal regions of the brain, although developmental trends and comorbid diagnoses (e.g., ADHD) complicate findings (Fredericksen et al., 2002; Hong et al., 2002). Developmental trends are also noted for the corpus callosum, where cross-sectional areas are reported to be increased for children with TS (Baumgardner et al., 1996), but reduced for adults with TS (Peterson et al., 1994). Although interpretation of anatomical findings in TS is complicated, there is strong evidence from structural MRI and other functional neuroimaging studies implicating frontal–striatal pathway dysfunction as underlying tic behavior and TS (Gerard & Peterson, 2003).

TURNER SYNDROME

Turner syndrome (TuS) stems from a partial or complete absence of the X chromosome. Physical characteristics are a result of the genotype and include short stature, webbing of the neck, lack of pubertal maturation, and neuropsychological weaknesses in visual–spatial abilities and attention. MRI evidence combined with neuropsychological data suggests deviances in specialization of brain structure and function in TuS. Consistent with patterns of neuropsychological strengths and weaknesses, differences in brain tissue distribution are noted for girls with TuS compared to controls. Girls with TuS had a smaller proportion of tissue within the right inferior parietal–occipital region and increased cerebellar gray matter relative to controls (Brown et al., 2002; Reiss, Mazzocco, Greenlaw, Freund, & Ross, 1995). Given the preserved or even superior language skills in girls with TuS, the temporal lobes of the brain are another area of interest in morphometric studies. The right superior temporal gyrus was found to be increased in both white and gray matter volume, whereas the left superior temporal gyrus was found to have increased white matter only (Kesler et al., 2003). In a study using MRS, enlarged temporal lobe regions have also been found to correlate negatively with choline-containing compounds, suggesting a developmental failure to prune neurons in this region of the brain (Rae et al., 2004). Other volumetric studies found reduced volumes of the genu of the corpus callosum, the pons, and vermis lobules VI–VII, and increased volumes of the fourth ventricle, in adolescent females with TuS compared to controls (Fryer, Kwon, Eliez, & Reiss, 2003).

THE CENTRAL THEME: BRAIN MALFORMATION

The central theme of most of the discussion above is that brain malformation is often associated with some established genetic aberration. Often some of the most significant changes in brain structure may be manifested in ventricular abnormality. Also, there are various disorders that affect primarily hindbrain development. Ramaekers, Heimann, Reul, Thron, and Jaeken (1997) have shown that the majority of children with cerebellar structural abnormalities had some form of an autosomal recessively inherited disease. The importance of identifying any abnormalities, including deviations from normal size, is that such abnormalities often have a significant effect on cognitive and neurobehavioral development (Reiss, Abrams, Singer, Ross, & Denckla, 1996).

CONCLUSIONS

Most genetic disorders that influence the brain are associated with structural abnormalities that can be detected by standard neuroimaging techniques. Increased or decreased brain volume and subtle focal structural brain anomalies probably represent aberrant neuronal organization that is diffuse and that results in characteristic cognitive and behavioral deficits associated with a genetic disorder. Although the relationship is not linear, generally the greater the structural defect, the greater the neurobehavioral and cognitive deficits. Contemporary neuroimaging techniques are a vital part of any workup in individuals with genetic disorders. Imaging findings should be available to professionals involved in diagnosis and treatment planning for the individual.

In neuropsychiatric disorders, structural analysis of the brain reveals only subtle anomalies. Multimodal approaches, including functional imaging techniques and neuropsychological evaluation of cognition and behavior, should greatly extend our understanding of brain mechanisms underlying neurobehavioral disorders. Investigation of white matter integrity and brain organization via DTI, especially when combined with other anatomical and functional data, may also lead to a better understanding of the causal mechanism of genetic disorders.

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PART II

Disorders Primarily Affecting Learning and Behavior

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5

LEARNING DISABILITIES

SAM GOLDSTEIN
KORDELL KENNEMER

The behaviors, skills, and mindset necessary to meet the daily demands of adulthood are very different from those of childhood. In childhood, certain skill weaknesses or temperamental traits may be liabilities—but through appropriate education, planning, transition assistance, and sometimes the processes of resilience, they do not have a significant adverse effect on adult outcome. However, according to the preponderance of the current research literature, the generalization that children with learning disabilities (LDs) grow up for the most part to be adults with LDs is correct. The questions remaining to be answered then relate to a variety of outcomes, including psychiatric status, achievement, vocation, substance use, antisocial behavior, and general life functioning.

In 1989, Minskoff, Hawks, Steidle, and Hoffmann proposed six variables as predictive of adult outcome for those with childhood LDs: intelligence, cognitive processing, language, academic achievement, psychological adjustment, and employability. The more individuals demonstrated functionality in these areas, the better their outcome. In this model, individuals with mild LDs as adults were described as having above-average intellect, limited processing of language deficits, high academic achievement, adequate psychological adjustment, and at least some of the key skills necessary for successful employment. Those with moderate deficits were described as possessing average intelligence, some cognitive and language problems, one or more specific academic residual disabilities, some psychological adjustment problems, and weak vocational skills. Finally, those at the severe end of the continuum demonstrated below-average intellect, significant cognitive processing or language deficits, low academic achievement, poor psychological adjustment, and very weak vocational skills. Individuals who present at the more severe end of this continuum require greater and more diverse services to make a successful transition into adult life (Schloss & Smith, 1990).

Over the last 20 years, researchers have described a rough correspondence between child and adult subtypes of LDs. However, the most common, language-based LD frequently described in children (Mather & Goldstein, 2001) is not as easily identified in adults. It has been suggested that linguistically weak children evolve into more globally impaired adults with general LDs and life skills disabilities (Spreen, 1987).

This chapter provides an overview of what is likely one of the most common groups of genetic atypicalities in the human species—LDs. Readers should be aware that research

in the field of adult LDs is quite new, particularly in comparison to the studies generated over the past 50 years in childhood. This chapter discusses definitions of LDs, genetics and etiological considerations, neuropsychological impairments, and outcomes across a variety of life issues; it also provides brief guidelines for evaluation and treatment of adult LDs. Readers interested in an in-depth examination of this field are referred to Swanson, Harris, and Graham (2003).

DEFINITIONS

It has been suggested that there is little empirical evidence to distinguish children with LDs from the larger, unclassified school-age population of children without disabilities but with low achievement (Jenkins, Pious, & Peterson, 1988). However, the great majority of data indicate that children with LDs can be distinguished from those with weak intellect or cognitive deficits by a broad range of achievement and performance factors (Mather & Goldstein, 2001). For example, reading disabilities, the most common of the LDs, have traditionally reflected a myriad of neuropsychological impairments in the acquisition of reading and spelling skills: problems with phonemic segmentation (Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopulos, 1990), ability to recognize and decode single words fluently (Lyon, 2003), and articulation (Huettner, 1994). Deficits in phonological development (Vellutino, Fletcher, & Snowling, 2004) and naming speed have been suggested in a double-deficit theory of dyslexia (Wolf & Bowers, 1999). This theory has been used to differentiate children with true reading disability from those who may simply read poorly as the result of low cognitive ability. Similarly, Mangrum and Strichart (1988) have proposed a wide range of problems that presumably differentiate college students and adults with LDs from others who are academically unprepared to attend college or participate in vocational training. These problems include the following:

1. Poor decoding rate and comprehension problems when reading.
2. Difficulty with legibility, capitalization, spelling, punctuation, and syntax when writing.
3. Difficulties with computation, arithmetic reasoning, and verbal problem solving in mathematics.
4. Weak auditory comprehension, working memory, and oral expression.
5. Low academic self-esteem, poor social reasoning, and inconsistent personal relations.
6. Weak executive skills, including difficulty with organization, note taking, outlining, studying, and test taking.

There continues to be a lack of consensus about a definition of LDs in adulthood beyond the simple intellect–discrepancy formulations. One of the most concise definitions of LDs in adults has been proposed by Reiff, Gerber, and Ginsberg (1993):

> Learning disabilities in adulthood affect each individual uniquely. For some, difficulties lie in only one specific functional area; for others problems are more global in nature, including social and emotional problems. For many, certain functional areas of adult life are limited compared to others. Adults with learning disabilities are of average or above average intelligence but intelligence often times has no relation to the degree of disability. Learning disabilities persist throughout the life span, with some areas improving and others worsening. Although specific deficits associated with learning disabilities are real and persistent, such deficits do

> not necessarily preclude achievement and, in some cases, may have a positive relationship with achievement. In almost all cases, learning disabilities necessitate alternative approaches to achieve vocational and personal success. (pp. 19–20)

The Reiff and colleagues (1993) definition is an extension of the consensus definition endorsed by six professional organizations in 1981 (Hammill, Leigh, McNutt, & Larsen, 1981):

> Learning disabilities is a generic term that refers to a heterogeneous group of disorders manifested by significant difficulties in the acquisition and use of listening, writing, reasoning or mathematical abilities. These disorders are intrinsic to the individual and presumed to be due to central nervous system dysfunction. Even though a learning disability may occur concomitantly with other handicapping conditions (i.e., sensory impairment, mental retardation), social and emotional disturbances or environmental influences (i.e., cultural differences, insufficient/inappropriate instruction, psychogenetic factors), it is not the direct result of those conditions or influences. (p. 218)

In 1987, the Interagency Committee on Learning Disabilities maintained this basic definition, but added deficits in social skills as potentially stemming from LDs as well. These definitions strongly reinforce the implication that performance rather than etiology defines LDs. The term appears to best reflect the belief that individuals with LDs are unable to accomplish academic or interpersonal tasks that others can, and that this lack of accomplishment is not the result of poor teaching, environmental deprivation, or limited experience, but of a biological process (Kavanaugh, 1988).

Despite efforts at sophisticated and scientific diagnostic classification, LDs over the last 25 years have remained a heterogeneous category of disorders characterized by low achievement that persists into adulthood (Algozzine & Ysseldyke, 1983). In fact, it has been suggested that those with LDs are simply individuals at the lower end of the learning spectrum who do not possess specific deficits (Shaywitz, Shaywitz, Fletcher, & Escobar, 1990). Thus, as Yanok (1992) noted, this "classification conundrum" has resulted in underprepared and possibly unintelligent students' managing to enter higher educational settings and ultimately misdiagnosed as having LDs. Vogel (1987) reported that the initial statewide administration of the California assessment system for adults with LDs resulted in the disqualification of approximately 40% of individuals who had been previously classified as having LDs as children. Structured postsecondary special education programs, such as those at the University of Connecticut and at Adelphi University, have been reported to differ very little from the more common campus developmental learning centers that assist all low-functioning students (Shaw, Norlander, & McGuire, 1987). All of these programs aim ultimately to provide supplemental instruction that will allow academically underprepared students to succeed in the educational mainstream.

Over the past 25 years, efforts have been made to define LDs in adult populations by subtype patterns. McCue, Shelly, Goldstein, and Katz-Garris (1984) replicated Rourke's (1982) work with children, identifying adults who performed well on the Wide Range Achievement Test Reading subtest relative to the Arithmetic subtest as having deficits in visual–spatial skills, nonverbal problem solving, and complex psychomotor abilities. Those with relatively good arithmetic and poor reading scores had higher ability levels but relatively poor linguistic skills. This pattern was reported by others in research with the Wechsler Adult Intelligence Scale (WAIS) and the Luria–Nebraska Neuropsychological Battery (Harvey & Wells, 1989). Differences in level of performance were found among intellectual, academic, and neuropsychological measures.

In 1985, Joschko and Rourke suggested that a profile of weak subtest performance on the Arithmetic, Comprehension, Information, and Digit Span subtests of the WAIS (the so-called "ACID pattern") was indicative of LDs in adults. This pattern was replicated by Katz and Goldstein (1993), but was not associated with a particular subtype of LD and thus may reflect a general information-processing deficit. Goldstein, Katz, Slomka, and Kelly (1993) evaluated 102 adults with LDs, using cognitive profiles and rule-based empirical classification systems. They focused on levels of reading and arithmetic to generate subtypes of LDs. Both methods found that a specific reading disability was associated with the most impaired cognitive profiles of the three subtypes identified. Both methods discriminated among subtypes more by pattern than by level of performance. The Rourke subtypes are based entirely on pattern: As long as the pattern is present, the subtype can be identified across a wide continuum of performance levels. In this study, cluster analysis of the WAIS found a group with global disability; a "poor arithmetic" subgroup, characterized by poor performance on the Information, Digit Span, Vocabulary, Arithmetic, and Digit–Symbol subtests; and a "poor reader" subgroup, with a similar pattern but a lower level of performance. Neither classification method, however, produced a remarkable profile of pattern differences among the subtypes. Level rather than pattern of performance was the major distinction between groups. Walters (1987), in a population of 100 college students in need of academic assistance, found that the Rourke type I deficit (all achievement scores below a standard score of 85) and the type II deficit (reading difficulty with relatively good arithmetic) were not present. Over 30 cases of the Rourke type III deficit (arithmetic problems with relatively good reading) were found in this population.

Shafir and Siegel (1994), in a population of 331 adults, reported several specific subtypes of LDs. Individuals with arithmetic disability, reading disability, or combined disabilities were evaluated on a variety of cognitive and achievement measures and compared to a normally achieving group. The groups with reading and combined disabilities demonstrated deficits in phonetic knowledge, phonological processing, vocabulary, spelling, and short-term memory. The performance of the group with arithmetic disability was similar to that of the normally achieving group on reading and phonological processing, but worse on word reading and vocabulary. Greiffenstein and Baker (2002) compared IQ scores of three groups each containing 45 adults with reading deficiency, arithmetic deficiency, and dual deficiency (reading and arithmetic). Generally lower IQ and nonverbal reasoning/constructional problems were noted for the group with arithmetic deficiency.

Minimal differences in subtest Wechsler scores between subjects with reading impairment and controls were reported by Feldman and colleagues (1993). These authors reported a difference in Block Design performance on the WAIS-R, with better Block Design subtest performance among subjects with dyslexia. This pattern has been reported by others with the WISC (Rugel, 1974). In the Feldman and colleagues study, the individuals with dyslexia tended to continue their education beyond high school to the same extent as familial controls. It is important to note that the mean IQ of both groups in this study was 110, two-thirds of a standard deviation above the average. These authors also did not find a higher proportion of males in their sample with reading impairment. This supports the suggestion made by other authors that the disproportionate number of males diagnosed with reading problems may be due to reporter bias rather than to a true gender difference in the incidence of the disorder (Shaywitz et al., 1990). Moreover, the Feldman and colleagues study reported that left-handers were not disproportionately represented among persons with reading disability—a phenomenon reported by others (Hugdahl, Synnevag, & Satz, 1990). In fact, over a 6-year period during childhood, no relationship was reported between crosslaterality, intelligence, and achievement (Sulzbacher, Thompson, Farwell, Temkin, &

Holubkov, 1994). It is reasonable to conclude that adults with LDs demonstrate similar patterns of conceptual and rote/automatic strengths and weaknesses as children. In this model, reading and other language-based disorders are the result of verbal conceptual and/or rote/automatic deficits, while visual–motor-based LDs (also referred to as nonverbal LDs) result from nonverbal conceptual and/or rote/automatic deficits (see Table 5.1). For an in-depth review of this model, readers are referred to Goldstein (1997).

The *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR; American Psychiatric Association, 2000) lists four academic skill disorders: reading disorder, mathematics disorder, disorder of written expression, and learning disorder not otherwise specified. All four are qualified as reflecting standardized test data indicating performance substantially below what would be expected from the individual's age, intelligence, and educational experience. According to the DSM-IV-TR criteria, the problem must interfere with the individual's academic performance or activities of daily living. The not otherwise specified category, for example, reflects LD as an isolated weakness (e.g., spelling independent of other written language difficulties) that significantly affects daily functioning. The DSM-IV-TR also contains a diagnosis of developmental coordination disorder, reflecting weak large or fine motor skills that may interfere with academic achievement or daily living and are not the result of a specific medical condition.

The definition of LDs in adults is also driven in part by need. Adults seeking assessment for an LD may present with either or both of two sorts of inquiries. Some individuals are simply interested in improving their status in life by understanding a lifelong pattern of difficulty and seeking remediation. An increasing number, however, are well aware of their disabilities and seek evaluation in an effort to meet requirements set by institutions of higher learning or vocational settings as individuals with LDs, in an effort to qualify for accommodations under the Americans with Disabilities Act of 1990 or the Rehabilitation Act of 1973. The consensus among these standards is that an LD must be defined through the utilization of a number of well-accepted assessment instruments, as well as a long-standing history of impairment and accommodation; most importantly, it must be based upon a discrepancy of at least 1.5 standard deviations between achievement and ability. The Americans with Disabilities Act and the Rehabilitation Act collectively create the right to be free from discrimination based on one's disability. According to these acts, an individual with a disability is someone who has a physical or mental impairment that substantially limits one or more of the person's major life activities; who has a record of such an impairment; or who is regarded as having such an impairment. Such an individual is considered otherwise qualified because, though possessed of the disability, he or she would be

TABLE 5.1. Categories of Academic Skills

	Auditory–verbal	Visual–motor
Conceptual	Verbal conceptual skills	Visual, nonverbal conceptual skills
Rote/automatic	Auditory–oral motor skills	Letter perception
	Auditory perception	Spatial organization and nonverbal integration
	Rote auditory-sequential memory	Rote visual-sequential memory and retrieval
	Rote and association memory and retrieval	Motor sequencing and fine motor control

Note. Adapted from a table prepared by Sally Ingalls. Copyright 1991 by Neurology, Learning and Behavior Center, Salt Lake City, UT. Adapted by permission.

eligible for the job, education, or program benefit with or without a reasonable accommodation (for a review, see Latham & Latham, 1997).

Gordon, Lewendowski, Murphy, and Dempsey (2002) surveyed 147 clinicians to assess their understanding of the Americans with Disabilities Act and the diagnostic approaches they utilized to justify claims of LDs, attention-deficit/hyperactivity disorder (ADHD), and psychiatric disabilities. These authors identified substantial disagreement on several fundamental issues, including the basic intent of the law, the metrics for assessing impairment, and the criteria for assessing ADHD in adulthood.

GENETICS AND ETIOLOGY

The scope of questions concerning the outcome of adults with LDs has also focused upon etiological considerations. Compared with controls in one small study, those with familial dyslexia had similar incidence of perinatal complications, left-handedness, and right–left confusion as others, but experienced a greater degree of early reported speech and language problems (Benton & Pearl, 1978). Those with weaker academic skills into adulthood also demonstrated greater symptoms of depression and anxiety, but were more likely to suffer from what is now called ADHD as well, suggesting that the comorbidity of the conditions may contribute to vulnerability. In this study, individuals with LDs demonstrated similar marital history, stability, and mean income. Faraone, Biederman, and Lehman (1993) found that the risk for LDs was highest among relatives of probands with combined LD and ADHD diagnoses.

Heredity accounts for the majority of LDs by affecting proficiency in certain skills essential for mastering basic academic and interpersonal activities. From 35% to 40% of close relatives of children with LDs report experiencing similar problems. Genetic research involving twins has identified heritable, familial factors in from 25% to 50% of those with reading disability (DeFries, 1985; DeFries & Fulker, 1988). In some families, reading disability has been linked to a genetic marker on chromosome 15 (Smith, Kimberling, Pennington, & Lubbs, 1993), while in others chromosome 6 has been implicated (DeFries & Dekker, 1982). Environmental factors such as toxins, maternal drug use, or low socioeconomic status may also play a role in a child's failure to develop basic academic skills at a critical period. This failure may then lead to a chronic LD.

In 1981, Nichols and Chen, after an extensive study of nearly 30,000 children, reported that LDs were associated with demographic and maternal variables (e.g., large family size, frequent changes in residence, low socioeconomic status, younger siblings with intellectual disabilities, and receipt of public assistance); pregnancy and delivery variables (e.g., lack of prenatal visits during pregnancy, hospitalizations during pregnancy); and child variables (e.g., small head circumference, low intellect, and right–left discrimination problems). Among school-age children, speech and language problems, clumsiness, incoordination, right–left confusion, and mixed or inconsistent cerebral dominance have all been associated with impaired reading ability (Benton & Pearl, 1978). Identification as having a reading disability has been reported to correlate with large family size (Thomson & Raskin, 2003; Varlaam, 1970), antisocial behavior (Rutter, Graham, & Yule, 1970), autoimmune disorders (Pennington, Smith, Kimberling, Green, & Haith, 1987), and perinatal complications (Rutter, 1978).

Galaburda (1985, 1989, 1991) reports the presence of microscopic changes in the cortex of the brains of individuals with LDs upon postmortem analysis, involving poor organization of brain cells, focal cortical heterotopias (misplaced nests of cells in the outer-

most layer of the cortex), and the presence of polymicrogyria (deeper folds in the cortex). Convolutional patterns are also atypical in polymicrogyria (Filipek, 1996). Anatomical asymmetries and symmetries differing from those of adults without LDs have also been found in the brains of adults with LDs (Hynd, Hern, Voeller, & Marshall, 1991).

Anatomical research on LDs has focused on multiple parts of the brain or aspects of its development:

- *Planum temporale*. Geschwind and Levitsky (1968) reported an asymmetry of the planum temporale, an area that contains the bilateral auditory association cortices, in postmortem brains. A pattern of smaller left planum than right planum (reversed asymmetry) has been reported in children with dyslexia (Hynd et al., 1990).
- *Gyral morphology of the perisylvian region*. In a postmortem magnetic resonance imaging study of 120 left and right hemispheres of individuals presumably without LDs, Steinmetz, Ebeling, Huang, and Kahn (1990) classified four types of gyral morphology patterns. Heinmenz and Hynd (2000) attempted to link this classification system to reading disabilities by comparing the gyral morphology of individuals with dyslexia and controls. One type, found in only 5%, was discovered to be much more common in the individuals with dyslexia on postmortem examination.
- *Cortical abnormalities of the temporal–parietal region*. Differences caused by focal dysplasias or heterotopias and polymicrogyria may contribute to the impairments of individuals with dyslexia (Hynd, Morgan, & Vaughn, 1997). It is not clear what causes these disturbances. Maternal influenza, trauma, secondary fetal asphyxia, and genetic transmission have been implicated (Hynd et al., 1997).
- *Decreased neuronal pruning*. Researchers have theorized that asymmetry or reversed asymmetry of the plana is due to decreased rates of ontogenetic cell death in the left planum temporale during the period of corticogenesis that occurs between the fifth and seventh months of human fetal development (Hynd & Semrud-Clikeman, 1989). Galaburda (1985) suggested that this decreased rate of cell death during corticogenesis may be associated with a familial tendency toward autoimmune and allergic disorders, possibly dyslexia, and left-handedness.

The primary underlying cognitive deficit in the most common type of LD, reading impairment, is hypothesized to be related to deficits in phonological processing and rapid naming speed (Wolf & Bowers, 1999), as noted earlier in this chapter. Additional evidence strongly suggests that an orthographic or visual component impedes reading for some individuals as well (Eden, Van Meter, Rumsey, & Zeffiro, 1996). The neurobiological correlates that may well underlie these deficits appear to be centered around the left temporal–parietal region. Morphology of these areas of the brain is probably related to genetic factors as well as to variability in fetal development. Thus, although reading disabilities may occur frequently in some families, only 50% of the variance may be explained by genetics alone (Wadsworth, Olson, Pennington, & DeFries, 1992). Recently, a series of studies completed by Yale faculty members (Shaywitz & Shaywitz, 2003) suggests that three important neural systems, all primarily in the left hemisphere, are implicated in reading. These include an anterior system in the left inferior frontal region, and two posterior systems—a parietal–temporal system (including the angular gyrus, superior marginal gyrus, and posterior portions of the superior temporal gyrus) and an occipital–temporal system (including portions of the middle and inferior temporal gyrus and middle and inferior occipital gyrus).

Over the past 40 years, researchers have clearly identified a significant increase in risk for a childhood reading disability when a parent also has a history of disability. As noted,

several studies implicate chromosomes 6 and 15 in reading disabilities (for a review, see Grigorenko et al., 1997) and spelling disabilities (Schulte-Körne, 2001). Some researchers suggest that dyslexia is the result of an autosomal dominant transmission with variable expression and incomplete penetrance (Ebert & Seale, 1988). This would mean that each child of a parent with the genes hypothesized to cause dyslexia has a 25% probability of inheriting these genes. These genes are not gender-linked, and in children who inherit the genes, the expression of dyslexia can range from the nonapparent to severe impairments. The profile of impairment may vary across family members. Twin studies indicate that 50% of the variance in reading problems experienced by children with dyslexia is due to heritable influences, but it has also been suggested that there is a significant environmental component (Wadsworth et al., 1992).

NEUROPSYCHOLOGICAL IMPAIRMENTS

Some authors have suggested that the classification of LDs across the lifespan should be based on four considerations:

1. Multidimensional factors.
2. Multidisciplinary data providing for variation within age group and sample.
3. Provision for variation in measurement used by different investigators.
4. Taxonomy of clinical and research usefulness for the definitions (Silver & Hagin, 1990). These authors suggest that diagnoses of LDs should apply to those whose academic achievement is below that expected from their age and intelligence. Although these and other authors have suggested that LDs are sets of broad, nonspecific symptoms for which causes have yet to be identified, it has yet to be demonstrated that different causes lead to different types of LDs or require different treatments.

Efforts at defining subtypes of LDs according to neuropsychological impairments have been fairly extensive. Efforts at similar classification in adults pale by comparison (for a review, see Goldstein, 1997). Among subtyping efforts in childhood are those of Boder (1973) and Bakker (1979), suggesting three types of groups of children with dyslexia:

1. A "dysphonetic" group, lacking word analysis skills and having difficulties with phonetics.
2. A "dyseidetic" group, experiencing impairment in visual memory and discrimination.
3. A "mixed dysphonetic and dyseidetic" group.

Multivariate analyses suggest that differences between those who read well and poorly may reflect impairment in minor skills, such as oral word rhyming, vocabulary, discrimination and reversed figures, speed of perception for visual forms, and sequential processing (Doehring, 1968).

In 1979, Petrauskas and Rourke used a factor-analytic method to describe the difficulties of children with deficient reading as falling into four subtypes:

1. Primarily verbal problems.
2. Primarily visual problems.
3. Difficulty with conceptual flexibility and linguistic skills.
4. No specific weakness.

Mattis, French, and Rapin (1975) identified children with three distinct syndromes of reading disability:

1. Those struggling to read as a result of language problems.
2. Those with articulation and graphomotor problems affecting academic achievement.
3. Those with visual–spatial perceptual problems. The third group displayed better verbal than nonverbal intellectual abilities. Almost 80% of the children fell in the first two groups.

Satz and Morris (1981) found five distinct groups of children with reading disabilities, again along a verbal–nonverbal continuum:

1. Those with language impairment.
2. Those with specific language problems related to naming.
3. Those with mixed global language and perceptual problems.
4. Those with perceptual–motor impairments only.
5. An unexpected group in whom no significant impairments were identified.

The last group is often found in many studies of individuals with LDs and presents a thorny problem for etiological considerations. Some have suggested that this group experiences emotional problems that interfere with the capacity to learn. Phillips (1983) identified a pattern of LD subtypes similar that of Satz and Morris, including individuals with normal test scores, auditory processing problems, difficulty with receptive and expressive language, spatial weaknesses, and a global pattern of low test scores.

Oestreicher and O'Donnell (1995) used the Halstead–Reitan Neuropsychological Test Battery (Reitan & Wolfson, 1988) to demonstrate that the General Neuropsychological Deficit scale could discriminate individuals with LDs from those with no disabilities and with brain injury; the group with LDs fell somewhere between the other two populations. This finding confirmed the results of past research on adults with LDs (O'Donnell, Kurtz, & Ramanaiah, 1983). Although the scale could distinguish the group with LDs from the other populations, it did not identify subtypes of LDs. Naglieri, Goldstein, and Schwebach (in press) find that a model based on Luria's conceptualization of brain function reflecting skills related to attention, planning, and simultaneous and successive processing explains a significant amount of the variance in the rate at which children master basic academic skills.

From the neuropsychologist's perspective, a practical or functional conceptualization of LDs is of critical importance. It is the neuropsychologist's job not only to evaluate, but to transmit information to educators, vocational counselors, family members, and the affected individual in ways that will facilitate practical understanding, increase motivation, and define intervention.

The consensus of current factor-analytic research is that two broad groups of skills are necessary for efficient learning:

1. Auditory–verbal processes. Weaknesses in these areas result in reading disorders and other language-based learning problems.
2. Visual, perceptual, and motor processes. Weaknesses in these areas may result in reading problems, but are more likely to affect handwriting, mathematics, and certain social skills.

For an in-depth discussion of both these types of weaknesses and related research in childhood, readers are referred to Goldstein (1997) and Mather and Goldstein (2001).

Pelletier, Ahmad, Saadia, and Rourke (2001) distinguished children with basic phonological processing disabilities from those with nonverbal LDs. They found that children with language-based problems exhibited normal or relatively normal psychosocial functioning, whereas subjects with nonverbal LDs evidenced increased psychosocial dysfunction with age. It should be noted that the traditional approach of identifying learning disability through an IQ–achievement discrepancy has been demonstrated to be invalid (D'Anguilli & Siegel, 2003; Stage, Abbott, Jenkins, & Berninger, 2003).

In 1985, Bruck found that individuals with histories of LDs in childhood who were attending college at the time of assessment obtained higher achievement scores than individuals with the same educational level, intelligence, and socioeconomic status as measured during childhood who were not in college. If adults with childhood histories of reading disability were not in educational environments, they rarely engaged in literary activities. Bruck (1993) further found that adults with childhood histories of LDs had persisting problems in a wide general array of component reading and spelling skills.

OUTCOMES

This brief overview of outcomes for individuals with LDs into adulthood is organized by specific issues, including gender, emotional/psychiatric, cognitive, achievement, and vocational outcomes.

Gender

Finucci and Childs (1981) have observed that many research samples of individuals with LDs consist primarily of males. The tendency has been to assume that findings for males will generalize to females. Limited information is available concerning females. Flynn and Rahbar (1994) found that in order to be identified in the public schools as having LDs, females had to be lower in intelligence, to have more severe impairments in language and academic achievement, and to have greater aptitude–achievement discrepancy than their male counterparts.

Emotional/Psychiatric

Very little is known about the psychiatric outcomes for adults with histories of LDs. Although many authors hypothesize that these individuals experience greater problems with self-esteem (McNutty, 2003), life satisfaction, and general emotional functioning, current findings are inconsistent. Balow and Bloomquist (1965) and Dykman, Peters, and Ackerman (1973) reported a greater frequency of psychiatric problems among adults with reading disabilities. Beitchman, Wilson, Douglas, Young, and Adlaf (2001) completed a longitudinal study of children with LDs. They found that adolescents with a diagnosis of an LD at age 19 were more likely to have a substance use disorder or psychiatric mood disorder than controls. However, other authors (Feldman et al., 1993) have not consistently replicated this finding. Cosden (2001) reported that a majority of adolescents and adults with LDs do not abuse substances at a higher rate than the general population, yet they are

disproportionately represented in treatment programs. The following risk factors for psychiatric impairments comorbid with LDs have been suggested by these authors: poor understanding of one's disability, lack of skills for developing appropriate peer relationships, and the need for prolonged family support.

Cognitive

Although the severity of LDs is very clearly a contributor to adult cognitive outcome, intellect also appears to make a significant contribution (Rawson, 1968; Rogan & Hartman, 1990). The latter authors found that mean Full Scale IQ scores on a traditional intellectual test differed significantly for a group of college graduates with LDs (who obtained scores almost 1 full standard deviation above the average), high school graduates with LDs (who obtained average scores), and students in self-contained special education classrooms for those with more severe LDs (who obtained scores over 1 standard deviation below average).

Achievement

Adults with histories of reading disability in childhood have been found to experience similar problems into their adult years (Bruck, 1990, 1992; Vogel & Reder, 1998). These adults demonstrated word recognition difficulties associated with poor knowledge of spelling and poor levels of phonological awareness. Most of these adults were able to overcome some deficits, such as difficulty with sound–spelling correspondence; nonetheless, this group continued to experience spelling problems, reflecting more complex difficulty involving the use and knowledge of phonetic and orthographic information. For other individuals, deficits in sound–spelling correspondence knowledge persisted, but they developed more complex, linguistically based, and possibly visually based compensatory skills. Stanovich and West (1989) found that the ability to spell morphologically appearing words was related to a measure of print exposure. In another study, adults who read poorly and who had reported childhood histories of LDs performed worse than adults without LDs on nonword spelling (Scarborough, 1984).

Schonhaut and Satz (1983) reviewed 18 follow-up studies and concluded that socioeconomic factors were powerful variables related to the probability of developing learning problems and to academic prognosis. Age at identification has also been found to be an indication of poor prognosis, with children identified at younger ages faring worse than those identified later (Kavale, 1988; McGee, Williams, & Feehan, 1992). It is also important to note that when progression to conduct disorder is the dependent variable, LDs are not predictive of adverse outcome, whereas substance abuse, socioeconomic status, and the exhibition of oppositional behavior are predictive of adverse outcome (for a review, see Goldstein & Rider, 2004).

Murray (2003), studying a population of 84 college students diagnosed with LDs, found that Full Scale IQ scores and study habits (e.g., delay/avoidance of work) accounted for the variance in college grade point average. Wilczenski (1991) reported that almost all academic performance indicators, including graduation rate and timing of dropout, were lower for students with LDs attending college than for students without LDs. Although withdrawal rates did not differ significantly between the two groups, the students without LDs tended to drop out of college early in their careers, whereas the students with LDs appeared to drop out later in their careers. This is a troubling finding and suggests that

students with LDs may be unable to cope with the increasing demands of coursework ultimately required for graduation.

Beginning in the early 1990s, a series of studies by numerous authors began to identify continued achievement weaknesses, even in students with LDs who were capable of progressing into college. For example, Bruck (1993) found that college students with childhood diagnoses of dyslexia continued to have problems acquiring knowledge of the mappings between spelling and sounds. This group's knowledge and use of morphological and visual information for spelling were predicted by their reading problems. Bruck reported that although these individuals preserved the phonological structure of words, their spelling was still less than phonologically accurate—a finding also reported by others (Pennington et al., 1986; Scarborough, 1984).

The literature on postsecondary education for persons with LDs is small but growing. In 1990, Hughes and Smith reported that there was not a single published scientific study that directly evaluated the efficacy of developmental education programs for college students with LDs. More recent relevant articles published in authoritative journals have begun to examine outcome and predictive variables for this population, but for the most part they still contain only program descriptions, opinions, survey reports, and general commentary (Fairweather & Shaver, 1991; Heiman & Preceo, 2003; Janiga & Costenbader, 2002; Ruban, McCoach, McGuire, & Reis, 2003).

Until the mid-1980s, students with LDs were not a recognized population at the college level (Hoy & Gregg, 1986). However, this situation has clearly changed. In 1986, approximately 230,000 entering college freshmen identified themselves as having LDs (Fishlock, 1987), and the number of such students continues to increase. Moreover, Hoffman and colleagues (1987) reported that 29% of students with LDs surveyed had enrolled in technical, vocational, or trade school after high school. Fifty thousand recipients of high school diplomas and 161,000 students enrolled in postsecondary educational institutions during 1988 were identified as having LDs ("Illinois Program Helps," 1990). A report released by the American Council on Education's (1993) HEATH Resource Center stated that more than 40% of recent inquiries received by this national information clearinghouse concerned college programs for students with LDs.

These data suggest that persons with LDs will continue to seek access to higher education in substantial numbers. Moreover, these adults will arrive in advanced training settings with the expectation of receiving assistance. Although the provisions of Section 504 of the Rehabilitation Act of 1973, and of the Americans with Disabilities Act of 1990, require publicly supported institutions of higher learning to afford equal educational opportunity to persons with disabilities, private colleges and universities are not obligated to provide postsecondary special education services (Rothstein, 1986), and as yet there is still no consensus about qualifying criteria or about the breadth and scope of assistance provided.

In 1982, Dexter noted that on most college campuses, special classes, resource rooms, and other services common in elementary and secondary schools were not available. However, a nationwide survey of 300 campuses by Gruenberg (1983) found that 80% of the responding colleges and universities had established learning centers on their campuses. The general goals of these centers were to provide support for those students in need and to reduce the number of course failures and academic dismissals.

The National Longitudinal Transition Study (Wagner, 1989) reported that only 9% of adults with LDs were enrolled in 2- or 4-year college programs. Fourquean, Meisgeier, Swank, and Williams (1991) reported that 26% of students with LDs attended a college, vocational, or technical program, while another 35% completed other educational programs in on-the-job training or military service. Succimarra and Speece (1990) reported

that 17% of individuals with LDs entered job training, 8% went to private training, 6% were in community college, and 5% were in apprenticeship programs. The highest percentage of postsecondary participation was reported in a statewide study by Sitlington and Frank (1990). In this study of adults with LDs, 44% of the employed respondents and 50% of the unemployed respondents had received some training since high school.

The Office of Special Education and Rehabilitation Services (1986) reported that over 1.9 million students with LDs were served in 1985 in special programs. However, recent changes to the definition of LDs in the Individuals with Disabilities Education Act (1997) are likely to reduce the number of students identified and served as having LDs (Hale, Naglieri, Kaufman, & Kavale, 2004). As increasing numbers of youth with LDs complete high school, they are faced with more postsecondary opportunities, but also greater vocational demands. College is now a viable option, given the availability of special services. Indeed, students with LDs constitute the single largest category of students with disabilities participating in postsecondary education (Fairweather & Shaver, 1991). Limited data are available, however, for understanding the needs of this population and creating effective programs for them. As Vogel (1990) notes, only a longitudinal, prospective study can provide a valid assessment of the academic performance of these students. No such study has yet been undertaken. However, a related longitudinal study of resilience that followed children into adulthood over a four-decade period has identified successful vocations, satisfying family relationships, and community connections as significantly contributing to good life outcomes for this population (Werner & Smith, 2001).

Vocational

In a review of the available literature in 1968, Rawson reported favorable vocational and educational outcomes for a sample of boys with dyslexia who came from higher-income families and attended a private school for children with LDs. Naylor, Felton, and Wood (1990) reported that adults with reading impairments managed to complete high school for the most part and to obtain gainful employment when other risk variables were held constant. Thus the inconsistent outcomes across the studies described below may be attributed to related but indirect factors, such as socioeconomic status and intelligence. These factors fall under two broad umbrellas: either facilitating resilience and protection, or contributing to risk and vulnerability. In a number of follow-up studies, socioeconomic status and intelligence were clearly found to influence outcome in adulthood for the better in children with reading disabilities (Bruck, 1989; Schonhaut & Satz, 1983). However, neuropsychologists should be aware that many of these studies contain methodological shortcomings involving subject selection, measures used to assess outcome, and data analysis. Horn, O'Donnell, and Vitulano (1983) reported that up to the early 1980s, many studies did not screen subjects for neurological problems, psychiatric disturbance, or the presence of generally lower cognitive skills. The contributions of these phenomena would be likely to produce a heterogeneous sample of children whose deficits in reading were the results of numerous contributing factors beyond the specific skill weaknesses related to LDs.

In a series of studies in the early 1980s, Spreen (1981, 1982, 1984) evaluated the psychosocial and vocational outcomes of children with reading disabilities into adulthood. This group was reported to be more likely than others to drop out of school and to have lower occupational achievement. However, in contrast, other researchers have found no differences in educational or occupational achievement between individuals with and without reading disabilities (Bruck, 1985, 1986; Finucci, Gottfredson, & Childs, 1985).

Frauenheim and Heckerl (1983) followed a small sample of children with dyslexia into adulthood. This group, despite average intelligence, did not benefit from the academic remediation provided in childhood; thus, as adults, they continued to struggle academically. This finding is in contrast to the report by Naylor and colleagues (1990) that adults with histories of dyslexia who received remedial education in childhood demonstrated improved reading abilities into adulthood.

The consensus appears to be that individuals with LDs grow up and fail to achieve vocational and social competence at levels commensurate with others, despite receiving special services (Haring, Lovett, & Smith, 1990; Zigmond & Thornton, 1985). Nonetheless, a small percentage of individuals with LDs do progress to advanced academic placement. Rojewski (1999) utilized a national longitudinal data base to compare individuals with and without LDs 2 years after high school graduation. Individuals with LDs reported lower overall graduation rates, were more likely to be employed, and were less likely to be enrolled in postsecondary education. Women with LDs were more likely to aspire to low-prestige occupations. Walters and Croen (1993) reported that adults with LDs were found in medical school settings, but until recently were not identified or provided with special assistance. These authors described a cognitive skills program developed in 1989 at the Albert Einstein College of Medicine. Approximately 1% to 2% of each medical school class is referred for evaluation because of suspected LDs. Often these are intellectually gifted students possessing well-developed compensatory strategies that begin to be taxed by the demanding medical school curriculum.

It is common for individuals with histories of LDs to hold low-paying jobs (Herzog & Falk, 1991; Shapiro & Lentz, 1991). Even 2 years after graduation, students with LDs hold jobs paying near minimum wages. Many students with LDs end up in jobs other than the ones for which they are trained. Dickerson and Verbeek (2002) sampled 97 college graduates diagnosed with LDs. They observed that lower wages for these individuals were due to differences in productivity characteristics. A subsample of individuals who informed employers of their LDs did not appear to receive significantly lower wages.

Researchers have also hypothesized about the impact of LDs in the workplace, suggesting problems related to difficulty with social skills, poor memory, disorganization, auditory processing and linguistic weaknesses, and generally weak academic ability (Clement-Heist, Siegel, & Gaylord-Ross, 1992). There continues to be a paucity of scientific data, however. Even the contention that underemployment is a specific problem for adults with LDs has been difficult to demonstrate consistently. It is fair to conclude that although such individuals may have difficulty obtaining jobs, maintaining them, and succeeding in the workplace, the extent or exact nature of their problems is unclear. Some researchers have not reported that adults with LDs experience problems different from those of their counterparts without LDs in the workplace (Gerber, 1988). Some authors suggest considerable unemployment among adults with LDs (Haring et al., 1990), while others report equal levels of employment (Shapiro & Lentz, 1991). Even if the absolute percentage of employed individuals with LDs does not differ significantly from that of the general population, their level of vocational attainment may in fact be very different. In addition, other confounding factors, such as geographical location and socioeconomic background, may influence employment outcome for individuals with LDs more than the LDs themselves do. As noted earlier, even gender has been proposed as an outcome variable, with females suffering from LDs reported to be underemployed at a much higher rate than their male counterparts (Buchanan & Wolf, 1986).

It is clear that unemployment rates for dropouts, whether they have LDs or not, are twice the rates for high school graduates. Although data are scarce, the obvious conclu-

sion is difficult to deny: If appropriate vocational and educational programs are not provided to individuals with LDs leaving school, they will struggle vocationally and experience greater adjustment difficulties into adulthood (Minskoff, Sautter, Shelon, Steidle, & Baker, 1988).

The National Longitudinal Transition Study (D'Amico, 1991), identified a national sample of more than 8,000 youth between the ages of 13 and 23 years who were in special education programs during the 1985–1986 school year. In a description of the sample, Butler-Nalin and Wagner (1991) reported that subjects included youth with disabilities who were receiving special education services in public secondary schools or state-operated special schools. Sixty-two percent of the students who had worked during high school held jobs after graduation, compared with only 45% of the students who had not worked. Sixty-three percent of the students who had taken at least one vocational course during high school held jobs, compared to 48% of the students who had taken no vocational courses. Sixty-four percent of the students with LDs who graduated from high school were employed, compared to 47% of those with LDs who had either dropped out or been expelled. Interestingly, in rural areas, dropping out of high school did not affect employment (DeBettencourt, Zigmond, & Thornton, 1989). In urban areas, students with LDs who did not finish high school experienced greater difficulty finding employment than those who had graduated (Zigmond & Thornton, 1985). As Vogel and Adelman (1993) noted and as is still true today, no data are available on the effects of attending or completing a vocational program or graduating from college on the career attainment of students with LDs.

EVALUATION

As discussed earlier, the majority of adults seek assessment for LDs either to increase their personal knowledge or to meet eligibility criteria. In the former situation, measurement and definition of the specific neuropsychological impairments contributing to a lifetime of achievement deficits is certainly relevant. However, in the latter situation, the generation of neuropsychological data may be relevant and even necessary, but it is not sufficient to meet the eligibility criteria set by most institutions of higher learning and vocational settings. To meet these criteria, neuropsychologists must administer accepted tests or a set of tests to generate discrepancy data between ability and achievement; they must also obtain a careful, well-documented history defining the long-standing basis of the problem. It is beyond the scope of this chapter to provide a detailed discussion of all neuropsychological tools used to define the impairments often found in individuals with LDs. For in-depth reviews, the reader is referred to Goldstein (1997), Ingalls and Goldstein (1999), and Swanson and colleagues (2003). The cognitive and achievement parts of the Woodcock–Johnson III (Woodcock, McGrew, & Mather, 2001) are suggested as the most comprehensive means of generating an achievement–ability discrepancy. For details about the use of this instrument, readers are referred to Mather and Jaffe (2002). In lieu of the cognitive part of the Woodcock–Johnson III, neuropsychologists may administer the third edition of the WAIS (WAIS-III; Wechsler, 1997). As noted, supplemental testing assessing memory deficits, information-processing difficulties, and other neuropsychological impairments associated with LDs are often of value; however, unless an accepted discrepancy can be met (at least 1.5 standard deviations between measured achievement and ability), it is not likely at this time that an adult will be classified as having an LD in secondary or post-secondary educational or vocational settings.

The comorbidity of psychiatric problems with LDs remains poorly studied. As discussed, individuals with LDs are likely to experience a higher level of emotional and personality problems. It is recommended that as part of an assessment to qualify individuals as having LDs, neuropsychologists evaluate emotional status and personality. These factors, though not necessary to make the diagnosis of an LD, are likely to prove valuable in explaining daily behavior, response to treatment, and prognosis. Appropriate assessment tools, including the Beck Depression Inventory–II (Beck, Steer, & Brown, 1996), the Beck Anxiety Inventory (Beck & Steer, 1993), the Millon Clinical Multiaxial Inventory–III (Millon, Davis, & Millon, 1997), and the Minnesota Multiphasic Personality Inventory–2 (Butcher et al., 2001), are recommended.

TREATMENT

Precise predictors of life satisfaction and general functioning for adults with childhood histories of LDs have not been consistently studied or reported. In general, those variables that predict good life outcome for any child experiencing risk and vulnerability are likely to predict good outcome for children with LDs into their adult lives. As noted earlier,Werner and Smith (2001) followed a large population of children born into poverty into their fourth decade of life. Within this group was a subgroup of individuals with LDs. These authors concluded that those as adults who reported the highest level of life satisfaction and minimal impairment were not necessarily either those who had received the most education or specialized services during their childhood, or those who as adults demonstrated the most advanced academic abilities. Instead, those who seemed to be doing the best found vocations that they could succeed at and that enabled them to support their families; found stable marriage partners; developed the ability to communicate effectively, solve problems, and relate to others; and, finally, developed social consciences and made contributions to their community through charitable or voluntary work. Thus it is increasingly recognized that improving basic achievement in children with LDs may be necessary but is clearly not sufficient to ensure good life outcome. Educational plans written throughout the child and adolescent years for those with LDs must begin to focus on balancing asset goals with liability goals.

Once adolescents and adults with LDs are appropriately identified, many instructional and vocational interventions are available. For in-depth reviews, see Goldstein (1997) and Vogel and Reder (1998). For those in late adolescence or young adulthood, intervention usually focuses heavily on transition. Transition is a process rather than a product; it takes place over a period of time and is usually tailored to the needs of each person (Evelo & Price, 1991; Getzel, 1990; Rojewski, 1999). The Individuals with Disabilities Education Act mandates that a life transition plan be written for every child with an LD by age 14 to facilitate transition into post-high-school experiences, including work and independent living. As Ginsberg and Gerber (1990) note, their ethnographic studies indicate that understanding, acceptance, and supportive action are the key concepts in facilitating life success for adults with LDs. The guidance, intervention, and transition process must focus on remediation of basic academic skills, the development of vocational skills, and the development of compensatory strategies necessary for successful adult living.

It is still the case that there is no consistent means of determining which post-high-school options might serve which students with LDs best. A number of researchers have suggested guidelines, but even these are fairly generic. For example, Hoy and Gregg (1986) note that high motivation, a willingness to try new things, average or above-average intel-

lect, ability to comprehend abstract language, emotional maturity, socially appropriate behavior, and appropriate career goals are seven key variables in predicting the probability that a student with an LD will succeed in college. Neuropsychologists should also be aware that it is never "too late" to teach basic reading skills. Thus, when identified in adulthood, adults with LDs can and do improve their basic achievement when provided with remedial education involving teaching traditional phonics and sight word reading.

In counseling settings, adults with LDs have been reported to bring four basic issues to the counseling situation (Barton & Fuhrman, 1994): (1) stress and anxiety resulting from struggles to meet life's demands; (2) low self-esteem and feelings of incompetence; (3) grief over lack of accomplishments; and (4) helplessness. Left unattended, these areas of problems can and will undermine potentially effective intervention programs.

For more detailed coverage of treatment issues, readers are referred to Goldstein (1997) and Nadeau (2002) for discussions of psychosocial and therapy issues; Richards (1997) for a discussion of college programs and services; and Crawford (1997) for a discussion of vocational programs and practices. Readers interested in a theoretical discussion and review of relevant research concerning drugs that affect learning and memory are directed to Goldstein and Goldstein (1997).

CONCLUSION

Nearly 15% of the adult population experiences some type of specific LD. These disabilities exert anywhere from a minimal to a significant adverse impact on daily life leading to multiple impairments. Neuropsychologists are in a unique position to evaluate and understand the basic processes implicated in LDs, to provide appropriate assessments, and to design and implement effective treatment programs.

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6

ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER

SAM GOLDSTEIN
ADAM SCHWEBACH

In their discussion of attention-deficit/hyperactivity disorder (ADHD), Weiss and Hechtman (1993) suggest that understanding the continuity of childhood conditions into adulthood is far from a simple process. The traditional, dichotomous view that childhood conditions are either outgrown or continue to manifest themselves in adulthood in a similar way as in childhood (e.g., intellectual disabilities) must be countered by a number of other possibilities. For example, symptoms of a particular condition may persist into adulthood; however, changes in adult expectations and lifestyle, as well as the capacity of human beings to develop compensatory strategies, may minimize the condition's negative impact (or, for that matter, even its visibility) during the adult years. There are a number of other possible outcomes for childhood conditions. A condition may in part remit, but the residual symptoms may cause daily functional impairment. Or a condition may predispose an adult to certain other kinds of problems. Gradually, over the last 25 years, all of these hypotheses in regard to ADHD—including acceptance of the continuity of ADHD as an impairing condition throughout the lifespan—have been considered and examined, and are now better understood.

The existence of ADHD as a clinically impairing condition is irrefutable (Barkley, 1997; Goldstein & Goldstein, 1998). Though the etiology of the condition and its precise symptom profile remain debatable concepts, presenting symptoms and impairing consequences are easily observed and measured. In light of current theories portraying ADHD as a condition of impaired development, it should not be a great philosophical or academic leap to accept the condition as presenting throughout the lifespan (Barkley, 1997, 1998; Goldstein, 1999; Goldstein & Goldstein, 1998). Yet scientific method requires more than just hypotheses and theories before belief can confidently be described as fact. Though thousands of peer-reviewed studies dealing with ADHD in childhood have been published, the literature through 2004 still contains fewer than 200 peer-reviewed articles dealing with adult ADHD. The number of studies have been increasing significantly year by year, including the ongoing reported results from a number of longitudinal studies following children with ADHD into their adult years. Yet, as with any emerging condition, each published study holds the promise of new data, fresh insight, and perhaps a new path to follow in regard

to ADHD in the adult years. Time will determine which paths bear fruit and which may result in dead ends.

At this writing, the field of adult ADHD is driven more by trade texts and lay publications than by the availability of scientific literature to guide clinical practice. Even in clinical practice and research, the misunderstanding of the developmental nature of the diagnosis—particularly the fact that a set of childhood-derived symptoms is currently applied to adults—causes confusion and results in conveyance of inaccurate information to the public. For example, Hill and Schoener (1996) applied the categorical criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R) by reviewing nine prospective studies in which cohorts of children with ADHD were followed up between 4 and 16 years later to determine the number retaining the ADHD diagnosis. The authors subjected the data to nonlinear regression analysis to ascertain the relationship of the condition with chronological age. According to Hill and Schoener, there was an exponential decline over time in the condition. It was suggested that the presence of the condition declined 50% approximately every 5 years. Under this assumption, beginning with a prevalence rate of 4% in childhood, the authors concluded that the estimated rate of adult ADHD ranged from approximately 0.8% at age 20 to 0% at age 40. The study contained multiple methodological problems, but more importantly, it demonstrated the difficulty of applying childhood criteria to an adult population.

The number of ADHD symptoms necessary to reach the 1.5 standard deviation threshold criterion difference between an affected individual and an unaffected individual of similar age decreases with increasing age (Murphy & Barkley, 1996). These authors compared 172 adults with ADHD to 30 adults without ADHD. All had been referred to an adult ADHD clinic. The authors very succinctly demonstrated that the issue is not so much meeting the symptom threshold as experiencing impairment in relation to others. Those with ADHD demonstrated a specifically greater prevalence of oppositional, conduct, and substance use disorders and greater illegal substance use than did the group without ADHD. Those with ADHD also displayed greater self-reported psychological maladjustment, more driving risks, and more frequent changes in employment. Significantly, more individuals with ADHD had experienced suspension of their drivers' licenses; had performed poorly on, quit, or been fired from their jobs; and had histories of poor educational performance, as well as more frequent school disciplinary actions against them. Multiple marriages were also more prevalent in the group with ADHD.

In the last 15 years, the biopsychosocial nature of this condition across the lifespan has become increasingly apparent. Epstein and colleagues (1997) demonstrated that adults with ADHD exhibited a longer delay when their attention was misdirected with cues in a reaction time task measuring hemispheric control. That is, those with ADHD had difficulty switching when misdirected by cues to the right visual field when the target presented in the left visual field. Gansler and colleagues (1998) administered a battery of neuropsychological tests to 30 adults with ADHD; they demonstrated that this population, in comparison to a nondisabled sample, experienced specific problems with the skills necessary to perform test tasks involving visual tracking, auditory attention, and visual continuous performance . Deficits on these tasks suggest problems with executive control, probably linked to a dysregulation of the frontal lobes. Although consensus on this pattern of problems has not always been reached by other researchers, it has provided consistent evidence of deficits in a variety of tasks sensitive to executive function and self-regulation (Holdnack, Noberg, Arnold, Gur, & Gur, 1995; Jenkins et al., 1998).

Readers should consider this chapter a work in progress. Given the nearly exponential growth in peer-reviewed, published research dealing with adult ADHD, 50 or more

additional research studies exploring symptoms, problems, outcomes, and (most importantly) treatment of adult ADHD are likely to be published in the time span between the completion of this chapter and the publication of this text. Nonetheless, the available research suggests a consistent pattern of emerging trends. This chapter reviews these trends in regard to various cognitive, emotional, personality, familial, and vocational outcomes for individuals with ADHD; it also provides an overview of assessment and treatment issues. Though some authors have suggested that ADHD may reflect an adapted pattern of skills developed according to an evolutionary model (Hartmann, 1993; Jensen et al., 1997), the emerging research literature is sobering. Not a single childhood or adult study exists to suggest that those with ADHD hold any type of advantage over individuals without this condition (Goldstein & Barkley, 1998). Furthermore, the increased recognition that ADHD is not so much a problem with sitting still or paying attention as a problem of self-regulation or self-control provides a workable hypothesis to explain the myriad of problems currently identified for adults with histories of ADHD. This plausible explanation for ADHD suggests that rather than representing an adapted or evolved set of valuable qualities, ADHD is a set of weaknesses in the development of efficient self-regulatory and executive functions. These cognitive functions fall on a normative curve, much as height or weight does. Qualities of ADHD appear to place individuals at the lower tail of an adaptive bell curve for these skills.

The knowledge of adult ADHD at this time is drawn from a variety of sources, including extrapolation of childhood data; studies of comorbid conditions and their impact on adult outcome; family studies; longitudinal or long-term follow-up studies; and, finally, research on diagnosed adults.

OUTCOMES OF ADHD IN THE ADULT YEARS

The body of literature attesting to the emotional, cognitive, academic, vocational, substance use, and criminal risks of ADHD is growing. It has been estimated from available literature that approximately one-third of adults with ADHD progress satisfactorily into their adult years, that another third continue to experience some problems, and that the final third continue to experience significant problems and often develops new ones (for reviews, see Goldstein, 1995; Goldstein & Ellison, 2002; Hechtman, 2000). By combining a number of outcome studies, it is reasonable to conclude that from 10% to 20% of adults with histories of ADHD experience few problems; that 60% continue to demonstrate symptoms of ADHD and to experience social, academic, and emotional problems to at least a mild to moderate degree; and that the remaining 10% to 30% develop antisocial problems, in addition to their continued difficulty with ADHD and other comorbid problems (Barkley, 1990; Cantwell & Baker, 1989; Gittelman, Mannuzza, Shenker, & Bonagura, 1985; Herrero, Hechtman, & Weiss, 1994; Satterfield, Hoppe, & Schell, 1982; Weiss & Hechtman, 1993). Interestingly, many of these negative outcomes are linked to the continuity, severity, and persistence of ADHD symptoms. There are very limited data to suggest that females at outcome, when initial presentation is controlled for, are at less risk for antisocial problems than males with ADHD (Herrero et al., 1994). It is fair for clinicians to assume that the absence of significant comorbid disruptive behavioral problems during the childhood years is a good predictor for the absence of antisocial disorders in adulthood. Clinicians should be cautioned, however, that the presence of such problems in childhood is not necessarily predictive of antisocial outcome for all cases (Werner & Smith, 2001). In their follow-up study, Weiss and Hechtman (1993) found only 11% of adults

with ADHD to be symptom-free, with 79% experiencing some type of internalizing problem and 75% experiencing interpersonal problems. In this cohort, 10% had attempted suicide, and 5% were dead from either suicide or accidental injury.

The continuity of the condition, in the form of similar symptoms but different consequences, has been well demonstrated by Millstein, Wilens, Biederman, and Spencer (1997) in their study of clinically referred adults with ADHD. Ninety-eight% reported difficulty following directions; 92% reported poor sustained attention; 92% mentioned trouble shifting activities; 88% reported being easily distracted; 80% noted losing things; and 70% reported not listening, fidgeting, interrupting, and speaking out of turn.

Robin, Bedway, and Tzelepis (1998) demonstrated that beyond the risk of clinical comorbidity and the life impairment, adults with ADHD appear to be at greater risk of developing dysfunctional personality styles. Fifty percent of individuals with ADHD in their follow-up study, in comparison to 5% of those without ADHD, demonstrated a personality style characterized by pessimism, helplessness, and disorganization. Only 44% of those with ADHD, in comparison to 88% of the group without ADHD, demonstrated a personality style consistent with empathy, extroversion, and motivation.

Psychological/Emotional Problems

As the number of research studies on adults with ADHD is increasing, the evidence for increased vulnerability to a range of psychiatric problems that ADHD correlates with and may in fact mediate continues to grow. In their longitudinal study, Mannuzza, Gittelman-Klein, Bessler, Malloy, and LaPadula (1993) reported that at 24 years of age, those with ADHD demonstrated a higher incidence of antisocial personality disorder, as well as alcohol and other substance abuse. Though these authors did not report a higher incidence than controls for mood or anxiety disorders in this population, others have. For example, Millstein and colleagues (1997) reported that adults with the combined type of ADHD demonstrated a 63% incidence of major depression; 23%, dysthymia; 17%, bipolar disorder; 11%, panic disorder; 12%, simple (now called specific) phobia; 21%, generalized anxiety disorder; and 7%, obsessive–compulsive disorder. Even adults meeting only the inattentive criteria in this study were not immune from fairly similar rates of depression, although they appeared to experience fewer problems with bipolar and anxiety disorders. The true risk of ADHD in contributing to bipolar illness has yet to be defined. In contrast to Millstein and colleagues, Sachs and Baldassano (2000) found only 8 out of a group of 56 adults with bipolar disorder demonstrating a history of ADHD. These 8 were compared to 8 with bipolar disorder but without a history of ADHD. The age and onset of the first affective episode was lower for the subjects with both bipolar disorder and ADHD (mean age 12 years) than for those without a history of childhood ADHD (mean age 20 years). Though research on adult females is as sparse as the research literature on females with ADHD in childhood, at least one study has demonstrated that 70% of females with adult-diagnosed ADHD had a history of depression, and 62% had a history of anxiety (Rucklidge & Kaplan, 1997). The incidence of these two conditions in the general population reported in this study, though not insignificant (33% depression, 17% anxiety), was still dramatically less than in the clinical group.

Vitelli (1998) studied the relationship among childhood conduct disorder, ADHD, and adult antisocial personality disorder in a sample of maximum-security inmates. The results confirmed that childhood conduct disorder and ADHD were significantly related to adult antisocial personality disorder, psychopathy, and impulsivity. The combination of childhood

conduct disorder and ADHD appeared to predict significantly worse outcome in terms of problems related to adult violence, substance abuse, and institutional misconduct.

The volume of data describing the emotional and psychiatric risks for individuals with histories of ADHD continues to grow, including recently published studies demonstrating a higher prevalence of anxiety (Mancini, Van Ameringen, Oakman, & Figueiredo, 1999), panic disorder (Lomas & Gartside, 1999), and even seasonal affective disorder (Levitan, Jain, & Katzman, 1999) in those with ADHD. These last authors found the comorbidity of seasonal affective disorder with adult ADHD to be between 10% and 19%. Specifically, they found an apparent relationship among female gender, impulsive symptoms of ADHD, and seasonality.

Symptoms of ADHD have also been found to occur to a higher degree in adults with histories of panic disorder. Fones, Pollack, Susswein, and Otto (2000) reported childhood ADHD features by history occurring in 23.5% of adults with panic disorder. 9.4% satisfied the full DSM-III-R and DSM-IV criteria, while 14.1% had subthreshold diagnoses. Two-thirds of the patients with panic disorder and ADHD indicated persistence of symptoms into adulthood. Though the co-occurrence of ADHD was not reported to influence the clinical pattern of panic, the authors suggested that the comorbidity of ADHD with panic disorder may contribute to adverse social outcome.

Cognitive Deficits

Comparison studies of neuropsychological testing in a group of adults with ADHD have reported deficits in executive functioning relating to divided attention, visual scanning, and auditory attention (Gansler et al., 1998), as well as speed of processing and verbal learning (Holdnack et al., 1995). Holdnack and colleagues (1995) demonstrated that adults with ADHD exhibited slow reaction time to target stimuli; their psychomotor speed was slower than that of controls. These authors also demonstrated inconsistent application of a semantic clustering strategy on memory tasks for those with ADHD. Individuals with ADHD appeared susceptible to retroactive interference and item recall inconsistency. In sum, adults with ADHD appear to experience a selective pattern of deficits, revealing slow cognitive processing and significant problems with list learning. Thus these patterns of selective cognitive weaknesses appear continuous between the childhood and adult years (Ellison, 2002).

Academics

The risk of learning disabilities, as well as lower achievement secondary to scholastic effort, is supported by multiple lines of evidence. Those with ADHD appear to underachieve significantly, relative to controls (Barkley & Gordon, 2002; Gittelman et al., 1985; Weiss & Hechtman, 1986). Significantly fewer children with ADHD graduate from high school than the general population, and significantly fewer attend college. In the longitudinal studies, only 5% of those with ADHD earned a college degree.

Although the rate of outright learning disabilities appears to be higher among those with ADHD than in the general population, the lines begin to blur when specific cognitive skills are examined in an effort to explain the academic impairments found in those with ADHD. The most frequently discussed and evaluated deficits relate to those cognitive characteristics referred to as "executive dysfunction" (Denckla, 1994, 1996a, 1996b; Denckla

& Reader, 1992). It has been suggested that these impairments, over and above intelligence measures and emotional stability indicators, best explain why adults with ADHD are often viewed as experiencing learning disabilities. Denckla (2000) suggests that executive dysfunction is the "zone of overlap between ADHD and learning disabilities" (p. 307). From Denckla's perspective, these cognitive deficits originate from dysfunction of the frontal lobes or interconnected regions. This impairs a variety of abilities that ultimately affect academic as well as interpersonal relations. As Denckla notes, these problems are endemic but not restricted to populations identified with both learning disabilities and ADHD, as well as other conditions. Denckla cautions, however, that executive dysfunction is "easier to diagnose than ADHD in adults because adult norm neuropsychological tests and measures are available" (p. 307). Although these weaknesses in some cases are used as markers to explain the underlying deficits of some individuals with ADHD, it is unclear whether they serve as causative explanations, markers, or (for that matter) consequences.

It has also been hypothesized that nonverbal learning disabilities may overlap with ADHD or the construct of executive dysfunction, because the anterior portion of the right hemisphere is thought to be important in directing self-control and serves an important role in the self-regulatory loop or the brain's "braking system" (Castellanos et al., 1994, 1996). The characteristic descriptions of children with nonverbal learning disabilities may to some extent overlap with symptoms of ADHD, particularly the descriptions of being passively inattentive or disorganized. At this time, however, there are no published peer-reviewed studies examining symptom presentation, overlap, or clinical course for individuals with either of these conditions or for those who may suffer from both. Interested readers are referred to Semrud-Clikeman and Hynd (1990) for a review of research on nonverbal learning disabilities. Finally, to extrapolate from the available child clinical literature, it is reasonable for clinicians to assume that adults with histories of ADHD are more likely than not to have fallen behind academically—not because of skill deficit, but due to lack of practice for proficiency in those subjects requiring repetitive and sustained effort. Thus many academic areas, including nonphonetic spelling, execution in written language, math facts, and attention to detail in mathematics, may all prove to be areas of weakness in the absence of learning disabilities for many adults with ADHD.

Vocational Outcomes and Driving

As noted earlier, adults with ADHD are less likely to graduate from high school then their peers, less likely to attend college, and even less likely to graduate from college. They are more likely to enter the workforce at a lower level than their siblings, and less likely to be promoted (Barkley, Fischer, Edelbrock, & Smallish, 1990), although they are reportedly employed at a rate similar to that of the general population (Mannuzza, Gittelman-Klein, Konig, & Giampino, 1989; Mannuzza et al., 1998). They are also likely to experience many more job changes.

In a prospective follow-up study, Mannuzza, Klein, Bessler, Malloy, and Hynes (1997) followed males with ADHD and average intelligence for 17 years in their young adult lives. Those with ADHD obtained lower-ranking occupations. These disadvantages were not accounted for by adult mental status. Interestingly, those with ADHD were not unemployed at a rate beyond the general population.

The daily lives of adults with ADHD are reported to be fraught with problems that result from faulty self-control, including difficulty with driving. Young adults with histories of attentional problems have been reported to be at greater risk for motor vehicle ac-

cidents, drinking while driving, and traffic violations. To some extent, these outcomes are contributed to by personal character, gender, and conduct problems, as well as by driving experience; even after adjusting for these variables, however, Woodward, Fergusson, and Horwood (2000) found that ADHD during adolescence placed young adults at an increased risk of an injury, an accident, driving without a license, and other traffic violations. Furthermore, Barkley, DuPaul, and McMurray (1990) conducted a well-controlled, carefully administered assessment of basic neuropsychological abilities necessary for driving, as well as of driving knowledge, decision making, driving habits (both self-rated and as rated by others), and operation of a simulated motor vehicle. This investigation confirmed that ADHD is associated with a pervasive, multilevel impairment of driving abilities. The group with ADHD, in comparison to a control population, made more errors when rules governing testing performance were reversed. Deficits in multiple areas of driving knowledge and rapid decision making were also evident. During simulated driving, the group with ADHD was more erratic in controlling the vehicle and made many more errors in negotiating simulated driving courses. Both self-ratings and ratings by others indicated that the group with ADHD employed significantly fewer safe driving habits. Gender differences and those possibly due to subtypes of ADHD were not found to be significant. Interestingly, Barkley, Guevremont, Anastopoulos, DuPaul, and Shelton (1993) reported that teens with ADHD were also more likely to have driven an automobile illegally prior to the time they became eligible as licensed drivers, and were more likely to have their licenses suspended or revoked.

Substance Use and Abuse

In 1990, Shekim reported that 34% of a population of 56 adults with ADHD demonstrated alcoholism, while 30% demonstrated other drug abuse. An inpatient study was completed by Milin, Loh, Chow, and Wilson (1997) with a clinical sample of 36 adults, many of whom met criteria for a diagnosis of ADHD. Those with symptoms of ADHD tended to be more likely to have a history of alcohol combined with drug use disorders. The authors further reported that symptoms of antisocial personality disorder were far more prevalent in individuals with substance abuse and a history of both childhood and adult ADHD than in those without ADHD. Coure and colleagues (1999) reported histories of substance use in adults in an inpatient setting; in this setting, there were significant differences among the substance use disorder groups (divided by drug of choice) in the percentage of those presenting with ADHD. Of the ADHD subtypes, subjects with combined and inattentive types were significantly more likely to have ADHD symptoms continue into adulthood than were those with the hyperactive–impulsive subtype. Those with cocaine use were more likely to have a history of childhood ADHD than those with alcohol or combined substance abuse.

Wilens, Biederman, and Mick (1998) examined the rates of remission and duration of substance abuse in individuals with histories of ADHD. The duration of substance abuse was over 37 months longer in a population of adults with ADHD than in those without ADHD. The median time to remission was more than twice as long in the group with ADHD as in controls (144 vs. 60 months). The authors reported a need to replicate their data, but suggested that ADHD not only is a risk factor for the early initiation of, and a specific pathway for, substance abuse; it is also associated with longer duration and a significantly slower remission rate.

Finally, the rate of cigarette smoking in adults with ADHD has also been demonstrated to be higher than that in the general population (Pomerleau, Downey, Stelson, & Pomerleau,

1995). In a population of 71 individuals with ADHD with a mean age of nearly 34 years, 42% of the males currently smoked, 13% had formerly smoked, and 45% had never smoked. Comparative figures for males in the general population were 28%, 29%, and 42%, respectively. Thirty-eight percent of females in this group with ADHD currently smoked, 31 had formerly smoked, and 31% had never smoked, as compared to 23.5%, 19%, and 57.5%, respectively in the general population. Those who smoked had experienced greater symptoms of ADHD as children than those who did not smoke, and they scored higher on measures of childhood and adult psychiatric comorbidity. The authors suggested that persons with ADHD who smoke may need treatment with a stimulant and sustained nicotine replacement therapy before they can actually quit smoking.

Antisocial and Criminal Behavior

In Weiss and Hechtman's (1986) follow-up of a population with hyperactivity/ADHD, from 25% to 45% expressed some antisocial behavior; the lower figure, 25%, referred to those who qualified for a diagnosis of antisocial personality disorder. As noted earlier, this increased risk has been reported by multiple researchers (Barkley & Gordon, 2002; Robin et al., 1998). Anecdotal reports have long suggested an overrepresentation of ADHD in incarcerated individuals. In 1999, Curran and Fitzgerald examined 55 adult male offenders with a mean age of 26 years who had been referred to a prison psychiatric clinic. Only 9% met the DSM-IV criteria for ADHD, leading to a slightly higher than expected prevalence among this young adult prison population. This runs contrary to Eyestone and Howell's (1994) suggesting, in a population of 100 inmates, an incidence of 25% for ADHD. Furthermore, Kapuchinski (2000) suggests that a consulting psychiatrist in a prison setting will encounter a significant number of individuals who present with, or meet the symptom criteria and history for, ADHD.

TOWARD A WORKING DEFINITION OF ADULT ADHD

It is quite likely that a deficiency in attention as a theoretical, cognitive, or laboratory-measured concept is quite different from the behavioral symptom of inattention as it is defined for ADHD. Nonetheless, prior to reviewing the currently accepted ADHD diagnostic criteria and related issues, a brief discussion of attention as a theoretical construct is valuable.

"Attention" is considered a generic term used to designate a group of hypothetical mechanisms that collectively serve a function for the organism (Mesulam, 1985). Beginning with James (1890), researchers have identified attentional processes as essential prerequisites for higher cognitive functions. Hypothetical models of attention have included stage-wise developmental approaches (Blondis, Snow, Stein, & Roizen, 1991), as well as models suggesting a maturational process similar to the maturation of other executive or intellectual skills (Hagen & Hale, 1973). Although Posner and Snyder (1975) described attention as a complex field of study, others have suggested that attentional skills can be operationally and statistically defined with some confidence (Gordon & McClure, 1983). Skinner (1953) defined attention as a functional relationship between stimuli and response. His belief was that attention is not a thing, entity, or mental function, but a description of a set of relations between stimuli or events and responses to them. Gibson and Radner (1979) defined attention as the ability to perceive the environment in relation to a specific

goal. Posner (1987) suggested that attention may consist of automatic versus conscious aspects. Finally, Fuster (1989) provided a concept of "inhibition interference" in his neuropsychological model of executive function related to attention. All of these theories, including Titchener's (1924) description of attention as a pattern of consciousness, appear to be an extension of James's (1890) characterization of attention as bimodal. James hypothesized that attention is either passive, as in a reflective, nonvoluntary, and effortless approach, or active and voluntary. James defined "sustained attention" as the latter type; he described it as dependent upon repeated redirection of effort to the focus of attention, as well as upon resistance to coexisting attractions in the process.

Finally, Picano, Klusman, Hornbestel, and Moulton (1992) performed a factor analysis that suggested three factors for attention. The first factor accounted for 35% of the variance and involved skills related to visual–motor scanning and shifting abilities. The capacity to divide attention appeared to be key to this task. The second factor accounted for 16% of the variance; it reflected immediate attention and conceptual tracking, consistent with the ability to repeat digits forward and reverse. The third factor, accounting for 13.5% of the variance, reflected sustained, effortful processing consistent with distractibility tasks. This breakdown is consistent with factor analyses by others (Shum, MacFarland, & Bain, 1990).

From a neuropsychological perspective, the concept of attention as an executive function has gained increasing popularity. Measures of sustained mental effort, self-regulation, planning, execution, and maintenance are considered measures of executive functioning (Daigneault, Braun, & Whitaker, 1992). Mirskey, Antony, Duncan, Ahearn, and Kellam (1991) developed a neuropsychological model of attention, consisting of four basic concepts: the ability to focus, execute, sustain or code, and shift. Eight traditional measures of attention were used in a factor-analytic study to arrive at this model.

The Nature of ADHD Symptoms

Increasingly, there is a consensus that ADHD represents a problem of faulty performance rather than faulty input. It is not that this population of individuals does not know what to do, but rather that they do not do what they know consistently. It is a problem of inconsistency rather than inability (Goldstein & Goldstein, 1992). Even in their adaptive skills, this pattern of difference between possessing a skill and using it efficiently has been well defined for individuals with ADHD (Stein, 1997).

It is important for the neuropsychologist to possess a working understanding of the DSM-IV-TR diagnostic criteria for ADHD, a practical perception of the symptoms' impact on the individual's functioning, and a diagnostic strategy. The traditional disease model is not relative to the definition of ADHD (Ellis, 1985). ADHD is more like obesity or intelligence: Individuals differ not in having or not having the traits, but in the degree of manifesting them. ADHD symptoms are multidimensional rather than unitary (Guevremont, DuPaul, & Barkley, 1993). However, there continues to be discussion as to which dimensions represent the most distinguishing deficits of the disorder. The frequency and severity of symptoms fluctuate across settings, activities, and caregivers (Tarver-Behring, Barkley, & Karlsson, 1985; Zentall, 1984). There is a general consensus, however, that symptoms of ADHD fall into two broad factors: those related to the behavioral manifestation of faulty attention, and those related to hyperactivity and impulsivity. Symptoms of hyperactivity and impulsivity appear to co-occur at such a high frequency that it is difficult to separate them on a factor-analytic basis. It is also important for neuropsychologists to recognize

that at times the lines blur between the symptoms and consequences of ADHD. Thus a diagnostic strategy for adult ADHD should include identifying symptoms, as well as a list of skills and life problems hypothesized to be directly influenced by the symptoms. Having the symptoms but not being negatively affected by them would in fact preclude the diagnosis of ADHD, according to the current (DSM-IV-TR) criteria.

DSM-IV-TR Criteria for ADHD

The DSM-IV-TR diagnostic criteria (American Psychiatric Association, 2000) represent an effort to move forward and correct the mistaken concept that ADHD is a unipolar disorder. The field studies for the ADHD diagnosis in DSM-IV (which remains the same in DSM-IV-TR) were more comprehensive and better structured than previous efforts, but did not include adults. The DSM-IV-TR criteria appear in Table 6.1.

Of the 276 children diagnosed with ADHD in the DSM-IV field studies, 55% had the combined type, 27% the inattentive type, and 18% the hyperactive–impulsive type (Lahey et al., 1994). Fewer than half of those diagnosed with ADHD, hyperactive–impulsive type (44%), received that diagnosis when DSM-III criteria for attention deficit disorder with hyperactivity were used. These two diagnoses, therefore, only partially overlapped. Children with the hyperactive–impulsive type had fewer symptoms of inattention than children with the combined type. They also had fewer symptoms of hyperactive–impulsive problems, suggesting that this represents a less severe variant of the disorder. The hyperactive–impulsive type contained 20% females, the combined group 12%, and the inattentive group 27%. This last percentage represents neuropsychologists' perceptions that females more often demonstrate the inattentive type of ADHD. This overrepresentation has not been well explained by any theoretical model (Silverthorn, Frick, Kuper, & Ott, 1996); nor has it been understood why preliminary research suggests that females with ADHD may be less likely than males to demonstrate executive function deficits (Seidman et al., 1997). The hyperactive–impulsive population was younger than the other two groups in the field studies. In addition, these children had fewer disruptive symptoms of oppositional defiant disorder or conduct disorder than those with the combined type ADHD.

A number of researchers, utilizing a variety of clinical and laboratory measures, have demonstrated the validity of the DSM-IV-TR diagnostic conceptualization for ADHD. Such research has included a full battery of neuropsychological tests (Brand, Das-Smaal, & DeJonge, 1996; Halperin et al., 1993), reversal and memory tasks (O'Neill & Douglas, 1996), and neurological evaluation (Luk, Leung, & Yeun, 1991). The general consistency of symptoms, comorbidities, and related findings among large, well-controlled clinical and epidemiological studies suggest that the conceptualization of ADHD in DSM-IV-TR has become increasingly refined. Nonetheless, these criteria continue to focus excessively on inattention as the core problem for the disorder, limiting the scope and focus on the impact of impulsivity as the core deficit. This perpetuates a number of major misconceptions, including the idea that the inattentive type of ADHD represents a subtype of the combined disorder (Anastopoulos, Barkley, & Shelton, 1994). Increasing research suggests that it does not. It is more likely that the inattentive type represents a distinct disorder, primarily reflecting difficulty attending to repetitive, effortful tasks and problems with organization. The problems this group experiences may very well be the results of faulty skills, as opposed to inconsistent or inadequate use of skills.

Wender and colleagues (Ward, Wender, & Reimherr, 1993; Wender, 1995) were the first to develop specific criteria for the diagnosis of attention deficits in adults. Their "Utah

criteria" (Ward et al., 1993) suggest that a continuity of childhood attention deficits into adulthood involves attentional problems, motor hyperactivity, and associated features (including marital instability, academic and vocational difficulties, substance abuse, and stress intolerance). Diagnosis of ADHD in adulthood requires that the individual meet the DSM-IV-TR's five major diagnostic criteria (A–E in Table 6.1). Since this is a diagnosis that has been primarily researched and developed with a childhood population, the neuropsychologist must consider whether problems in adulthood are equivalent or parallel to those described for childhood. For most of the DSM-IV-TR inattentive and hyperactive–impulsive criteria, this is not a difficult task; with a few exceptions, they are written in a generic fashion. Neuropsychologists are urged, however, to attend to criteria B–E, including actively seeking data to support that the problems first presented in childhood and to determine that clinically significant impairment is in fact present in two or more settings. With regard to comorbidity, the same diagnoses common in childhood ADHD are generally common in adult ADHD. In fact, an adult with ADHD is more likely than not to present with a comorbid psychiatric condition (Biederman, Newcorn, & Sprich, 1991). These authors, as well as subsequent researchers, support the prevalence of comorbidity between 15% and 75% with depression, 25% with anxiety, between 30% and 50% with substance use, between 30% and 50% with personality disorders, and anywhere from 10% to 90% with learning disabilities. For an in-depth review of comorbidity issues, readers are referred to Johnson and Conners (2002).

GENETICS AND OTHER ETIOLOGICAL CONSIDERATIONS

ADHD is among the most common disorders across the lifespan. It is estimated that it affects between 3% and 5% of the school-age population and just slightly less of the adult population. Estimates vary, with the American Psychiatric Association (2000) suggesting a prevalence of 3–7%; this variance exists because different populations have been studied, and different thresholds and definitional criteria have been used. The genetic contribution to ADHD has been postulated by a number of authors (Hechtman, 1993; Rutter et al., 1990; Stevenson, 1992). The underlying genetic mechanism has recently been suggested to be a single dopamine transporter gene (Cook, Stein, & Kraskowski, 1995) as well as a variation in the D4 receptor gene (LaHoste, Swanson, & Wigal, 1996). Furthermore, it has been suggested by some that the trait locus for reading disability on chromosome 6 identified by Cardon and colleagues (1994) may also be a locus for ADHD (Warren et al., 1995).

Eaves, Silberg, and Hewitt (1993) note two complementary approaches to the genetic analysis of ADHD. The first, a dimensional approach, involves the study of a normal range of activity and assumes that ADHD is at one end of the continuum or trait. The second categorical approach is based upon studying children of families who meet diagnostic criteria and assumes that ADHD is a discrete disorder (Faraone, Biederman, Chen, & Krifcher, 1992). It is important for neuropsychologists to recognize that dimensional approaches have been found to predict life outcomes more accurately (Fergusson & Horwood, 1992).

Among researchers pursuing a trait approach, Willerman (1973) found the heritability of scores on an activity questionnaire to be 0.77 for a sample of 54 monozygotic and 39 dizygotic twin pairs. However, Goodman and Stevenson (1989) reported a heritability estimate of greater than 1.00 in a sample of 285 twin pairs. This finding appeared to be due to an extremely low dizygotic correlation in mothers' reports. Corresponding dizygotic correlations for fathers' and teachers' reports were much higher, resulting in herita-

TABLE 6.1. DSM-IV-TR Criteria for Attention-Deficit/Hyperactivity Disorder

A. Either (1) or (2):

(1) six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
(b) often has difficulty sustaining attention in tasks or play activities
(c) often does not seem to listen when spoken to directly
(d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
(e) often has difficulties organizing tasks and activities
(f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
(g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
(h) is often easily distracted by extraneous stimuli
(i) is often forgetful in daily activities

(2) six (or more) of the following symptoms of **hyperactivity–impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

(a) often fidgets with hands or feet or squirms in seat
(b) often leaves seat in classroom or in other situations in which remaining seated is expected
(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
(d) often has difficulty playing or engaging in leisure activities quietly
(e) is often "on the go" or often acts as if "driven by a motor"
(f) often talks excessively

Impulsivity

(g) often blurts out answers before questions have been completed
(h) often has difficulty awaiting turn
(i) often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive–impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Code based on type:

314.01 Attention-Deficit/Hyperactivity Disorder, Combined Types: if both Criteria A1 and A2 are met for the past 6 months

(*cont.*)

TABLE 6.1. (cont.)

314.00 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if Criterion A1 is met but Criterion A2 is not met for the past 6 months

314.01 Attention Deficit/Hyperactivity Disorder, Predominantly Hyperactive–Impulsive Type: if Criterion A2 is met but Criterion A1 is not met for the past 6 months

Coding note: For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, "In Partial Remission" should be specified.

Note. The diagnosis of Attention-Deficit/Hyperactivity Disorder Not Otherwise Specified is used for disorders with prominent symptoms of inattention or hyperactivity–impulsivity that do not meet criteria for Attention-Deficit/Hyperactivity Disorder. From American Psychiatric Association (2000, pp. 92–93). Copyright 2000 by the American Psychiatric Association. Reprinted by permission.

bility estimates from 0.48 to 0.68. A subsequent twin study by Thapar, Hervas, and McGuffin (1995), using the same three activity items, confirmed the low dizygotic correlation in maternal ratings; these authors suggested that dizygotic twins interact purposefully with each other to be different, or that mothers exaggerate differences between their dizygotic twins. The low dizygotic correlations may, however, be unique to these specific questions about activity level. Edelbrock, Rende, Plomin, and Thompson (1995) reported correlations predominantly from mothers of .86 for monozygotic twins and .29 for dizygotic twins, giving a heritability estimate of 0.66. Zahn-Waxler, Schmitz, Fulker, Robinson and Emde (1996) obtained a very similar estimate (0.72). However, somewhat lower heritability values were obtained from fathers' and teachers' ratings, and the correlations between raters was low.

From a categorical or diagnostic approach, Goodman and Stevenson (1989) demonstrated a proband-wise concordance rate of 51% in 39 monozygotic twin pairs and 30% in 54 dizygotic twin pairs, yielding a heritability estimate of 0.64. DeFries and Fulker (1985, 1988), utilizing a statistical method developed by Gillis, Gilger, Pennington, and DeFries (1992), estimated the heritability of ADHD as 0.91 plus or minus 0.36 for twins participating in a research project.

The issue of phenotypic definition is indicated by the variation in estimates of siblings' risk as 53%, 25%, or 17%, depending upon whether the behavior is defined as hyperactivity, attention deficit disorder, or ADHD; this speaks to the complexity of relating phenotype to genotype (Biederman, Faraone, Keenan, & Benjamin, 1992; Biederman, Faraone, Keenan, Knee, & Tsaung, 1990; Faraone et al., 1992; Safer, 1973). Levy, Hay, McStephen, Wood, and Waldman (1997), examining a cohort of 1,938 families with twins and siblings ages 4–12 years recruited from the Australian National Health and Medical Research Council Twin Registry. They concluded that ADHD is best viewed as an extreme form of behavior that varies genetically throughout the entire population, rather than as a disorder with discrete determinants. In this study, as with others, heritability estimates for monozygotic twins were significantly higher than for dizygotic twins. As Levy and colleagues note, ADHD has an exceptionally high heritability compared with other behavioral disorders. These authors reported that 82% of monozygotic twins and 38% of dizygotic twins met an eight-symptom ADHD cutoff for proband concordances.

Recent studies linking polymorphisms in the dopaminergic system to ADHD (Comings, Wu, & Chiu, 1996), and the dopamine D4 receptor polymorphisms to dimensional aspects of impulsivity (Benjamin et al., 1996; Ebstein et al., 1996), suggest that the polymorphisms identified to date do not account for all of the relevant variation in heritability. The findings of Sherman, Iacono, and McGue (1997) suggest that future molecular genetic

studies of ADHD may yield more information defining ADHD as a disorder composed of two quantitatively, continuously distributed dimensions—inattention and hyperactivity–impulsivity—rather than a homogeneous categorical disorder.

The etiology of ADHD must also be considered in relation to other disorders or teratogens. Fragile X syndrome, Turner syndrome, Tourette syndrome, neurofibromatosis, glucose 6 phosphate dehydrogenase, sickle cell anemia, phenylketonuria, Noonan syndrome, and Williams syndrome are all chromosomal and genetic abnormalities in which attentional problems and ADHD have been reported (Hagerman, 1991). Various types of exposure to toxins or medical problems, such as alcohol or cocaine exposure *in utero*, lead and vapor abuse, perinatal complications, hypothyroidism, encephalitis, and even radiation therapy secondary to leukemia, have all been reported as responsible for creating inattentive and impulsive problems (for a review, see Goldstein & Goldstein, 1998).

Understanding the cause of ADHD from the point of view of the brain as a neurological organ has interested many researchers. Early concepts such as underarousal and overarousal (Ross and Ross, 1982) were discarded after attempts to find the physiological basis for these theories met with limited success. A model characterizing frontal lobe dysfunction as causative of ADHD was first proposed by Conners and Wells (1986).

NEUROPSYCHOLOGICAL IMPAIRMENTS

The ecological validity of laboratory tests for identifying ADHD, defining it, and determining the severity of its symptoms has been increasingly questioned (Barkley, 1991; Barkley & Grodzinsky, 1994). Because ADHD is a disorder defined by behavior in the real world, it is not surprising that laboratory measures frequently fall short in defining and identifying symptoms of the disorder, in comparison to naturalistic observation, history, and organized reports in the form of questionnaires. Nonetheless, it has been increasingly recognized that neuropsychologists take comfort in supplementing their clinical impressions with laboratory-generated, objective scores (DuPaul, Guevremont, & Barkley, 1991). It is increasingly accepted, however, that these scores do not make the diagnosis of ADHD, but may be helpful in the process of differential diagnosis (e.g., when is impulsivity a function of ADHD vs. other disorders?) as well as the process of differentiating severity or related prognosis in a group of individuals with ADHD (Gordon, 1995; Hall, Halperin, Schwartz, & Newcorn, 1997).

The development of a norm-referenced, psychometric assessment battery specifically designed for ADHD has been an elusive goal for researchers and clinicians. Thus, when one reviews the extensive literature attempting to hypothetically and objectively define specific neuropsychological impairments as occurring consistently in children with ADHD, it is not surprising that no tried and true battery or pattern of impairment comes to light. As Levine (1992) has noted in an article title, ADHD symptoms appear to reflect "elusive entities and their mistaken identities." The comorbidity issue, and many tests' lack of specificity in discriminating ADHD from other disorders, further complicate this endeavor. Compromised scores may be due to a variety of causes, leading some researchers to suggest utilizing a profile of test scores to define and explain neuropsychological impairments in children with ADHD (Aylward, Verhulst, & Bell, 1993). Yet even the most widely used ADHD assessment tools frequently do not correlate with each other (Naglieri, Goldstein, & Schwebach, 2004). Neuropsychologists should be aware that when clinic or laboratory tests are used alone or in combination, these have been found to result in classification decisions that frequently disagree with diagnoses of ADHD in children based upon parent

interview, history, and behavior rating scales (DuPaul, Anastopoulos, Shelton, Guevremont, & Metevia, 1992). Szatmari, Offord, Siegel, Finlayson, and Tuff (1990) report that neuropsychological tests appear to distinguish children with ADHD from those with pure anxiety or mood disorders. However, they may not distinguish ADHD as efficiently from other disruptive behavior disorders. These authors concluded that neuropsychological tests are more strongly associated with externalizing than with internalizing diagnoses. They appear to correlate with psychiatric symptoms at school but not at home. All these findings lend weight to Barkley's (1991) suggestion that when results of the standardized behavior ratings, observations, and history conflict with laboratory measures, the latter should be disregarded in favor of the former, as these are considered more ecologically valid sources of data.

The following is a brief review of laboratory and clinical measures, and their hypothesized relationships to specific neuropsychological impairments in ADHD across the lifespan:

- Continuous-performance test (CPT) scores for omission and commission errors have been found to correlate statistically with a number of errors on some paper-and-pencil tasks. Only modest correlations have been found between CPT scores and direct observation of ADHD behavior in the classroom. Omission scores also appear to correlate only modestly with behavioral categories on the Gordon Diagnostic System. CPT performance has been found to be sensitive to stimulant medication, but not always reliably so (Barkley, 1978; Barkley, DuPaul, & McMurray, 1990; Barkley, Fischer, Newby, & Breen, 1988; Swanson & Kinsbourne, 1979). CPT scores, particularly commission scores, may have moderate ecological validity as assessed by parent and teacher ratings of inattention and overactivity. The neuropsychologist must question whether the CPT is necessary in the primary diagnosis of ADHD if similar information can be gleaned by obtaining history and parent–teacher ratings. For a thorough review of CPTs, readers are referred to Riccio, Reynolds, and Lowe (2001).
- Performance on cancellation tasks, such as the Children's Checking Task (Margolis, 1972), suggests that children with ADHD differ from those without disabilities on omission and commission errors (Aman & Turbott, 1986; Brown, 1982). They may not differ, however, from other clinical groups (Keough & Margolis, 1976). This type of measure may also be sensitive to the benefits of stimulant medication (Charles, Schain, Zelniker, & Guthrie, 1979).
- Correlations of the Matching Familiar Figures Test with parent and teacher ratings of ADHD have been low to moderate, but become nonsignificant when age and intelligence are partialed out (Brown & Wynne, 1982; Fuhrman & Kendall, 1986; Milich & Kramer, 1984). Milich and Kramer suggest that the ecological validity of the Matching Familiar Figures Test as a measure of impulsivity in children with ADHD appears weak.
- The Draw-a-Line-Slowly Test has been used to measure impulsivity, but has not been found to discriminate children with ADHD from children without disabilities or from other clinical groups once age and IQ are controlled for (deHaas & Young, 1984; Werry, Elkind, & Reeves, 1987).
- The Cookie Delay Test (Campbell, Szumowski, Ewing, Gluck, & Breaux, 1982), based on a model developed by Golden, Montare, and Bridger (1977), has found young children with ADHD to be significantly more impulsive than others. Rapport, Tucker, DuPaul, Merlo, and Stoner (1986) provided a similar delay-of-gratification procedure that involved much longer time delays. Ninety-four percent of the subjects with ADHD, as compared to 31% of the controls, chose the immediate over the delayed task. This issue holds significance for the neuropsychologist as consequences are chosen for behavior change programs.

- The ecological validity of devices for measuring movement or activity level, such as an actometer, stabilimetric cushion, or activity chair, is generally poor (Schulman & Reisman, 1959; Tryon, 1984). The actometer can discriminate children with ADHD from children without disabilities (Luk, 1985; Tryon, 1984), but not in all cases (Barkley, DuPaul, & McMurray, 1990; Koriath, Gualtieri, Van Bourgondien, Quade, & Werry, 1985). Unfortunately, these measurements have not correlated well with parent ratings of hyperactivity (Barkley & Ullman, 1975; Ullman, Barkley, & Brown, 1978). There may be an exception when actometer measures are taken over longer periods of time; they may then correlate better with parent and teacher behavioral reports (Stevens, Kupst, Suran, & Schulman, 1978).
- Observations of ADHD in laboratory analogue settings appear to yield encouraging associations with naturalistic reports. Analogue observations began with the work of Hutt, Hutt, and Ounsted (1963), in which the floor of a clinical playroom was divided into grids by using tape on the floor. A number of studies with similar methodology have demonstrated that children with ADHD display more grid crossings, more toy changes, and shorter durations of play with toys during free play than do children without disabilities (Campbell et al., 1982; Pope, 1970; Routh & Schroeder, 1976; Touwen & Kalverboer, 1973). Yet, again, some studies have not found differences between the groups with ADHD and others (Barkley & Ullman, 1975; Koriath et al., 1985). A few studies that have attempted to correlate free play with parent ratings of hyperactivity have yielded nonsignificant results (Barkley & Ullman, 1975; Ullman et al., 1978). It is when children with ADHD in analogue settings are asked to complete directed tasks with parents that they appear to have the most problems, not in free-play situations with parents.
- Analogue measures that evaluate being out of seat, being off task, vocalizing, and shifting attention during free play in restricted play settings have yielded more promising findings (Milich, 1984; Milich, Loney, & Roberts, 1986). These findings have correlated significantly with parent and teacher ratings of hyperactivity. Studies comparing children with ADHD to nondisabled and clinic control groups have found significant differences among children with ADHD, group, children with both ADHD and aggression, purely aggressive children, and children without disturbances (Milich, Loney, & Landau, 1982; Roberts, 1990). Barkley, McMurray, Edelbrock, and Robbins (1989) placed children in a playroom setting with a shelf full of toys, and asked them to sit at a small table and complete a written math task at or below their grade level for 15 minutes. They were told not to leave their seat or to touch the toys. They were then observed. This procedure was found to discriminate the children with ADHD from children without disabilities, but was inconsistent in discriminating those with ADHD from other clinical groups when behavior such as being off task, being out of seat, vocalizing, fidgeting, and playing with objects was evaluated (Barkley, DuPaul, & McMurray, 1990; Breen, 1989).

Cherkes-Julkowski, Stolzenberg, and Siegal (1991) suggest that perhaps the dropoff in performance for children with ADHD is a function of inability to control focus of attention. These authors suggest that when prompts are provided during testing, children with ADHD perform significantly better. In a study comparing children with ADHD (with and without medication) to children with learning disabilities and a group of nondisabled controls, Cherkes-Julkowski and colleagues found that the greatest gains for prompts occurred in the unmedicated group with ADHD. However, practitioners should be cautioned that prompts, especially on measures designed to evaluate response inhibition, may actually test a child's ability to follow directions rather than to inhibit

responding. Neuropsychologists should also keep in mind that level of reinforcement during test performance may also have an impact on scores. Devers, Bradley-Johnson, and Johnson (1994) found that an improvement in Verbal IQ scores of 12 points accrued when token reinforcers followed immediately for correct responses; the impact of praise on test performance has not been systematically evaluated. Finally, Draeger, Prior, and Sanson (1986) reported a deterioration in the performance of children with ADHD on a CPT, more so than in that of controls, when the examiner left the room. These authors suggest that even examiner presence acts to mitigate test performance. It may well be that some people who perform poorly on test measures under these circumstances have deficits in application rather than ability.

EVALUATION

Due to the pervasive, multisetting nature of the problems related to ADHD, as well as its high comorbidity with other childhood disorders, assessment for ADHD in adults involves a thorough emotional, cognitive, vocational, and behavioral evaluation. In 1997, the American Academy of Child and Adolescent Psychiatry (AACAP) published practice parameters for the assessment and treatment of children, adolescents, and adults with ADHD. These have been the only practice parameters published for adults to date. Basic parameters were developed by the AACAP's work group on quality issues and were based on an exhaustive review of the literature providing empirically based guidelines for assessment. These guidelines suggest the following:

1. An interview with the patient to obtain a developmental history; psychiatric history and past treatments; present and past DSM-IV (now DSM-IV-TR) ADHD symptoms; impairment history (including the domains of school, family, and peers); differential diagnosis of alternative and/or comorbid DSM-IV-TR disorders; an assessment of strengths, talents, and abilities; and a mental status examination.
2. Standardized rating scales completed by a parent of the patient (when available).
3. A medical history.
4. A family history.
5. An interview with a significant other or parent (if available).
6. A physical evaluation (if not completed within the past year).
7. School and work information.
8. Referral for additional evaluations if indicated, such as psychoeducational, neuropsychological, or vocational assessment.

Adults with histories of undiagnosed ADHD (who may represent a declining number in each future generation) may have been missed due to a comorbid condition, may have been extremely bright or compliant, may have come from a good home environment, or may possess interpersonal skills that have allowed them to succeed despite ADHD symptoms. The neuropsychologist must carefully evaluate for childhood problems from a developmental perspective, seeking to identify possible etiologies. Neuropsychologists should be aware that psychological and neuropsychological testing is suggested, but is described as "not necessarily required," in the AACAP's practice parameters.

It is suggested that neuropsychologists consider the following multistep process in the evaluation of adult ADHD:

1. A complete history must be obtained. This is not a cursory process. Sufficient time (approximately 1½–2 hours) should be set aside to obtain a narrative of the individual's development, behavior, extended family history, family relations, and current functioning. A standardized history form should be utilized. Conners, Epstein, and Johnson (2001) have developed a structured diagnostic interview for ADHD. The spouse or partner and significant other family members should be included, with the patient's permission. Within the context of the interview, efforts should be made to trace a developmental course that appears to fit a diagnosis of ADHD, as well as to identify core symptoms and those related to other disorders. Given the strong comorbidity of problems in childhood and adult ADHD, neuropsychologists must be well familiar with both common and uncommon conditions. ADHD in childhood, for example presents at a significantly higher rate for individuals with pervasive developmental disorders and other genetic conditions, such as fragile X syndrome and neurofibromatosis (for a review, see Goldstein, 1999).

2. Data obtained from the history should be supplemented by the completion of a number of standardized, factor-analyzed questionnaires concerning psychiatric problems. Although a broad-based questionnaire is likely to be a better starting point than a questionnaire designed to assess specific conditions, assessment tools designed for adults have generally omitted consideration of ADHD. It is therefore suggested that clinicians utilize a broad-band measure such as the Millon Clinical Multiaxial Inventory–III (Millon, Davis, & Millon, 1997) or the Minnesota Multiphasic Personality Inventory–2 (Butcher et al., 2001). These should be supplemented by questionnaires designed to assess symptoms specifically related to anxiety (e.g., the Beck Anxiety Inventory; Beck & Steer, 1993) and depression (e.g., the Beck Depression Inventory–II; Beck, Steer, & Brown, 1996). A number of questionnaires specifically intended to assess ADHD have entered the marketplace. Among them are the Conners Adult ADHD Rating Scale (Conners, 1997) and the Brown Attention Deficit Disorder Scales (Brown, 1995). Barkley and colleagues have collected a set of normative data utilizing a 4-point Likert scale on a self-report measure that includes the 18 DSM-IV-TR ADHD symptoms (Murphy & Barkley, 1995, 2000). Diagnosis of ADHD is likely to be best facilitated by instruments that specifically assess symptoms used in the DSM-IV-TR to make the diagnosis of ADHD. Neuropsychologists should be cognizant of the fact, however, that questionnaires alone do not provide sufficient information for diagnosis. They simply provide an organized report of behavior; that is, they describe what the individual or observer reports, but not why it is being reported.

3. Based upon the history and measures completed, the neuropsychologist should be able to generate a consistent set of data and a series of hypotheses to explain the individual's history and behavior across a variety of settings.

4. Although a number of paper-and-pencil and computer tasks have been used over the years in research settings to identify symptoms of ADHD, most have not lent themselves easily to clinical use. As reviewed above, these instruments may provide valuable insight into behavior but do not necessarily serve to confirm or rule out a diagnosis of ADHD and are not essential for the diagnosis.

5. As Murphy (1994) has noted, at this time the diagnosis of ADHD in adults is not an exact science. There is no single neurological or psychological test or test battery that conclusively determines whether or not an adult suffers from ADHD. In making the diagnosis, a neuropsychologist must consider the chronic and pervasive level of impairment required. Secondary symptoms, such as procrastination, lateness, or underachievement, do not in and of themselves indicate ADHD. Neuropsychologists must pay careful attention to other diagnostic conditions that could account for inattentive, hyperactive, and impulsive behavior.

TREATMENT

Treatment of adult ADHD must be multidisciplinary, multimodal, and long term (Goldstein & Ellison, 2002). By far the most effective interventions for adult ADHD reflect the combined use of medical, behavioral, and environmental techniques. Medication has demonstrated the ability to reduce the severity of impairment resulting from the core symptoms of ADHD. Behavior management increases the salience of acting in a way consistent with environmental expectations. The manipulation of the environment (e.g., making tasks more interesting and payoffs more valuable) reduces the risk of problems within the natural setting.

Regardless of the treatment modality employed, the basic underlying premise in managing problems of ADHD involves increasing the adult's capacity to inhibit impulsive responding before acting, which should lead to consistent, predictable, and functional behavior. This axiom fits with the theoretical construct that the core problem in ADHD is an inability to permit sufficient time to think or respond consistently to consequences.

Medication

Many adults with ADHD have histories of depression and anxiety, as well as of substance use and abuse (Biederman, Faraone, Doyle, & Lehman, 1993; Wilens, Spencer, & Biederman, 1995). Thus there is a need to develop effective pharmacotherapeutic strategies in the treatment of adult ADHD. Neuropsychologists should make an effort to seek out a physician in the community who is interested in working with adults with ADHD. Prince and Wilens (2002) suggest that in the treatment of adult ADHD, stimulants should represent the first line of pharmacotherapy. They also note that stimulants are not effective in treating comorbid problems. In comparison to the more than 200 controlled studies of stimulant efficacy in childhood ADHD, there have been only a handful of open and controlled studies of medication treatment in adults. These studies are summarized in Table 6.2.

Treatment with stimulants is moving in the direction of the longer-acting delivery systems, which require only a single dose during the day. Prince and Wilens (2002) suggest that typical adult dosing of methylphenidate can be up to 30 mg three to four times a day if short-acting preparations are utilized. If adults with ADHD are unresponsive to or experience significant side effects of methylphenidate, these authors suggest consideration of an alternative stimulant (such as pemoline or dextroamphetamine) or another class of medication. The side effects of stimulants in ADHD treatment for adults have been reported to be mild. Wilens and Spencer (2000) report that common side effects include insomnia, edginess, diminished appetite, weight loss, dysphoria, obsessiveness, tics, and headaches. No cases of stimulant-related psychosis at therapeutic doses have been reported in adults. Among nonstimulant medications, tricyclic antidepressants and bupropion have been reported to be effective second-line treatments. Serotoninergic, antihypertensive, and cholinergic-enhancing medications may improve some symptoms of ADHD but generally are not globally effective. The U.S. Food and Drug Administration has recently approved atomoxetine (marketed as Strattera) for the treatment of ADHD in adults. Atomoxetine is an antidepressant with selective noradrenergic reuptake inhibitor properties.

Prince and Wilens (2002, p. 179) suggest a basic clinical strategy for the pharmacotherapy of adults with ADHD as follows:

TABLE 6.2. Studies of Stimulant Pharmacotherapy in Adult ADHD

Study (year)	*N*	Design	Medication	Duration	Total dose (wt.-corrected)	Response rate	Comments
Wood et al. (1976)	15	Double-blind; open	MPH Pemoline	4 weeks 4 weeks	27 mg (0.4 mg/kg[a]) 37.5–70 mg (0.5–1.0 mg/kg[a])	73% 33%	Dx criteria not well defined; low doses of pemoline; mild side effects
Wender et al. (1981)	51	Double-blind; placebo crossover	Pemoline	6 weeks	65 mg (0.9 mg/kg[a])	50% (childhood onset)	Dx criteria not well defined; high rates of dysthymia; moderate side effects
Mattes et al. (1984)	26	Double-blind; placebo crossover	MPH	6 weeks	48 mg (0.7 mg/kg[a])	25%	Moderate rate of comorbidity; mild side effects
Wender et al. (1985)	37	Double-blind; placebo crossover	MPH	5 weeks	43 mg (0.6 mg/kg[a])	57%	68% dysthymia, 22% cyclothymia; mild side effects
Gualtieri et al. (1995)	8	Double-blind; placebo crossover	MPH	2 weeks	42 mg[a] (0.6 mg/kg[a])	70%	Problematic outcome measures
Shekim et al. (1990)	33	Open	MPH	8 weeks	40 mg (0.6 mg/kg[a])	70%	Problematic outcome measures

Spencer et al. (1995)	23	Double-blind; placebo crossover	MPH	7 weeks	30–100 mg (0.5, 0.75, and 1.0 mg/kg)	78% dose relationship	No plasma level associations; no effect of gender or comorbidities
Iaboni et al. (1996)	30	Double-blind; placebo crossover	MPH	4 weeks	30–45 mg (0.6 mg/kg[a])	Moderate	Improvement in neuropsych. and anxiety
Wilens et al. (1996)	42	Double-blind; placebo crossover	Pemoline	10 weeks	150 mg (2 mg/kg)	61%	35% reduction in criterion A symptoms; moderate effects >2 mg/kg
Spencer et al. (1 999)	27	Double-blind; crossover	Adderall	7 weeks	30 mg b.i.d.	70%	Dose–response relationship
Total	292	Double-blind: *N* = 9; open: *N* = 2	MPH, Adderall, and pemoline	2–10 weeks	40 mg (MPH) (0.6 mg/kg[a]) 105 mg (pemoline) (1.5 mg/kg[a]) (Adderall) 30 mg b.i.d.	Variable	Dx not well defined; high rate of comorbidities; side effects in 30%; apparent dose–response relationship

Note. Duration of medication trial includes placebo phase. MPH, methylphenidate; Dx, diagnosis. From Prince & Wilens (2002). Copyright 2002 by Elsevier Science. Reprinted by permission.

[a]Weight-normalized dose using 50th-percentile weight for age.

- Set clear, realistic treatment goals with a patient.
- Stimulants are the first-line medications.
- If the first stimulant is not effective or tolerated, consider an alternative stimulant.
- When comorbidities are present, prioritize treatment.
- Use additional therapies to support and complement the effects of medication.
- Use remedial services to support the patient in work and educational settings.

Psychosocial Treatments

Psychosocial treatments include psychotherapy, life skills coaching, marital and relationship counseling, and vocational counseling and/or support. Though many of these interventions hold intuitive appeal and have been described in single-case studies as effective, there are only limited data to support their benefits in directly reducing symptom severity and consequent impairment resulting from ADHD in the adult years. As with all supportive psychotherapies, however, there is reason to suspect that these interventions can be of benefit in helping affected individuals learn to cope and live with a lifetime condition that has caused significant, chronic, multisetting adversity (Brooks, 2002). Neuropsychologists interested in these psychosocial treatments are referred to Nadeau (2002) and Young (2002) for discussions of psychotherapy; Kilcarr (2002) for a discussion of marital issues and strategies; Crawford and Crawford (2002) for a discussion of career impact and vocational issues in ADHD; Ratey (2002) and Robin (2002) for discussions of the role of life coaching and lifestyle issues in adult ADHD; Latham and Latham (2002) for an overview of legal findings and legislative issues relative to ADHD; and Phelan (2002) for a discussion of strategies and interventions when parents struggle with ADHD.

In a discussion of the nontraditional neurobiological approach to psychotherapy in treating adults with ADHD, Nadeau (2002) points out that psychotherapists often have to play an active role—not only focusing on enhancing self-esteem, relationships, and coping behaviors, but also providing assistance and support in helping clients develop life skills (e.g., time and money management skills). The key component is the importance of helping clients set short-term, reachable goals as a means of enhancing self-confidence, developing adequate coping strategies, and building upon success.

CONCLUSION

Neuropsychologists must be empathic and understand the lifetime adversities that adults with ADHD have faced and continue to face. Although the body of scientific knowledge is increasing, at this time it must be supplemented by common sense and good clinical practice in making the diagnosis, designing a treatment plan, and implementing the plan. Neuropsychologists must provide, as Brooks (2002) points out, "realistic hope by offering strategies for success . . . they must strive to replace a negative mindset with a mindset with a mindset filled with optimism and promise" (p. 146).

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7

GILLES DE LA TOURETTE SYNDROME

LAURA ARNSTEIN CARPENTER
RONALD T. BROWN

OVERVIEW

Historical Context

In the early 19th century, Jean-Mark Itard reported a case history of a French noblewoman who began to display involuntary motor movements at age 7 and later began to make involuntary vocalizations, including screams and strange cries (Kushner, 1999). The case report documented a rather chronic course, and the woman was plagued by severe tics until her death at 85 years of age. In 1885, Georges Gilles de la Tourette reported on the cases of nine patients with this same syndrome. His original description of the disorder was similar to modern constructions of the disorder, including the multiple motor and vocal tics, the waxing and waning quality, the early age of onset, and the hypothesized genetic contribution (Kushner, 1999). The syndrome was subsequently named Gilles de la Tourette syndrome and later shortened to Tourette syndrome (TS).

Clinical Characteristics

TS is a neuropsychiatric disorder defined by chronic motor and vocal tics (American Psychiatric Association [APA], 2000). According to the diagnostic criteria set forth by the APA, TS is characterized by the presence of multiple motor tics and one or more vocal tics that occur many times per day nearly every day or occur intermittently for more than a year. Over the course of the disorder, the motor and vocal tics may appear either together or separately over different time periods. Interestingly, the clinical characteristics of TS seem to be independent of culture (Freeman et al., 2000), suggesting a biological or more specifically a genetic etiology.

A tic is a "sudden, rapid, recurrent, nonrhythmic, stereotyped movement or vocalization" (APA, 2000, p. 108). Motor tics can be simple (e.g., eye blinking, grimacing, and coughing) or complex (e.g., jumping, touching, and smelling). Simple motor tics are often meaningless movements that last less than 1 second. Individuals with TS, particularly young patients, may be unaware of simple motor tics. Complex motor tics last longer and may be

more purposeful (e.g., smelling an object). Simple and complex motor tics may be combined into sustained, complex movements known as "paroxysms." Some individuals may also display self-injurious tics, such as slapping, hitting, or biting. Similar to motor tics, vocal tics can also be simple (e.g., grunting, barking) or complex (e.g., repeating words and phrases). Complex verbal tics may include the use of obscene words and phrases ("coprolalia"), the repetition of one's own sounds or words ("palilalia"), and repetition of the last words of others ("echolalia"). Although many people believe that coprolalia is a defining feature of TS, this symptom is relatively uncommon and occurs in approximately 14% of those with TS (Teive, Germiniani, Coletta, & Werneck, 2001). However, in a retrospective study of adults with TS, approximately 22% reported that they suffered from coprolalia during their "worst" period (Goetz, Tanner, Stebbins, & Leipzig, 1992)

There are four types of tic disorders as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR; APA, 2000). These include TS, chronic motor or vocal tic disorder, transient tic disorder, and tic disorder not otherwise specified (see Table 7.1 for an overview of these four disorders). TS is distinguished as the most "severe" of the tic disorders by its early age of onset (by age 18), severity (both motor and vocal tics), and duration (the tics must occur for a year or many times a day every day). However, rather than being conceptualized into separate categories, these diagnoses may actually represent a continuum of tic disorders, with TS representing the more severe end of the continuum (Gillberg, 1998). Clinically, it has been suggested that TS may be divided into three primary types (Robertson, 2003). Simple TS only involves motor and vocal tics. Full-blown TS involves motor and vocal tics including "coprophenomena" (tics involving obscene words or gestures), "echophenomena" (tics that mimic another's words or behaviors), and "paliphonomena" (tics that mimic one's own words or behaviors). Finally, a "TS-plus" group may exist. These individuals typically suffer from several co-occurring conditions—including symptoms of attention-deficit/hyperactivity disorder (ADHD), obsessive–compulsive disorder (OCD), and self-injurious behaviors—as well as from TS.

Tics tend to be characterized by nonrandom patterns of "bursts," in which periods of high tic frequency are punctuated by tic-free periods (Peterson & Leckman, 1998). Patients with TS often report that they have an urge to engage in a tic prior to engaging in the tic behavior, and feelings of relief following tic performance. Tics are almost always suppressible for a period of time. However, individuals who suppress tics often suffer from an associated increase in tension that results in more forceful tic expression when the suppression ceases (Leckman, Peterson, King, Scahill, & Cohen, 2001). Tics may be triggered by a wide range of stimuli that vary from individual to individual. For example, tics may be exacerbated by stress and attenuated by absorption in an activity (Arzimanoglou, 1998). Tics may also be suggestible. For example, when a person with TS is interviewed about tic symptoms, tics that have disappeared may reappear for a short period of time (Leckman, Peterson, et al., 2001).

A substantial minority of patients with TS (approximately 40%) experience what are known as "premonitory sensory phenomena" prior to the production of a tic (Banaschewski, Woerner, & Rothenberger, 2003). Premonitory sensory phenomena typically take the form of an urge to engage in the tic behavior. For example, a tense or painful sensation in the mouth area may precede a grimace. Premonitory sensory phenomena are often localized to a small area, such as the midline of the stomach or the throat, or they may be more generalized, as in general inner tension (Leckman, Peterson, et al., 2001). Adolescents and adults are more likely to report these phenomena than are children (Banaschewski et al., 2003). Although it was once believed that tics were involuntary movements, it now appears that for almost 70% of patients with TS, tics are voluntary movements made in re-

TABLE 7.1. DSM-IV-TR Diagnostic Criteria for the Tic Disorders

Tourette's Disorder

A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently. (A *tic* is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization.)
B. The tics occur many times a day (usually in bouts) nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months.
C. The onset is before age 18 years.
D. The disturbance is not due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or postviral encephalitis).

Chronic Motor or Vocal Tic Disorder

A. Single or multiple motor or vocal tics (i.e., sudden, rapid, recurrent, nonrhythmic, stereotyped motor movements or vocalizations), but not both, have been present at some time during the illness.
B. The tics occur many times a day nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months.
C. The onset is before age 18 years.
D. The disturbance is not due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or postviral encephalitis).
E. Criteria have never been met for Tourette's Disorder.

Transient Tic Disorder

A. Single or multiple motor and/or vocal tics (i.e., sudden, rapid, recurrent, nonrhythmic, stereotyped motor movements or vocalizations).
B. The tics occur many times a day, nearly every day for at least 4 weeks, but for no longer than 12 consecutive months.
C. The onset is before age 18 years.
D. The disturbance is not due to the direct physiological effects of a substance (e.g, stimulants) or a general medical condition (e.g., Huntington's disease or postviral encephalitis).
E. Criteria have never been met for Tourette's Disorder or Chronic Motor or Vocal Tic Disorder.

Specify if:
Single Episode or **Recurrent**

Tic Disorder Not Otherwise Specified

This category is for disorders characterized by tics that do not meet criteria for a specific Tic Disorder. Examples include tics lasting less than 4 weeks or tics with an onset after age 18 years.

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sponse to the involuntary premonitory sensations (Kwak, Vuong, & Jankovic, 2003). Some individuals find that premonitory sensory phenomena are as distracting and bothersome as the tics themselves; for this reason, it has been suggested that premonitory sensory phenomena may contribute to some of the attentional problems that frequently co-occur with TS (Leckman, Peterson, et al., 2001). In addition to premonitory sensory phenomena, there are auditory or visual stimuli (e.g., specific words or sounds) that can trigger tics in some individuals with TS (Leckman, Cohen, Goetz, & Jankovic, 2001).

Prevalence

TS is estimated to occur in between 1 and 10 per 10,000 individuals (Singer, 2000). Similar to many neurodevelopmental disorders (e.g., autism, ADHD), TS is more prevalent in males than females. The prevalence of TS is estimated to be between 1 and 8 cases per 1,000 males, and between 0.1 and 4 cases per 1,000 females (Robertson, 2003). Interestingly, there may be considerable variation in symptom presentation between males and females. Males with TS may be more likely to have comorbidities such as ADHD, oppositional defiant disorder, conduct disorder, learning disabilities, and social skills deficits; their female counterparts may be more likely to have self-injurious behaviors, trichotillomania, or even no comorbidities (Freeman et al., 2000).

Developmental Course

TS is a lifelong disorder that typically emerges in early childhood, with a mean age of onset at 6 years (Robertson, 2003). According to DSM-IV-TR (APA, 2000), the disorder must have an onset prior to the age of 18 years in order to qualify for a diagnosis of TS. In fact, some research suggests that 93% of individuals with TS were actually symptomatic by age 10 (Freeman et al., 2000). Motor tics such as eye blinking typically appear in early childhood (between ages 3 and 8), with vocal tics typically following several years later. For most individuals with TS, tics occur in bouts over the course of a day. The tics may wax and wane over time. As a child grows older, tics often become progressively worse. Preadolescence is often the most difficult period for a child with TS. In one investigation, patients reported that the most severe period occurred approximately between the ages of 8 and 12 years (Leckman et al., 1998). During this "worst-ever" period, about one-quarter of patients were so severely affected that school functioning was significantly impeded or nearly impossible. Coprolalia often emerges during adolescence, although it remits as a patient enters adulthood.

Symptoms of TS generally become worse throughout childhood and early adolescence, and then begin to dissipate steadily (Goetz et al., 1992). As the individual ages, tics become more stable and less unpredictable. Although TS is considered to be a lifelong disorder, many patients are not bothered by symptoms in adulthood (Bruun & Budman, 1997). By age 18, nearly half of those with TS are tic-free (Burd et al., 2001; Leckman et al., 1998). There is some evidence, however, that the percentage of adults who continue to suffer from symptoms of TS may be higher than suggested by self-report data. Pappert, Goetz, Louis, Blasucci, and Leurgans (2003) collected both self-report and videotape data on a group of adults who were diagnosed with TS as children. These investigators found that while most adults considered themselves to be tic-free, 90% nonetheless continued to display objective evidence of tics when videotapes were coded. Although the majority of patients show symptom improvement in adulthood (Pappert et al., 2003), a small group of individuals with TS suffer from debilitating tics during adulthood that either persist from childhood or reemerge in adulthood in dramatic ways. For this small minority of individuals (Goetz et al., 1992), TS can severely limit personal and occupational aspirations. The best predictor of tic severity in adulthood is tic severity during the individual's worst tic period, which is typically at adolescence (Goetz et al., 1992). Those individuals with mild tics during their worst period usually have a less severe presentation of TS in adulthood. Interestingly, childhood tic severity does not predict adult tic severity.

Although most adults with tic disorders suffered from TS as children, there are some isolated reports of spontaneous, adult-onset tic disorders. Eapan, Lees, Lakke, Trimble, and Robertson (2002) published case studies of eight individuals with adult-onset tic disorders. For each patient, a potential trigger event was identified; these events included drug exposure, infection, physical trauma, cerebrovascular disease, or psychiatric illness. Half of the patients described in these cases reported a personal or family history of tics or obsessive–compulsive behavior. Although severe tic behavior is relatively rare among adults with TS, the majority of patients in this report experienced severe tics. More than half evidenced a poor response to pharmacotherapy. These results suggest that adult-onset tic disorders may be associated with poorer outcome.

Not surprisingly, social and educational impairments seem to be more common during childhood than in adulthood. In a longitudinal investigation of TS, Pappert and colleagues (2003) found that more than one-half of children with TS experienced social or educational problems. Almost 40% of the children in their sample required special education services. Among this same group of individuals, approximately 30% still continued to experience dysfunction in adulthood. Interestingly, 13% of patients who did not experience dysfunction in childhood developed later problems in adulthood.

ETIOLOGY

The search for the biological bases of TS has been complex. Although there is extensive evidence pointing to a genetic component in TS, it is also clear that environmental stressors play a role in the syndrome's etiology. It is believed that genetic factors interact with environmental risk factors to produce neurobiological abnormalities that result in the TS phenotype (Leckman, Cohen, et al., 2001). In this section, we review the literature regarding the genetics of TS, the neurobiological bases of TS, and the environmental factors that may play a role in the phenotypic expression of the disorder.

Genetics

It is well established that TS has genetic determinants. The mode of transmission is believed to be by a single major locus inherited in a mendelian manner. However, despite evidence that TS and the TS phenotypic spectrum of tic disorders and obsessive–compulsive behaviors are genetically mediated, researchers have not yet identified a specific gene involved in the etiology of the disease. Twin studies have been conducted to explore the role of genetic factors in the transmission and expression of TS. In a review of this research, Pauls (2001) reported concordance rates of 53–56% for monozygotic (MZ) twins and about 8% for dizygotic (DZ) twins. The concordance rate for any tic disorder in cotwins is considerably higher among both MZ and DZ twins (Pauls, 2001).

Family studies employ structured interviews to collect data from patients with TS and their first-degree family members. Results of family genetic studies suggest that the risk for TS among family members ranges between approximately 10% and 15% across studies, and that tics occur in 15–20% of family members (Pauls, 2003). Family studies provide strong support for the hypothesis that major genes are involved in TS (Pauls, 2003). Family segregation analyses (explorations designed to explore hypotheses regarding familial transmission of a disorder) have been conducted with the data sets from family studies.

Pauls (2003) reported complex findings from these family segregation studies. All studies but one have provided support for some type of mendelian transmission (i.e., inherited characteristics) in TS. Many studies have provided support for an autosomal dominant inheritance model. However, several additional studies have demonstrated that penetrance (i.e., expression of tic symptoms) of heterozygous individuals (those carrying only one allele for TS) to be somewhere between the penetrance of homozygous individuals (those carrying both alleles for TS or neither allele for TS). Finally, one study has provided evidence for a significant multifactorial (multiple-etiologies) background in TS (for a review, see Pauls, 2003).

Various genetic association and genetic linkage studies have been conducted in an attempt to identify genes for TS. With these methodologies, several regions of the genome have been implicated in the search for the TS genes (Pauls, 2003). However, no single locus has been identified and replicated. Findings in this area are still preliminary, and scientists must next localize and describe the genes associated with TS (Pauls, 2003).

Neurobiology

The neuroanatomical bases of TS have not been conclusively identified. Postmortem studies of brain tissues of patients with TS have been conducted. Although the data are limited by the number of samples available, the results of this research suggest increased packing density of neurons in the striatum, increased dopaminergic innervation of the striatum, and reduced glutaminergic output from the subthalamic nucleus in patients with TS (Swerdlow & Young, 2001).

Volumetric magnetic resonance imaging (MRI) studies have revealed abnormalities in the caudate or lenticular nuclei in patients with TS (Singer, 2000). An investigation of the corpus callosum in children with TS and/or ADHD revealed significant increases in the size of this structure for children with TS (Baumgardner, Singer, Denckla, & Rubin, 1996).

The development of sophisticated neuroimaging techniques (positron emission tomography [PET], single-photon emission computed tomography [SPECT], and functional MRI [fMRI]) has allowed investigators to examine brain morphology and cerebral function more meticulously than in previous years, and have revealed abnormal activation in the cortical and subcortical areas in patients with TS. The cortical–striatal–thalamic–cortical circuits of the brain have been implicated in TS and related illnesses (Peterson, 2001). Evidence from MRI studies suggests that adults show activation of the prefrontal cortex and caudate nucleus, along with bilateral deactivation of the putamen and globus pallidus during voluntary tic suppression (Peterson et al., 1998). The basal ganglia may play a central role in the pathogenesis of the disorder through connections with the cerebral cortex and limbic system (Leckman, Cohen, et al., 2001). Perhaps not surprisingly, given their associations with TS, the same pathways may be affected in OCD and ADHD. Activity in the orbital–frontal cortex has been linked with associated features of TS, including obsessions, compulsions, impulsivity, coprolalia, self-injury, and attention (Braun et al., 1995).

Although most of the literature regarding the course and treatment of TS has focused on children, the majority of functional imaging studies have employed adult participants. In a review of anatomical and functional neuroimaging studies in TS, Gerard and Peterson (2003) pointed out that lenticular nucleus volumes are reduced in adults with TS. Caudate nucleus volumes are reduced in both adults and children with TS. Interestingly, adults with TS show reduced prefrontal volumes, while children with TS show larger prefrontal vol-

umes. The authors caution that such discrepancies in findings between children and adults may reflect compensatory central nervous system changes resulting from TS, rather than pathophysiology's being etiological in the disorder (Gerard & Peterson, 2003). These observations call into question the conclusions drawn from studies conducted in this area.

Some researchers have suggested that TS may be related to dysfunctions in the neural systems that allow for habit formation. Habits such as those involved in driving allow individuals to engage in motor actions without conscious guidance. According to Leckman, Cohen, and colleagues (2001), tics may represent habits that are responsive to cues from the body and external world. Mink (2001) suggests that TS may be related to faulty inhibition of these habits or patterns of behavior and may be associated with basal ganglia dysfunction.

No consistent abnormality in neurotransmitter functioning has been confirmed. However, there is evidence that dopamine abnormalities may be implicated in TS. Given the success of haloperidol (a dopamine receptor antagonist) in the management of TS, there has been a great deal of interest in the role of dopamine in TS. For example, it has been hypothesized that abnormalities in the postsynaptic dopamine receptors (either increased number or increased sensitivity) or the presynaptic neurons (excessive release or abnormal function) may be related to TS (Singer, 2000).

Environmental Risk Factors

Evidence from family and twin studies suggests that the presence of a TS gene or genes is probably not sufficient for development of the full disorder (Walkup, 2001). A number of risk factors are hypothesized to be etiological in the phenotypic expression of TS. For example, biological insults and environmental stressors may play a role in TS development. In a review, Walkup (2001) reported that birth complications (especially forceps delivery) have been found to be more common in individuals with TS. Furthermore, increased maternal nausea and vomiting during the first trimester have been associated with tic severity in offspring. Similarly, maternal stress during pregnancy has been associated with tic severity in offspring. In twin studies, the twin with lower birth weight is at greater risk for the development of more severe tic symptoms.

There is a somewhat controversial hypothesized association between TS and antistreptococcal antibodies and antinuclear antibodies. Swedo and colleagues (1998) described the cases of 50 children with sudden onset of tics and/or obsessive–compulsive symptoms temporally associated with streptococcal infection. This syndrome has been termed "pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection" (PANDAS). It is hypothesized that antibodies induced after group A streptococcal infection alter activity of the basal ganglia, resulting in symptoms of TS. Symptoms in these cases tend to begin very abruptly following streptococcal infection. They then follow a relapsing–remitting pattern similar to non-PANDAS TS. In a recent study of both children and adults with and without TS, patients with TS demonstrated increased rates of recent group A streptococcal infection and of anti-basal-ganglia antibodies (Church, Dale, Lees, Giovannoni, & Robertson, 2003). In a study of adults with TS, antibodies against some types of M proteins (major virulence factors of group A streptococci) were found to be elevated in patients with TS, but not in comparison controls (Muller et al., 2001). However, several studies have failed to find differences in antistreptococcal antibodies in children diagnosed with TS (Loiselle, Wendlandt, Rohde, & Singer, 2003). In addition, the rates of psychiatric disorders in relatives of patients with PANDAS are similar to those in patients with tic disorders and OCD not associated

with streptococcal infection (Lougee, Perlmutter, Nicolson, Garvey, & Swedo, 2000), suggesting similar genetic linkage in PANDAS and non-PANDAS TS. Although PANDAS is typically described in children, there is one case study of a 25-year-old man who developed OCD (not TS) following severe pharyngitis (Bodner, Morshed, & Peterson, 2001), suggesting that PANDAS may not be specific to children and may also affect adults. Clearly, this is an area destined forfuture investigation.

Neuropsychological Characteristics

General intellectual ability is not impaired in patients with TS (Como, 2001). There is limited evidence to suggest that some patients with TS may perform more poorly on nonverbal tasks (Performance IQ) than on verbal tasks (Verbal IQ), although this remains an area of controversy (Como, 2001). Patients with TS are at increased risk for school-related problems, including learning disabilities, but this association may be related to comorbid symptoms of ADHD rather than to TS per se. According to Como (2001), cognitive difficulties are most common among patients with comorbid psychiatric conditions such as ADHD or OCD.

The majority of the literature on neuropsychological functioning in TS relates to children with TS. One study examined neuropsychological functioning over time in an adult with TS. Results showed a pattern of improvement across time, with no indication of neurological dysfunction (Newman, Barth, & Zillmer, 1986).

Consistent findings in the literature include deficits in visual–motor integration, impaired fine motor skills, and executive dysfunction among individuals with TS (Como, 2001). Specific deficits have been observed in the area of visual–motor integration among these children. Schultz and colleagues (1998) found that children with TS performed more poorly on a test of visual–motor integration than did matched controls, suggesting poor integration of visual–motor inputs and motor outputs. Similarly, an investigation by Brookshire, Butler, Ewing-Cobbs, and Fletcher (1994) demonstrated both visual–motor and expressive language deficits in children with TS, suggesting a deficit in the output of information.

Some researchers have noted that symptoms such as attentional difficulties and obsessive–compulsive symptomatology observed in TS may be more debilitating than the tics themselves (Como, 2001). In a study of children's ability to inhibit the processing of distracting visual stimuli, Ozonoff, Strayer, McMahon, and Filloux (1998) found that children with TS and comorbid ADHD performed poorly on the task, whereas the performance of participants with TS was similar to that of comparison controls. These results suggest that the comorbidities associated with TS may account for some of the neuropsychological deficits erroneously attributed to the disorder.

DIAGNOSTIC GUIDELINES

Clinical Assessment

Diagnosis of TS requires that the individual display multiple motor tics along with one or more vocal tics (APA, 2000). However, these multiple tics do not need to be present at the same time in order to warrant a diagnosis of TS. The diagnosis of TS can be complicated by the fact that tics tend to be characterized by changes in frequency and location across time, making assessment at any given time strongly dependent on the accuracy of the individual's report.

By DSM-IV-TR definition, TS has an onset before 18 years of age (see Table 7.1). Therefore, an adult presenting with a new-onset tic disorder should be carefully evaluated to determine alternative tic causes. Substance use (including stimulant medications) may cause tics to appear in a patient who does not have TS. Similarly, a medical condition (e.g., Huntington disease, postviral encephalitis) may be responsible for the onset of a tic disorder in an adult. Although adult onset of tics is unusual, it may also be associated with a more pathological course. Eapen, Lees, Lakke, Trimble, and Robertson (2002) reported case studies of eight patients with adult-onset tics. When compared to individuals with a developmental history of TS, these individuals had more severe symptoms, greater impairment, and poorer response to neuroleptic medication treatment.

When one is assessing an individual presenting with tics, it is important to note the type of tics, tic onset, and course of tics. The assessment of TS should also include measures of the frequency, intensity, onset, suddenness, and complexity of tics. Individuals may have differing abilities to inhibit tics in various settings, and this should be carefully assessed. Furthermore, certain conditions may exacerbate or attenuate tic symptoms, and this can be useful information in determining a diagnosis and treatment plan. For example, the following conditions may exacerbate tic symptoms in certain patients: use of decongestants, streptococcal infections, warmer weather, fatigue, and stress (Lombroso, Mack, Scahill, & King, 1991; Scahill, Ort, & Hardin, 1993). It may be helpful to present an individual with a list of motor and vocal tics, to help him or her identify less common or more complex tics (Leckman, Riddle, Hardin, & Ort, 1989). Many individuals are not aware that certain complex behaviors are in fact tics. It is also important to determine the degree to which the tics interfere with daily functioning.

TS can be quite difficult to measure, despite the overt manifestations of many tics. According to Goetz and Kompoliti (2001), this is due in part to the fact that a variety of tics may be present at any given time, and these tics may appear and disappear spontaneously. Furthermore, there are a multitude of factors to consider for each tic type, including frequency, intensity, complexity, suppressability, and interference. In addition, some individuals may be able to suppress tics, and certain conditions may suppress or elicit tics. Assessment of TS in adults may also be complicated by the fact that these individuals may be subject to inaccurate self-assessment, as noted earlier. In a study investigating 31 adults with documented childhood TS, 50% of those who considered themselves to be tic-free still had objective evidence of tics (Pappert et al., 2003). Conversely, those adults who reported experiencing continued tics did indeed show objective evidence of tic activity. The results of this investigation suggest that in-depth assessment, including observation and collateral reporting, may be needed in the case of a patient presenting with a childhood history of TS. In order to facilitate accurate assessment and diagnosis, a number of rating scales are available, including clinician rating scales, self-report rating scales, and videotape observation protocols.

Clinician Rating Scales

Clinician rating scales are designed to be completed by an experienced clinician following a structured interaction with the patient. The Shapiro Tourette's Syndrome Severity Scale (Shapiro & Shapiro, 1984) contains five factors: the degree to which the tics are noticeable to others; whether the tics elicit comments or curiosity; whether others consider the patient to be unusual or bizarre; whether the tics interfere with functioning; and whether the patient is incapacitated, homebound, or hospitalized because of the tics. The ratings on each of these five factors can be summed to yield a global severity score.

The Tourette's Syndrome Global Scale (Harcherik, Leckman, Detlor, & Cohen, 1984) is a multidimensional scale used to rate the frequency and disruption of simple and complex motor and phonic tics. The scale also provides a rating of associated symptoms (i.e., motoric restlessness, behavior problems, and school/work impairment). Adequate reliability and convergent validity data are available for this instrument.

The Yale Global Tic Severity Scale (Leckman et al., 1989) is completed by a clinician after a semistructured interview with the patient. The severity of motor and vocal tics are rated along five separate dimensions: number, frequency, intensity, complexity, and interference. A separate rating of impairment is also made; this specifically focuses on the tic disorder's impact on the patient's daily life, including self-perception, self-esteem, relationships with family and friends, and the individual's ability to perform in an occupational or academic setting. The scale has been used with both children and adults, and it has adequate construct, convergent, and discriminant validity.

Finally, the Tourette Syndrome Diagnostic Confidence Index (Robertson et al., 1999) is an instrument measuring the likelihood that an individual has or ever had TS in his or her lifetime.

Self-Report Scales

Self-report scales are designed to be completed either by the patient or by a caregiver or close family member. The most widely used self-report rating scales for TS are the Tourette Syndrome Questionnaire (TSQ; Jagger et al., 1982) and the Tourette Syndrome Symptom List (TSSL; Leckman, Towbin, Ort, & Cohen, 1988). The TSQ is a 35-page questionnaire that asks for detailed information about the patient's current condition and past history. The TSSL is a 29-item checklist that assesses behaviors in the following areas: motor tics, vocal tics, and other behaviors (e.g., compulsions). The Daily Record of Treatment (Shapiro, Shapiro, Young, & Feinberg, 1988) is used to monitor symptoms of TS during the course of treatment. The patient is asked to rate motor tics, vocal tics, other symptoms, medications, and adverse side effects each day throughout treatment.

Although these scales are useful for both clinical and research purposes, they do not provide normative data to aid in diagnosis. The Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey (MOVES; Gaffney, Sieg, & Hellings, 1994) is a self-report rating scale for TS that contains 16 items and five subscales: Motor Tics, Vocal Tics, Obsessions, Compulsions, and Associated Symptoms. The MOVES is significantly associated with a number of examiner rating scales and has good sensitivity and specificity data.

Videotaped Ratings

Patient videotaping is sometimes used in assessment procedures in order to obtain a more objective assessment of tic severity. Videotaping procedures vary, but can include conditions such as patient alone, patient with the examiner, patient taped through a one-way mirror, or patient engaged in a task (Kompoliti & Goetz, 1997). Goetz, Leurgans, and Chmura (2001) requested that patients videotape themselves in a variety of settings; they found that individuals had the highest tic scores when videotaped at home alone, and the lowest tic scores at work with an observer present. The investigators concluded that this finding is particularly significant, since it suggests that the actual rate of tic behaviors may be quite different from the rate observed in a clinical visit. As described earlier, Pappert and colleagues (2003) employed videotape data in a follow-up study of adults diagnosed

with childhood TS. They found that the types of data were important, given that tics are fleeting and may occur at the same time in different parts of the body.

Although studies have used a variety of videotape protocols, there is a standardized videotape protocol available. The Rush Video-Based Tic Rating Scale involves a 10-minute videotape rating of tic behaviors (Goetz, Pappert, Louis, Raman, & Leurgans, 1999). The protocol calls for two views (close and far) and two conditions (with and without an examiner). Five domains are scored, including number of body areas, frequency and severity of vocal tics, and frequency and severity of motor tics. The domains are combined to provide a measure of overall tic disability.

Differential Diagnosis

Tics associated with TS are known as "primary" tics, indicating that there is no identifiable cause. The diagnostic criteria for TS indicate that other tic causes, such as tics due to the direct physiological effects of a substance or to a general medical condition, must be excluded in order to assign a diagnosis of TS (APA, 2000). In addition to TS, many different disorders and factors are associated with tics, including infections, medications, toxins, developmental abnormalities, and chromosomal disorders (Jankovic, 2001). Tics may be confused with hyperkinetic movement disorders, including chorea (i.e., irregular, brief, jerky movements); dystonia (i.e., slow twisting movements interspersed with prolonged states of muscular tension); and myoclonus (i.e., brief, shock-like muscle contractions). Tics must also be distinguished from abnormal movements caused by such neurological disorders as Huntington disease, Wilson disease, Parkinson disease, multiple sclerosis, or traumatic head injury. Tics are further considered to be distinct from the stereotypic movements seen in autism spectrum disorders and in stereotypic movement disorders, since these stereotyped motor mannerisms are more rhythmic and intentional than those seen in tic disorders. The differential diagnosis between TS and OCD can be difficult, because a complex tic can be topologically similar to a compulsion, and because some patients with TS also have complex behavioral rituals that accompany the tics (Eapen, Robertson, Alsobrook, & Pauls, 1997). However, differential diagnosis is very important for guiding tic treatment in these cases.

When one is treating adults with movement disorders, it is particularly important to assess for a childhood history of tics or TS. Kulisevsky, Berthier, Avila, Gironell, and Escartin (1998) presented the cases of four adults who were being treated for psychiatric diagnoses and were referred for evaluation of "psychogenic tremor." Upon evaluation, it was discovered that all four patients had family histories of TS and personal histories of childhood tics. Furthermore, similar to patients with TS, they described somatic symptoms that they tried to alleviate through movement. None of the patients responded to placebo treatments, but all four responded to haloperidol.

Comorbidities

A diagnosis of TS is associated with a wide variety of comorbidities, including ADHD, OCD, and other psychiatric disorders. In fact, only about 12% of people with TS have no reported comorbidities (Freeman et al., 2000). Psychiatric comorbidities are common in individuals with TS (Hyde & Weinberger, 1995). However, it has been suggested that comorbidities may be overestimated in this population, because studies are likely to be

conducted with clinic-referred individuals, who in turn are more likely to suffer from complex symptomatology. OCD and ADHD are most commonly associated with TS, and these associations are reviewed in detail in the following sections.

Obsessive–Compulsive Disorder

The association between TS and OCD is well documented (Como, 1995; Miguel et al., 1995; Pauls, Alsobrook, Goodman, Rasmussen, & Leckman, 1995; Swedo & Leonard, 1994). Patients with TS are at greater risk for developing OCD than the general population. As individuals with TS approach adulthood, obsessive–compulsive symptoms often begin to emerge. Approximately 40% of patients with TS display obsessive–compulsive behaviors (Pauls et al., 1995). Similarly, patients with OCD may also suffer from tics, although they are not as likely to suffer from sensory tics as patients with TS (Chee & Sachdev, 1997). Pediatric patients diagnosed with OCD are at greater risk of developing TS than are their healthy peers (Leonard, Lenane, Swedo, & Rettew, 1992).

There is compelling evidence that some forms of OCD may be genetically related to TS (Eapen & Robertson, 2000). First, as noted above, there are increased rates of comorbidity between the two disorders. In addition, there is a greater rate of tic disorders in the families of patients with OCD (Pauls et al., 1995), as well as increased rates of obsessive–compulsive symptoms in families of patients with TS (Hanna, Janjua, Contant, & Jankovic, 1999).

Although there is now greater recognition of the high rates of obsessive–compulsive symptoms in TS, experts also are beginning to identify differences in symptomatology in patients diagnosed with primary TS. Specifically, there is evidence that the type of obsessive–compulsive symptomatology observed in patients with primary TS differs from that seen in patients with primary OCD (Eapen et al., 1997). The obsessions seen in TS are more likely to be violent and sexual than those seen in OCD alone (Eapen et al., 1997; Zohar et al., 1997). There are also differences in the compulsions typically noted in TS. Eapen and colleagues (1997) found that symmetry (making things even), saying or doing things "just right," and touching compulsions were more prevalent compulsions in TS than in OCD. Zohar and colleagues (1997) found more harm avoidance compulsions in patients with TS than in those with OCD alone. Finally, patients who are comorbid for TS and OCD are more aggressive and evidence more self-damaging compulsions than those with OCD alone (George, Trimble, Ring, & Sallee, 1993).

In addition to differences in the types of obsessions and compulsions noted in the two disorders, the phenomena that precede tics and/or compulsions differ in patients with TS plus OCD and patients with OCD only. Miguel and colleagues (1995) demonstrated that symptoms of OCD are preceded by cognitive phenomena (ideas, thoughts, or images), while tics are preceded primarily by sensory phenomena. Similarly, Miguel, Baer, Coffey, and Rauch (1997) reported that patients with TS had more sensory phenomena and fewer cognitions prior to their tics than did patients with OCD alone.

Attention-Deficit/Hyperactivity Disorder

ADHD has been reported in many patients with TS and may be the most common comorbidity in TS (Freeman, 1997; Robertson, 2000). According to a review by Robertson (2000), ADHD occurs in from 21% to 90% of clinic populations of individuals with TS, depending on the population being studied. Eapen and Robertson (1996) found that 40% of patients with TS had comorbid ADHD.

The presence of comorbid ADHD in individuals with TS may be associated with poorer outcome in these patients. After reviewing the available literature, King and Scahill (2001) concluded that TS plus ADHD may be particularly problematic in terms of increased vulnerability to other conditions such as OCD, other anxiety disorders, and mood disorders. For example, Carter and colleagues (2000) found that children with TS plus ADHD had more behavior problems and poorer adaptation than those with TS alone and comparison controls. This relationship may be quite complex. Peterson, Pine, Cohen, and Brook (2001) followed longitudinally a large sample of children diagnosed with TS into adulthood. Findings revealed that childhood tics were predictive of OCD symptoms in late adolescence and early adulthood. Similarly, ADHD symptoms in adolescence predicted OCD symptoms in early adulthood. The converse relationship was also true: OCD symptoms in adolescence predicted OCD symptoms in early adulthood. Interestingly, tics alone did not predict ADHD symptoms in prospective analyses.

The rate of attentional problems is greater in families of individuals with TS than in the general population (Knell & Comings, 1993). In fact, the association has been so strong that some researchers have suggested that there could be a genetic relationship between TS and ADHD (Comings, 2001). However, it is also possible that the high rate of comorbidity between the two disorders may not be due to a genetic relationship. First, the stimulant medications that are often used to manage symptoms of ADHD can cause or exacerbate tics. This may increase the probability that patients with ADHD will be diagnosed with TS. Second, because of the deleterious influence of tics on cognitive and motoric functioning, attention and impulse control may be difficult to assess accurately in this population. Finally, Comings (1995) has argued that both ADHD and TS are associated with a range of behavioral problems, and that both disorders are associated with a high frequency of externalizing behavioral disorders in relatives.

Other Comorbidities

A number of other disorders have been linked to TS, including mood disorders, anxiety disorders other than OCD, personality disorders, and learning disorders (Robertson, 2000). Disruptive behaviors and self-injurious behaviors have also been associated with TS. Among children with TS, a syndrome of episodic rage has been reported in approximately 25–70% of patients (Budman, Rockmore, Stokes, & Sossin, 2003). Similarly, approximately one-third of patients with TS display self-injurious behavior, including head banging, scratching, slapping, punching, or eye gouging (Robertson, Trimble, & Lees, 1989). In a study investigating personality disorders in adults with TS, Robertson, Banerjee, Hiley, and Tannock (1997) found that nearly two-thirds of individual with TS met criteria for a personality disorder, compared to 6% of control participants. Furthermore, patients with TS were more likely than comparison controls to have more than one personality disorder. In a follow-up study of adults who were diagnosed with TS as children, Pappert and colleagues (2003) found that about one-fourth of their sample was disabled and suffered from significant problems, including alcohol abuse, unemployment, and problems with the law. The remaining three-quarters of the sample were reported to be functioning quite well.

The nature of the relationship between TS and associated psychiatric syndromes such as anxiety and depression is controversial (King & Scahill, 2001). For example, Spencer and colleagues (1998) conducted a large-scale study of children with and without TS and found that associations with other disorders may actually be accounted for by comorbidity with ADHD, rather than by TS itself (Spencer et al., 1998). In addition, King and Scahill (2001) argue that studies conducted with clinical samples are biased toward finding high

rates of comorbidity, since those with more severe symptomatology may be more likely to seek or attract clinical attention; they also contend that the type of clinical setting (OCD clinic vs. ADHD clinic) may affect the type of patients likely to be included in the sample. Kurlan and colleagues (2002) conducted a large community-based study to avoid the problems associated with clinic-referred populations. They found that in a non-clinic-referred population of over 300 children with tics, rates of several disorders were elevated, including OCD (as well as other anxiety disorders), ADHD, mood disorders, and oppositional defiant disorder. After a careful review of the literature, King and Scahill concluded that, unlike the close relationship between TS and OCD, the relationships between TS and other anxiety disorders and between TS and mood disorders are less distinct. They have posited that these difficulties may reflect biological vulnerability, as well as interpersonal and experiential factors.

Despite the reports of high rates of psychiatric conditions among patients with TS, there is no evidence of increased rates of TS in inpatient adult psychiatry settings (Eapen, Laker, Anfield, Dobbs, & Robertson, 2001). The results of this study suggest that whereas individuals with TS are at increased risk for comorbid psychiatric disorders, individuals with other psychiatric disorders are not at increased risk for TS.

TREATMENT

Treatment of patients with TS can be challenging, given the heterogeneity of tic symptoms, as well as the complexity of such associated symptoms as attentional problems and obsessive–compulsive behaviors. Patients often require multidisciplinary treatment approaches, including pharmacological treatment, behavior therapy, and (in some cases) surgical intervention (Babel, Nemeth, Gadoros, & Bihari, 2003).

Psychopharmacological Interventions

Psychopharmocological interventions are the most commonly employed treatments for patients with TS (Piacentini & Chang, 2001). In a retrospective study of treatment outcomes among adults with TS, findings revealed that more than four-fifths of patients achieved control of symptoms with medication management (Mesulam & Petersen, 1987). Most studies investigating pharmacotherapy for TS have employed children and adolescents as participants. Therefore, although results are expected to generalize to adult populations, further research will be needed to validate many treatments for adults with TS. According to Sandor (2003), clonidine (an agent previously used to control hypertension) is often the first line of treatment for TS, given its minimal adverse side effects and its efficacy in addressing the symptoms of ADHD that are often comborbid with TS. A failed trial of clonidine is often followed by a low dose of a neuroleptic agent (Sandor, 2003). Other treatments are used when these agents are not successful or when adverse side effects are intolerable. The major pharmacological treatment approaches are reviewed below.

Neuroleptic Agents

The most common medications employed for the management of TS are the antipsychotic neuroleptic agents. For example, haloperidol may be effective in suppressing tics in 70–80% of patients (Lang, 2001). Unfortunately, the adverse side effects may make this medi-

cation difficult for many patients to tolerate. Short-term adverse side effects may include mood problems and sedation. More serious side effects include extrapyramidal effects, such as dystonic reactions (e.g., stiffening of neck, eyes rolled back under lids), parkinsonian effects (e.g., drooling, tremors, lack of arm swing), akathisia (motor restlessness and pacing), akinesia (diminished gestures, movement, and speech), cardiovascular reactions, seizures, and neuroleptic malignant syndrome (a rare and life-threatening condition characterized by hyperthermia and parkinsonian symptoms). Pimozide has been demonstrated to be more effective than haloperidol in the managment of tics (Sallee, Nesbitt, Jackson, Sine, & Sethuraman, 1997). More importantly, it also has been shown to be better tolerated than haloperidol (Sallee et al., 1997).

Because of the adverse effects associated with the older antipsychotic agents, there has been an increased focus on the newer atypical neuroleptics (e.g., clozapine, sulpiride, olanzapine, and risperidone) for the management of tics. Risperidone was compared to clonidine in a double-blind trial with children and adolescents (Gaffney et al., 2002). Results indicated that both pharmacotherapies were equally effective in reducing tic severity. Two recent randomized, double-blind, placebo-controlled trials of risperidone have also demonstrated its efficacy in TS management. One investigation was conducted with children and adults (Scahill, Leckman, Schultz, Katsovich, & Peterson, 2003), and the other with adolescents and adults (Dion, Annable, Sandor, & Chouinard, 2002); both studies demonstrated excellent reduction in tic severity with risperidone. There is also emerging evidence to support the efficacy of olanzapine, zisprasidone, and quetiapine in the treatment of patients with TS, although the research supporting the efficacy with these agents is still limited (Sandor, 2003). Onofrj, Paci, D'Andreamatteo, and Toma (2000) conducted a double-blind crossover investigation of olanzapine versus pimozide with four adults with severe TS. Although both agents were found to be effective in managing symptoms of TS, all four patients opted for continued olanzapine treatment following the conclusion of the study, due to the milder adverse side effects experienced with this agent.

Treatment of Comorbidities

In addition to their use in the treatment of tics, psychopharmacological interventions are often used to manage the symptoms of ADHD and OCD that frequently accompany TS (Kwak & Jankovic, 2000). Symptoms of ADHD are often managed with stimulant medications such as methylphenidate. Unfortunately, stimulant medications can induce tics in patients without TS (Varley, Vincent, Varley, & Calderon, 2001), making this treatment approach somewhat risky for patients with TS. Research suggests that methylphenidate can be an effective treatment for symptoms of ADHD in patients with ADHD and TS, although these treatment gains have been associated with measurable (albeit small) increases in tic frequency (Gadow, Nolan, Sprafkin, & Sverd, 1995).

As noted above, clonidine, a medication traditionally used to manage hypertension, has been used successfully in the management of TS. A recent investigation has demonstrated the efficacy of combining clonidine with methylphenidate for children with ADHD and TS (Tourette's Syndrome Study, 2002). Although both pharmacotherapies were found to decrease tic severity, the combined treatment had the best effect on lessening tic severity and helping with symptoms of impulsivity, hyperactivity, and inattention. Importantly, this trial did not reveal worsening of tics with methylphenidate treatment. However, there have been case examples of tic exacerbation with clonidine treatment (Kessler, 2001). Desiprimine (a tricyclic antidepressent) has also been demonstrated to reduce tics and symptoms of ADHD in children and adolescents with comorbid chronic tic disorders and ADHD

(Spencer et al., 2002). Clonidine tends to have few adverse side effects and is often a first-line treatment for both children and adults with TS (Sandor, 2003). An alternative treatment to clonidine is guanfacine, another medication often used to manage hypertension. This medication may be associated with fewer adverse side effects than clonidine, and a double-blind, placebo-controlled study has supported its efficacy in managing tics and symptoms of ADHD in children with TS and ADHD (Scahill et al., 2001). A direct comparison between clonidine and guanfacine has not been conducted. In a randomized, placebo-controlled study of pergolide, a dopaminergic agonist, this medication was found to be effective in managing tics in children (Gilbert et al., 2003). Furthermore, this agent was also helpful in improving symptoms of ADHD.

Patients with TS may also present with obsessive–compulsive symptoms that may require separate medication managment. Selective serotonin reuptake inhibitors (SSRIs; fluoxetine, paroxetine, sertraline, fluvoxetine, and citalopram) have been used with success to manage obsessive–compulsive symptoms in patients with TS (Kwak & Jankovic, 2000). In an investigation with both children and adults with comorbid TS and obsessive–compulsive behaviors, fluoxetine was shown to decrease the obsessive–compulsive behaviors (Eapen, Trimble, & Robertson, 1996). It has been suggested that SSRIs may also be useful in decreasing tics in some patients by decreasing the obsessions that trigger the tics (Kwak & Jankovic, 2000). However, it has been documented that the presence of tics may predict a less favorable response to SSRIs, although the evidence for this finding has received mixed support (Miguel, Shavitt, Ferrao, Brotto, & Diniz, 2003).

Alternative Treatments

Alternative and largely experimental treatments for tics have also demonstrated some evidence for efficacy; these treatments include marijuana (tetrahydrocannabinol, or THC) and nicotine. In a randomized, double-blind, placebo-controlled study of THC, the agent was shown to be effective in treating tics in a group of adults with TS (Mueller-Vahl, Schneider, et al., 2003). Importantly, it has been documented that adults with TS can be maintained on THC treatment without deleterious effects on neuropsychological performance (Mueller-Vahl, Prevedel, et al., 2003). Transdermal nicotine patches have also been reported to be helpful in controlling symptoms of TS. In one study, nicotine patches were demonstrated to be superior to placebo patches in reducing symptoms in patients who were already receiving haloperidol (Silver et al., 2001). Unfortunately, adverse side effects (including nausea and vomiting) make this treatment of limited utility for many patients. However, Silver and colleagues (2001) suggest that nicotine may be useful on an as-needed treatment for patients who desire short-term management of tic symptoms.

Nonpharmacological Interventions

The most promising nonpharmacological treatments for TS are behavioral approaches. In practice, behavioral management is most frequently used in conjunction with medication or when medication management has failed (Piacentini & Chang, 2001). In addition, some patients experience unacceptable adverse effects from medications or have concerns regarding long-term medication maintenance and seek behavioral intervention. Behavioral treatment approaches for TS include massed negative practice, contingency management, relaxation training, self-monitoring, and habit reversal. Although promising research exists regarding the short-term efficacy of many of these interventions, future research will

need to focus on the long-term effects of these treatments. Furthermore, because these treatment approaches are often offered to patients in a "package" format, it will also be important to determine what the most efficacious treatment packages and combinations should include.

Massed negative practice is one of the first behavioral treatments employed for TS. The treatment involves asking the patient to perform a tic voluntarily and rapidly in a repetitive manner for an extended time period (e.g., 30 minutes). The patient is sometimes asked to perform the tic for brief periods interspaced with brief periods of rest (Peterson, Campise, & Azrin, 1994). In theory, the patient is expected to experience fatigue, which eventually will lead to a decreased ability to produce the tic voluntarily. After reviewing the literature, Piacentini and Chang (2001) have concluded that there is no theoretical support for this procedure, and that the treatment itself has limited empirical validity for its efficacy.

Contingency management treatment approaches are based on the theory of operant conditioning. The treatment approach consists of manipulating environmental contingencies to reinforce the absence of tics and to punish tic behaviors. For example, functional behavior assessment methodology has been used to identify the function of tic behavior and to design individualized treatment plans (Roane, Piazza, Cercone, & Grados, 2002). Research suggests that in some cases, tics are indeed affected by environmental contingencies such as positive reinforcement, and that they can be maintained by automatic reinforcement (either by a positive sensation or by the alleviation of negative sensation). Once the behavioral function is identified, a treatment plan can be devised. In its simplest form (i.e., reinforcement for the absence of tic behaviors), contingency management is often included in multicomponent treatment packages (Peterson et al., 1994).

Relaxation training has been employed to reduce anxiety in patients with TS. Tic severity in TS may be related to a patient's level of anxiety or emotional distress following stressful life events (Silva, Munoz, Barickman, & Friedhoff, 1995). Silva and colleagues (1995) identified 17 environmental factors associated with increases in tic symptoms. Although anxiety was the most common factor, other factors included being fatigued, attending social gatherings, being alone for an extended period of time, and watching television. For some patients, a negative cycle is created in childhood when adults try to eliminate tics through punishment or humiliation, resulting in increased anxiety and concomitant tic severity (Shapiro & Shapiro, 1988). As the result of these findings, researchers have attempted to decrease tics by decreasing anxiety through relaxation training. Relaxation training often includes instruction in deep breathing, progressive muscle relaxation, and guided imagery in order to teach the patient to decrease stress. A number of studies have found reductions in tic frequency during relaxation training procedures (Peterson & Azrin, 1992). However, these effects often do not last following the cessation of therapy (Piacentini & Chang, 2001). Bergin, Waranch, Brown, Carson, and Singer (1998) conducted a controlled trial of relaxation training, using a double-blind methodology. The treatment group did not differ from the control group in terms of tic symptomatology at the end of treatment and at 3-month follow-up.

Self-monitoring is often used alone or in combination with other techniques to develop the patient's awareness of the tic behaviors. Self-monitoring strategies include providing the patient with visual feedback (e.g., review of videotape) and teaching the patient to record tics (e.g., through use of a counter or data sheet). It has been hypothesized that increased awareness of tics through self-monitoring can lead directly to a reduction in tic behaviors (Azrin & Peterson, 1988). Azrin and Peterson (1988) reported a 44% reduction in tic frequency following a self-monitoring procedure.

Habit reversal is a treatment technique developed specifically for the management of tics and such problem habits as skin picking and nail biting (Azrin & Nunn, 1973). Habit reversal treatment involves teaching the client to engage in a competing motor response following the urge to engage in the tic (Peterson & Azrin, 1993). A competing response might include the conscious tensing of specific muscles that are counter to the individual's motor tic. The opposing muscles are contracted for 1–2 minutes contingent on the emission of the tic or on the urge to engage in the tic. For example, a man with an arm jerk might push his hand down against his thigh contingent upon the urge to jerk the arm. A woman with a vocal tic might be taught to breathe deeply through her nose contingent upon the urge to engage in the tic. For habit reversal to be effective, individuals may require awareness training to become aware of, recognize, and label their premonitory sensory phenomena (Banaschewski et al., 2003). The treatment typically consists of awareness training, competing-response training, and motivational components (Piacentini & Chang, 2001). In a review of the literature, Peterson and colleagues (1994) found strong empirical support for this treatment; these authors concluded that habit reversal can lead to reductions in tic frequency of up to 80–90%, making this intervention one of the most promising treatments for individuals with TS.

Exposure-based treatments have been employed successfully to treat patients with OCD. In traditional exposure plus response prevention for OCD treatment, the individuals are exposed to fears and are not permitted to engage in compensatory compulsions. For example, a woman with a cleanliness obsession might be asked to put her hand in a toilet and would not be permitted to wash her hands following immersion in the toilet. This treatment approach has been very successful for patients with OCD (Neziroglu, Hsia, & Yaryura-Tobias, 2000). This treatment has been applied to patients with TS by having patients resist the urge to engage in a tic when they are experiencing premonitory sensory phenomena, so that they are exposed to these phenomena without engaging in the tic (Hoogduin, Verdellen, & Cath, 1997). Only one report regarding the efficacy of this behavioral procedure has been published, and this report involved the treatment of three adults and one child (Hoogduin et al., 1997). Three out of the four patients in this investigation did habituate to the premonitory sensations during treatment, suggesting that this is a viable treatment option and warrants further investigation.

There is evidence to suggest that combined treatment approaches may be particularly effective for patients with TS. O'Connor and colleagues (2001) conducted an evaluation of a 4-month treatment program for patients with tic and/or habit disorders. The treatment approach included habit reversal training along with awareness training, relaxation, and cognitive restructuring. Of patients who completed treatment, 65% had an excellent initial response (more than 75% control over tics), and 52% continued to have an excellent response at the 2-year follow-up. Importantly, patients also showed significant reductions in symptoms of anxiety and depression following treatment.

Surgical Interventions

For patients whose symptoms do not improve with either behavior therapy or pharmacotherapy, a surgical treatment option may be considered. These options include surgical ablation procedures and deep brain stimulation (DBS). A variety of surgical options have been attempted to manage symptoms of TS, including ablation procedures targeting the frontal lobe, the limibic system, the thalamus, and the cerebellum (Temel & Visser-Vandewalle, 2003). In a review of the literature, Temel and Visser-Vandewalle (2003)

reviewed reports of about 65 clients who have been treated surgically for TS. Unfortunately, they found that the results of these surgical options have been largely unsatisfactory or have led to very serious adverse side effects (e.g., hemiplegia). Serious concerns are raised regarding the poor localization of ablation and the lack of a rationale for chosen targets.

DBS is a new, nonablative surgical procedure in which electrodes are placed in an area of the patient's brain that is thought to be associated with the target symptoms. These electrodes can then be activated to block activity in that part of the brain. The procedure has been used with success in patients with multiple sclerosis, Parkinson disease, and seizure disorders. There are three documented cases of patients who have undergone DBS targeting the thalamus bilaterally to treat symptoms of TS (Temel & Visser-Vandewalle, 2003). All three cases had relatively positive outcomes. Temel and Visser-Vandewalle (2003) conclude that this procedure is "promising" and warrants further investigation.

SUMMARY AND CONCLUSIONS

Scientific knowledge about and understanding of TS have expanded significantly in the past two decades. Once believed to be rare, the disorder is now known to affect about 1% of individuals (Robertson, 2003). Furthermore, it is now recognized that the syndrome exists on a continuum that ranges from mild and uncomplicated to very severe. Research on the etiology of TS has been expanding rapidly. There is now compelling evidence to support the role of genetic factors in the pathogenesis of the disorder. Although a specific gene has not yet been identified, recent research findings suggest that such a gene or combination of genes may be implicated in the disorder in the near future. Moreover, there is now evidence that a broader TS phenotype (which may include tics as well as symptoms of OCD and ADHD) exists among families of patients with TS. The neurobiological bases of TS are beginning to be better understood through the use of advanced imaging technology. There is evidence of both structural and functional neurological abnormalities in individuals with TS. Finally, there is growing evidence for the possible role of various environmental associations in some cases of TS, including birth complications and autoimmune factors. Future research will probably continue to focus on the association of TS with such disorders as OCD and ADHD, in order to better clarify the mechanisms at work in these disorders.

In the area of treatment, a growing arsenal of pharmacological treatments is available for the management of the disorder, including clonidine and various neuroleptic agents. Advances have also been made in the management of such comorbid conditions as ADHD and OCD. There are several promising behavioral treatments for TS as well, including habit reversal and exposure based treatments. Perhaps most exciting are multimodal therapies that include both pharmacological and behavioral components. These "package" treatments may allow for better management of symptoms, along with more moderate doses of medication.

Much of the research regarding TS thus far has focused on children. This is due in part to the lower incidence of the active disorder among adults (Bruun & Budman, 1997). However, adults represent a significant group of patients where greater research efforts with TS are needed. For a minority of patients, symptoms of TS can be extremely severe in adulthood and can include comorbid obsessions and compulsions. In addition, it appears that the disorder may be more common among adults than was once believed. As noted earlier, Pappert and colleagues (2003) found that 90% of people who had been diagnosed

with TS as children continued to demonstrate evidence of tic behaviors on videotapes, despite the fact that most of these patients denied active symptoms. Future research will need to focus on developmental changes associated with TS, as well as on specific treatment strategies for both children and adults that may enhance their quality of life.

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8

ANXIETY DISORDERS

ALICIA E. MEURET
STEFAN G. HOFMANN

Anxiety disorders are among the most commonly encountered mental illnesses in clinical practice, with about 13% of the adult U.S. population affected by them. The economic burden is considerable—approximately $40 billion in annual costs in the United States in the 1990s (Greenberg et al., 1999). Substantial progress has been made in the treatment of these disorders in recent years, however. In this chapter, we give an overview of anxiety diagnoses and introduce elements of a definition of anxiety. We then outline a current model of the disorders' development, and review neurobiological research on anxiety and fear. Finally, we present current evidence on treatment approaches for anxiety disorders, including pharmacological treatments.

DIAGNOSES

The formal nomenclature of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR; American Psychiatric Association, 2000) lists 12 anxiety disorder categories: panic disorder with agoraphobia, agoraphobia without a history of panic disorder, social phobia, specific phobia, generalized anxiety disorder (GAD), obsessive–compulsive disorder (OCD), posttraumatic stress disorder (PTSD), acute stress disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder, and anxiety disorder not otherwise specified. Epidemiological studies of adult community samples (e.g., Kessler et al., 1994) indicate that anxiety disorders are among the most commonly occurring forms of psychological disturbances.

Panic disorder with or without agoraphobia is characterized by unexpected and recurring panic attacks, followed by persisting concern about having additional attacks or their consequences. The attacks can lead to significant changes in behavior (agoraphobia), such as avoiding places and situations, or physical sensations. Sufferers experience a wide array of physical sensations during panic attacks, such as shortness of breath, heart palpitations, and dizziness. These are often accompanied by cognitive misappraisals, such as the fear of losing control, fainting, or having a heart attack. Individuals with agoraphobia without a history of panic disorder fear that they will be unable to escape or

get help in the event that they develop certain symptoms (e.g., dizziness, diarrhea) in a variety of situations (e.g., shopping, crowds). The lifetime prevalence rate of panic disorder with or without agoraphobia is between 1% and 2%. The disorder without agoraphobia is diagnosed twice as often in women as in men. Panic disorder with agoraphobia is approximately three times as common in women as in men.

Social phobia (social anxiety disorder) is characterized by excessive fear, self-consciousness, and avoidance of social situations due to the possibility of embarrassment or humiliation. Whereas some individuals with social phobia fear mostly performance-oriented situations, such as public speaking, others show a more generalized fear of interacting socially. Panic attacks with marked physical symptoms can occur during exposure to the feared situation. Social phobia is the most common of all anxiety disorders and the third most common mental disorder. Recent epidemiological studies estimate that the lifetime prevalence rate of social phobia may be as high as 13%. Although epidemiological studies suggest that social phobia is more common in women than in men, in most clinical samples the sexes are equally represented or the majority is male.

Specific phobia is characterized by intense and persisting fear cued by the presence or anticipation of a clearly discernible and circumscribed object or condition, such as certain situations, animals, blood/injection/injury, natural environmental events (e.g., thunder), or other stimuli (e.g., vomiting, contracting an illness, etc.). Although adults with such phobias often realize that these fears are irrational, confrontation often triggers panic or severe anxiety. Estimates of the lifetime prevalence rates range between 7.2% and 11.3%. Depending on the specific phobia subtypes, the gender ratio varies, but the disorder is typically more common in men than in women.

Prolonged, uncontrollable, and excessive worry and tension about multiple life circumstances (health, money, family, or work) are key features of GAD. Physical symptoms, such as muscle tension, are also prominent features. However, unlike in panic disorder, physiological arousal in GAD is reduced when individuals are confronted with threatening, worry-related stimuli. Unlike people with other anxiety disorders, people with GAD rarely avoid any particular situations. The lifetime prevalence rate is 5%, and GAD affects twice as many women as men.

The cardinal symptoms of OCD are recurring, intrusive thoughts, images, or impulses (obsessions), followed by repeated behaviors or mental acts aimed at reducing distress (compulsions). Although the disease causes severe life interference due to its time-consuming nature, sufferers generally recognize their obsessions as products of their own minds, in contrast to the delusional thoughts of persons with psychotic disorders. The lifetime prevalence rate of the disorder is between 1% and 2.3%, and it affects men and women in approximately equal numbers.

Whereas acute stress disorder is a short-term response to extreme stress (duration less than 1 month), the core features of PTSD are persistent, frightening thoughts and memories following exposure to a traumatic event during which individuals experience intense fear, horror, or helplessness. Sleep problems, feelings of detachment or numbness, or being easily startled are common symptoms. In U.S. community-based studies, the lifetime prevalence rate of PTSD is about 8%. Women are more likely than men to develop the disorder.

Anxiety disorders are highly comorbid, as suggested by a large study on clinic outpatients (Brown, Campbell, Lehman, Grisham, & Mancill, 2001). Based on clinical interviews of 1,127 individuals to assess for DSM-IV diagnoses, Brown and colleagues (2001) reported that 55% of patients with a principal anxiety or mood disorder had at least one additional anxiety or depressive disorder at the time of the assessment. When lifetime

diagnoses were examined, this rate increased to 76%. The principal diagnoses of PTSD, major depression, dysthymia, and GAD had the highest comorbidity rates, whereas specific phobia showed the lowest comorbidity rate. The presence of social phobia or specific phobia was associated with a decreased likelihood of panic disorder with agoraphobia, and vice versa. These latter findings may be a result of the hierarchical rules for differential diagnoses in the DSM-IV (and now the DSM-IV-TR).

TERMINOLOGY

Before we review the contemporary literature on anxiety disorders, it is necessary to define a number of related terms, especially "anxiety" and "fear." Anxiety is a future-oriented mood state that prepares the organism for an anticipated negative event. In contrast, fear is a short-lived and abrupt emotional response to imminent threat. Episodes of intense fear can therefore be viewed as alarm responses to perceived danger. Anxiety disorders associated with maladaptive cognitions contribute to so-called "false alarms," because the alarm reaction occurs in the absence of actual danger cues. Anxiety, fear, false alarms, and maladaptive cognitions are all intimately linked with the general diathesis–stress model of anxiety disorders. These concepts and some related ideas are briefly defined below. At a later point during our discussion, we present Barlow's (2002) triple-vulnerability model of anxiety disorders—an elaboration of the general diathesis–stress model.

Anxiety, Fear, and Panic

The DSM-IV-TR (APA, 2000) defines anxiety as "the apprehensive anticipation of future danger or misfortune accompanied by a feeling of dysphoria or somatic symptoms of tension" (p. 820). No separate definition is given for fear, but the term is included in the many definitions of the DSM-IV-TR anxiety disorders. For example, the diagnostic manual defines specific phobia as the "marked and persistent fear of clearly discernible, circumscribed objects or situations" (p. 443), and social phobia as a "marked and persistent fear of social or performance situations in which embarrassment may occur" (p. 450). In earlier editions of the DSM, panic attacks were defined as discrete periods of intense fear (or discomfort) unique to the diagnosis of panic disorder. In DSM-IV and DSM-IV-TR, however, it has been assumed that panic attacks can occur in the context of several different anxiety disorders, such as specific phobias or social phobia.

The creation of these DSM anxiety disorder categories was partly the result of studies that were aimed at distinguishing two types of anxiety disorders, based on patients' pharmacological treatment responses (Klein, 1964; Klein & Fink, 1962). Specifically, Klein and his colleagues observed that imipramine, an antidepressant, was effective for spontaneous panic attacks, but not against chronic and anticipatory anxiety. Klein concluded that panic and anticipatory anxiety reflect two qualitatively different underlying biological processes.

Throughout the history of psychology, the concepts of fear and anxiety have occupied a central role in various models of psychopathology. Early versions of the psychoanalytic theory assumed that an accumulation of sexual tension constitutes the specific etiology of anxiety neuroses; indeed, such tension was believed to be at the root of most, if not all, psychopathologies (Breuer & Freud, 1895/1976). In this early formulation, Freud did not

distinguish between fear and anxiety. Later, however, Freud defined "anxiety" (*Angst*) as the vague state of apprehension without an identifiable object that serves the function of signaling the presence of potential threat or danger (Freud, 1926/1959). When anxiety has an object, Freud referred to it as "fear" (*Furcht*). Freud's assumption that fear and anxiety can be distinguished based on the presence versus absence of external triggers is still represented in contemporary definitions of these two terms. In addition, it is assumed that anxiety, as opposed to fear, is either a blend of different emotions or a diffuse network of affective memory that is associated with future-oriented responses, serving the adaptive purpose of preparation to potential danger (e.g., Barlow, 2002; Izard, 1992; Lang, 1985).

In contrast to fear, anxiety is conceptualized as a cognitive association or elaboration that connects basic emotions (such as fear) to events, meanings, and responses (Izard, 1992). As compared to basic emotions, cognitive associations are less "hard-wired" and show considerable variations between different individuals and situations. Many contemporary emotion researchers view anxiety as a diffuse cognitive–affective structure that is associated with a high level of negative affect, perception of uncontrollability and unpredictability of aversive events, and maladaptive shifts in attention (e.g., Barlow, 2002).

MODELS OF ETIOLOGY AND MAINTENANCE

False Alarms, True Alarms, and Learned Alarms

In his influential model of anxiety, Barlow (2002) emphasizes the role of panic attacks in the etiology and maintenance of anxiety disorders. Based on a comprehensive review of the literature, Barlow concludes that there is no indication that panic attacks are qualitatively different from episodes of intense fear. Similarly, there is no evidence to suggest any functional neurobiological differences between patients with panic disorder and individuals without panic. In fact, panic attacks are not unique to any particular group of anxiety disorders and are commonly found in the general population. The only distinguishing feature between clinical and nonclinical panic appears to be that nonclinical panic is less intense and less frequent than the attacks reported by individuals with panic disorder. Because these attacks appear to be an expression of the body's fight-or-flight response system in the absence of any actual danger, Barlow refers to them as "false alarms." False alarms that are associated with neutral objects or conditioned stimuli can become "learned alarms." If alarms occur in the presence of actual danger, they are referred to as "true alarms."

These three forms of alarms constitute different pathways for the etiology of panic and phobias. For example, some individuals who experience a false alarm followed by the development of anxious apprehension over the next panic attack may develop panic disorder, given the presence of specific vulnerabilities. Other people may experience true alarms and consequently develop PTSD, or experience learned alarms and subsequently develop specific phobias. Other anxiety disorders, such as OCD and social phobia, may reflect a combination of the occurrence of false alarms, true alarms, and learned alarms and the development of anxious apprehension. For example, a person with social phobia may experience a false alarm in social and evaluative situations following a stressful event. As a result, this person then focuses attention inward (on the anxiety response, as well as on other possible threatening aspects of the situations); this further perpetuates anxious apprehension and thereby increases the likelihood of developing panic attacks in social situations. Similarly, individuals with OCD may focus their anxiety on intrusive, unacceptable thoughts that may themselves trigger panic attacks.

Maladaptive Cognitions

In the contemporary view, cognitions, or thought processes, are thought to play a crucial role in the maintenance and development of the anxiety response.

Although maladaptive cognitions are not always considered central defining features of each of the anxiety disorders, cognitive processes (e.g., attributions, predictions) are typically seen as essential to the development of these disorders. For example, in the case of panic disorder, the cognitive model (e.g., Clark, 1986) assumes that panic attacks result from the catastrophic misinterpretation of certain bodily sensations (palpitations, breathlessness, dizziness, etc.). An example of such a catastrophic misinterpretation would be a healthy individual's perceiving palpitation as evidence of an impending heart attack. The vicious cycle of the cognitive model suggests that various external stimuli (i.e., the feeling of being trapped in a supermarket) or internal stimuli (i.e., body sensations, thoughts, or images) trigger a state of apprehension if these stimuli are perceived as threatening. It is assumed that this state is accompanied by fearful bodily sensations, which, if interpreted in a catastrophic fashion, further increase the apprehension and the intensity of bodily sensations. This model further states that the attacks appear to come from "out of the blue," because patients fail to distinguish between the triggering body sensations and the subsequent panic attack on the one hand, and the general beliefs about the meaning of an attack on the other. Similar negative predictions are common in individuals with other anxiety disorders. In cases of social phobia, for example, the focus is usually placed upon the consequence of public scrutiny and subsequent negative evaluation ("Nobody is going to like me," "I'm going to make a fool of myself").

Although some of the cognitions typically associated with each diagnosis may be disorder-specific, there are also a number of commonalities among cognitions across the anxiety disorders. First, the maladaptive cognitions associated with the anxiety disorders tend to be future-oriented perceptions of danger or threat (e.g., what is about to happen). This sense of danger may involve either physical threat (e.g., having a heart attack) or psychological threat (e.g., anxiety focused on embarrassment). In addition, these cognitions tend to focus upon a sense of uncontrollability over the situation or symptoms of anxiety. Another hallmark of anxious cognitions is that they tend to be automatic or habitual, such that a person puts no effort into conjuring up such thoughts. Instead, they occur instantaneously and sometimes in response to subtle cues. Often, a feeling of anxiety is accompanied by hypervigilance or scanning of the environment to determine any potential sources of threat. Given that the anxious responses typical of persons with anxiety disorders tend to be unrealistic in the absence of any actual external dangers, individuals tend to search inward to explain the reason for their distress ("I am going to be ill," "I am not performing well"). This often results in inaccurate assessments of the cause of their anxiety, as well as their ability to cope with the situations they are facing.

THE TRIPLE-VULNERABILITY MODEL

Barlow (2002) distinguishes among three sets of vulnerability factors that determine whether false alarms (or true alarms and learned alarms) will lead to a clinical disorder or not. These vulnerability factors are (1) generalized biological vulnerability (genetic and neurobiological contributions); (2) generalized psychological vulnerability (perception of diminished control); and (3) specific psychological vulnerability. We discuss next the most relevant re-

search studies within the framework of Barlow's triple-vulnerability model, with a particular emphasis in a later section on the neurobiological contribution.

Generalized Biological Vulnerability

Familial aggregations are typically found for all anxiety disorders. For example, Merikangas, Avenevoli, Dierker, and Grillon (1999) found that the offspring of parents with anxiety disorders have on average 3.5 times more risk (range 1.3–13.3 times) for developing any type of anxiety disorder. Furthermore, the authors found that familial aggregation for anxiety disorders was similar for male and female offspring (when the criteria of impairment and avoidance were excluded). Risk for offspring anxiety is further increased by other forms of parental psychopathology, such as depression (Biederman et al., 2001).

Hettema, Neale, and Kendler (2001) conducted meta-analyses on data from family and twin studies of panic disorder, GAD, phobias, and OCD, exploring the roles of genetic and environmental factors in their etiology. Large-scale twin studies were only available for panic disorder and GAD, attributing 30–40% of the variance in liability to additive genetics in panic disorder and 31.6% in GAD. Estimated heritabilities were significantly lower than for schizophrenia or bipolar disorder, leaving the largest proportion of the variance in liability to be explained by individual environmental factors.

Whereas the heritability coefficients of anxiety disorders as defined by DSM-IV and DSM-IV-TR are rather modest, higher heritability coefficients are found for certain psychological traits that are believed to be the vulnerability factors for developing these disorders. In particular, negative affect (neuroticism/emotional instability) is thought to act as an important vulnerability factor placing individuals at risk for anxiety and other disorders, particularly depression (Zinbarg & Barlow, 1996). In fact, Jardine, Martin, and Henderson (1984) found that about 50% of the variation in negative affect in a large sample of twins (n = 3,180) was explained by additive genetic effects. Lake, Eaves, Maes, Heath, and Martin (2000) examined the hypothesis that environmental transmission is a significant factor in individual differences for neuroticism. The authors surveyed 45,850 members of extended twin kinships from Australia and the United States; they found that there is no evidence for environmental transmission, and that a simple genetic structure underlying familial resemblance for the personality trait of neuroticism in monozygotic twin studies can lead to inflation of nonadditive genetic effects.

Similar results were found for behavioral inhibition and early childhood temperament (DiLalla, Kagan, & Reznick, 1994; Robinson, Kagan, Reznick, & Corley, 1992). These studies found that monozygotic twins were more similar in their inhibited behaviors than dizygotic twins. Genetic influence for negative affect and internalizing symptoms are further shared with both anxiety and depression, suggesting that both appear to be variable expressions of the heritable tendency toward negative affect (Mackinnon, Henderson, & Andrews, 1990).

Generalized Psychological Vulnerability

The neurobiological processes underlying the general biological vulnerability factors for developing anxiety disorders appear to be strongly influenced by early psychological processes. We review these neurobiological processes in detail further below. Our discussion

here focuses on the general psychological factors that contribute to the development of anxiety disorders.

In particular, two psychological vulnerability candidates—perceived predictability and controllability—have emerged in the literature as important etiological factors for the development of anxiety disorders. Although experiments on controllability and predictability have been carried out with a variety of laboratory animals ever since the work of Pavlov, some of the most compelling evidence comes from research conducted with primates (e.g., Mineka & Hendersen, 1985). These studies are consistent with a wealth of human experiments suggesting that perception of emotional control is at the heart of mood and anxiety disorders (e.g., Alloy, Abramson, & Viscusi, 1981), and that a lack of perceived control is associated with subjective, behavioral, and physiological distress (e.g., Geer, Davison, & Gatchel, 1970; Glass & Singer, 1970; Sanderson, Rapee, & Barlow, 1989). There is evidence to suggest that a family environment characterized by limited opportunity for personal control is associated with negative affect, and that the relationship between the family environment and negative affect is mediated by low perceived control (Chorpita, Brown, & Barlow, 1998). The literature further suggests that early environmental experiences lead to negative affect and other precursors of anxiety or mood disorders by changing the person's perception of control over environmental events, whereas later in development, perception of control may act as an amplifier (and moderator) for environmental events (Chorpita & Barlow, 1998).

Specific Psychological Vulnerability

The final determinants for the specific emotional disturbance are typically learned early in life, primarily through modeling and vicarious learning. For example, an adult person is more likely to engage in sick role behavior when these behaviors were differentially attended to or reinforced during the individual's childhood (Turkat, 1982; Whitehead, Winget, Fedoravicius, Wooley, & Blackwell, 1982). Similarly, an individual with the vulnerability to develop an anxiety or mood disorder may learn as a child from parents and other role models to focus his or her attention on certain potentially threatening stimuli. In panic disorder, for example, these stimuli may be somatic or other cues signaling the possible occurrence of another false alarm. In social phobia, the person may learn early in life that social evaluation is potentially dangerous, because poor social performance can lead to disastrous consequences. In specific phobia, the vulnerable individual may learn that a particular object of situation is potentially dangerous, or a concerned parent may differentially reinforce the anxious behavior. In OCD, a vulnerable person may learn that "thinking is as bad as doing," or may learn that it is simply wrong to have certain thoughts. This may then lead to attempts to suppress these unwanted thoughts or urges, which result in obsessions and compulsions.

In sum, the literature provides no convincing evidence to suggest that there is a specific "anxious gene." Instead, it is more likely that many genes from different locations on various chromosomes contribute to generalized biological vulnerability factors for developing anxiety disorders (Plomin, DeFries, McClearn, & Rutter, 1997). The heritability estimates of these vulnerability factors (e.g., negative affect) range between 30% and 50%.

These underlying genetically determined vulnerability factors are assumed to be normally distributed across population through the additive effect of many genes ("polygenic"),

while environmental factors account for the necessary environmental contribution ("multifactorial") (Kendler, 1995). Studies further suggest that anxiety disorders and depression have a common genetic basis, and that specific differences in these disorders are best accounted for by environmental factors (e.g., Andrews, Stewart, Allen, & Henderson, 1990; Kendler, 1996; Martin, Jardine, Andrews, & Heath, 1988). However, the generalizability of genetic studies is often compromised by the scarcity of twin studies or the lack of data from adoption studies. In addition, the evaluation of genetic factors largely depends on multivariate genetic analyses, which are limited in many ways, such as by frequent confounding of error variance with the variance attributable to unique environmental experience (Craske, 2003).

In addition to these general biological vulnerability factors, we can assume that early environmental influences encouraging the individual to view negative events as being unpredictable and uncontrollable constitute a general psychological risk factor. Depending on specific learning experiences, these risk factors can then lead to the expression of specific anxiety disorders or depression.

The following section reviews in some detail the neurobiological processes of anxiety disorders. These processes are partly genetically determined and partly shaped by environmental influences and the interaction between environment and biology.

NEUROBIOLOGY OF FEAR AND ANXIETY

Neurobiological research has identified several parts of the brain that are believed to play a key role in a highly dynamic interplay that gives rise to fear and anxiety. Although the precise neurobiological mechanisms of fear and anxiety are still controversial, recent technological advancements in brain imaging and neurochemical techniques have greatly enhanced our understanding of these underlying processes. This section briefly reviews the most relevant literature on neurobiological processes, with a particular emphasis on the distinction between fear and anxiety as outlined earlier.

Hemispheric Differences

The literature on brain activity and anxious or fearful responding reports inconsistent findings. Some studies have reported higher levels of brain activity bilaterally in a variety of specific brain regions (Baxter et al., 1988; Fredrikson et al., 1993; Nordahl et al., 1989; Reiman, Raichle, et al., 1989), whereas other studies have found no such effects (Gur et al., 1988; Mountz et al., 1989; Nordahl et al., 1990; Tomarken & Davidson, 1994).

In an attempt to account for these discrepancies, it has been suggested that anxiety may be related to asymmetries in the alpha frequency band in favor of the left hemisphere, whereas fear and panic may be related to alpha asymmetries in favor of the right hemisphere (Carter, Johnson, & Borkovec, 1986; Heller, Etienne, & Miller, 1995; Heller, Nitschke, Etienne, & Miller, 1997; Tucker, Antes, Stenslie, & Barnhardt, 1978; Tyler & Tucker, 1982). Much as in our earlier discussion, Heller and colleagues (1995) subsume panic under the more general concept of "anxious arousal" (Watson et al., 1995), and anxiety under the concept of "anxious apprehension" (Barlow, 2002). Anxious arousal is defined as an emotional experience characterized by physiological hyperarousal and somatic symptoms. In contrast, anxious apprehension is assumed to involve primarily worry and verbal rumination, typically about future events.

Asymmetry in the electroencephalographic (EEG) alpha frequency band seems to be associated with different emotional experiences (e.g., Tomarken, Davidson, Wheeler, & Doss, 1992). More specifically, it is assumed that the left and right anterior regions are specialized for approach and withdrawal processes, respectively (Davidson, 1992). Heller (1993) hypothesized that activity of the right parietotemporal region is positively correlated with levels of arousal, whereas relatively greater left versus right frontal activation is associated with positive versus negative valence, respectively.

Similar results have been reported in a more recent EEG study that measured frontal brain asymmetry (Wiedemann et al., 1999). This study found greater right than left frontal hemispheric activation, as indicated by reduced right frontal alpha power in patients with panic disorder (without depression) during a resting phase and when confronted with panic-relevant stimuli (pictures of emergency situations). In contrast, control subjects did not show brain asymmetry in the alpha frequency band of the frontal region during these conditions. Furthermore, no frontal brain asymmetry was found in either patients with panic disorder or controls when they were watching emotionally neutral pictures. Similarly, another recent EEG study found that, compared to nonanxious controls, individuals with social phobia showed a marked increase of right-sided activation (less alpha-1 power, which is in the range of 8–10 Hz) in the anterior temporal and lateral prefrontal scalp region when being confronted with an upcoming public speech (Davidson, Marshall, Tomarken, & Henriques, 2000). Together with the increase in heart rate, the EEG changes accounted for 48.7% of the variance in the increase in negative affect during this anticipation phase.

In contrast to fear and panic, anxiety appears to be associated with relatively greater left-hemispheric activation. For example, a study by Heller and colleagues (1997) found a larger asymmetry in the alpha frequency band in favor of the left hemisphere in anxious subjects than in controls. In contrast, during a task designed to elicit anxious arousal (i.e., fear), anxious participants showed a selective increase in EEG activity of the right parietal region. These results are also consistent with studies conducted on children (Davidson, 1992, 1995; Fox & Davidson, 1988). Fox and Davidson (1988), for example, found that children who were avoidant or fearful in unfamiliar situations showed greater desynchronization of alpha frequencies over the right frontal area than over the left frontal area. Furthermore, 9- and 24-month-old children who were classified as "highly reactive" based on behavioral indicators showed greater activation of the right frontal area, whereas those with lower reactions showed greater activation of the left frontal area (Fox, Calkins, & Bell, 1994). It has also been shown that patients with GAD exhibited greater cortical activity (less delta and alpha) than controls in a study that used only left-hemisphere and midline leads (Buchsbaum et al., 1985). Furthermore, a study measuring EEG beta band activity during a worry episode found a smaller asymmetry favoring the right hemisphere in students who were classified as so-called "worriers" on the basis of questionnaire data than in those classified as "nonworriers" (Carter et al., 1986). Finally, positron emission tomography (PET) studies suggest that in the absence of a panic attack, patients with panic disorder who are vulnerable to lactate-induced panic show less cerebral blood flow, blood volume, and oxygen metabolism in the left than in the right side of the parahippocampal gyrus (Reiman, Raichle, Butler, Herscovitch, & Robins, 1984), and a greater whole-brain metabolism and abnormal susceptibility to episodic hyperventilation (Reiman et al., 1986), than controls. Furthermore, patients with panic disorder who experienced a panic attack as a result of sodium lactate infusion in one study showed a greater increase in right occipital blood flow, as compared to patients with panic disorder who did not panic and to controls without any disorder (Stewart, Devous, Rush, Lane, & Bonte, 1988).

In summary, these studies suggest that panic, fear, and the associated hyperarousal of the fear reaction seems to be associated with right frontal brain activity (less alpha), whereas anxiety is more closely related to left frontal brain activation.

Septohippocampal Area

An influential neuropsychological model of anxiety and fear points to the septohippocampal area of the limbic system (Gray, 1982; Gray & McNaughton, 1996). Gray's model postulates the existence of three different fundamental neuropsychological systems in the mammalian brain: the behavioral approach system (BAS), the fight-or-flight system, and the behavioral inhibition system (BIS).

In order to identify a stimulus as novel, the BIS needs to compare the incoming stimulus with what is expected. The system is activated when there is a mismatch between actual incoming information and expected information, or when the expected information is aversive and no overt avoidance is possible. Gray hypothesizes that this comparator system is mediated by the septohippocampal system and the associated Papez circuit, which is the loop from the subiculum via the mammillary bodies, anterior ventral thalamus, and cingulate cortex back to the subiculum. The BIS has been associated with anxiety, and the fight-or-flight system with fear. The fight-or-flight system is activated by unconditioned punishment and nonreward, whereas the BIS is activated by signals of punishment or nonreward (i.e., by conditioned stimuli), innate stimuli, and novel stimuli. In contrast to the BIS, the fight-or-flight system leads to autonomic arousal and the associated action tendencies of escape, active avoidance, or defensive aggression (Gray & McNaughton, 1996). This fight-or-flight system is located in areas of the hippocampus (medial and central) with descending control by the amygdala, which also provides inputs to the BIS and may relay its outputs to the hypothalamus and autonomic nervous system, thereby mediating anxious arousal (fear and panic). Finally, the BAS facilitates approach to safety signals, such as rewards and nonpunishment, by involving the medical forebrain bundle.

The neurobiological literature reports mixed support for Gray's theory. Reiman (1997) reviewed six studies using PET to investigate the neuroanatomical correlates of emotions. These studies suggest that the temporal lobe regions primarily participate in the evaluation of the emotional significance of exteroceptive sensory information. Reiman hypothesized that the anterior insular regions may be associated with the evaluation of cognitive and interoceptive sensory information, and that the anterior cingulate, the cerebral vermis, and the midbrain regions may participate in the pathological forms of fear and anxiety. For example, lactate-induced panic in patients with panic disorder and anticipation of a painful shock in healthy volunteers (Reiman, Fusselman, Fox, & Raichle, 1989) were associated with significant blood flow increases bilaterally in the temporal poles. Another PET scan study using patients with GAD showed that, as compared to controls, patients had lower absolute metabolic rates in their basal ganglia and white matter, but greater metabolism in the left inferior frontal gyrus, the right posterior temporal lobe, and the right precentral frontal gyrus during a passive viewing task (Wu et al., 1991). In contrast to an earlier study by Reiman (1987), who found abnormal hemisphere asymmetries in parahippocampal blood flow, blood volume, and oxygen metabolism in panic disorder, the results obtained by Wu and colleagues (1991) did not reveal significant limbic abnormalities in patients with GAD. However, changes in anxiety scores were significantly correlated with changes in the limbic system and basal ganglia for patients with GAD who received

a pill placebo treatment. Treatment with benzodiazepines resulted in a decrease of absolute metabolic rates for cortical surface, limbic system, and basal ganglia.

Amygdala

In the late 1930s, researchers began to find evidence that the amygdala is involved in the emotion of fear. Ablations of certain brain areas, such as the removal of the temporal lobes (e.g., Kluever & Bucy, 1939), caused animals to approach objects they had previously feared, eat indiscriminately, and act hypersexually. In 1990, LeDoux discovered that tracer substances injected into the central nucleus of the amygdala moved retrograde to certain regions of the thalamus, though not to the region activated by auditory stimuli. However, tracer substances injected into the lateral nucleus of the amygdala demonstrated connections with the thalamic region activated by auditory stimuli. Lesions of the lateral nuclei blocked fear conditioning by cutting off reception of acoustic stimuli from auditory parts of the thalamus. This observation suggests that the lateral nucleus receives the frightening auditory stimuli, while the central nucleus sends out messages to the systems that generate fear reactions (LeDoux, 1990).

The amygdala is composed of about a dozen regions, of which only a small number are involved in fear conditioning. Numerous studies have demonstrated that the amygdala responds to facial expressions of emotion—in particular, fearful facial expressions (Morris et al., 1996; Whalen et al., 2001) Responses to fearful expressions seem to be more fixed, automatic, and perhaps even preattentive (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003), whereas responses to happy, neutral, or disgusted expressions are perhaps more variable and elaborative (Canli, Sivers, Whitfield, Gotlib, & Gabrieli, 2002; Somerville, Kim, Johnstone, Alexander, & Whalen, 2004). Some facial expressions (such as disgust) do not even lead to an activation of the amygdala, but only of the anterior insular cortex (Phillips et al., 1997).

Hippocampus

In addition to the amygdala, the hippocampus seems to be an important structure involved in the development of anxiety and fear. In fact, the hippocampus is part of one of the most important cognitive systems of the brain: the temporal lobe memory system. Studies have shown that the hippocampus is smaller in people who have undergone severe stress because of child abuse or military combat (Bremner et al., 1995; Stein et al., 1997). The reduced size could help explain why individuals with PTSD have flashbacks, deficits in explicit memory, and fragmented memory for details of their traumatic events.

A study by Bechara and colleagues (1995) discovered that patients with bilateral damage to the amygdala, the hippocampus, or both reacted differently to visual or auditory fear conditioning. Patients with bilateral damage to the amygdala still showed a declarative reaction but no fear reaction, compared to patients with bilateral damage of the hippocampus, who showed a fear reaction but no declarative reaction. Patients with bilateral damage of both showed neither fear reaction nor declarative learning. This and other experiments (e.g., Phillips & LeDoux, 1992) emphasize the role of the hippocampus in the conditioning of fear reactions and encoding information into memories.

Finally, animal studies showed that, as compared to controls, rats with hippocampal lesions showed little freezing behavior when being placed in a fear-conditioning box after

undergoing some fear-conditioning trials. However, the lesioned rats did start to freeze once the conditioned stimulus was presented (Phillips & LeDoux, 1992). Thus the hippocampal lesion seemed to selectively eliminate the fear response elicited by contextual stimuli, without affecting the fear response elicited by the conditioned stimulus (LeDoux, 1998).

TREATMENT APPROACHES FOR ANXIETY DISORDERS

Psychosocial treatments (particularly cognitive-behavioral therapy, or CBT) and pharmacotherapies are the two most commonly used types of treatments for anxiety disorders. A combination of proven pharmacotherapies and psychotherapies may be a clinically prudent approach to treatment for specific anxiety disorders. Many patients still use complementary and alternative treatments, in spite of the research on and progress in these relatively well-defined therapies (Kessler et al., 2001). Below, we present the two forms of treatments (psychotherapies and pharmacotherapies) and discuss their empirical findings.

Psychotherapies

The past few decades have witnessed an increase in the development and evaluation of innovative CBT approaches for treating anxiety disorders (Barlow, 2002). Numerous controlled and uncontrolled trials have indicated that the methods used in CBT can be highly effective in reducing symptoms and avoidance. In contrast to pharmacotherapy, CBT concentrates directly on eliminating exaggerated fears and the avoidance responses that are believed to be directly involved in the maintenance of anxiety disorders. CBT combines several treatment components, such as psychoeducation, relaxation techniques (breathing and muscle relaxation techniques), cognitive restructuring, and exposure. Cognitive restructuring interventions are aimed at helping patients eliminate catastrophic thoughts (e.g., "I am having a heart attack") that intensify anxiety. Particular attention is provided to minimizing patients' tendencies to overestimate the likelihood of negative outcomes and to catastrophize about their (in)ability to cope should these outcomes occur. During exposure, patients repeatedly confront feared sensations (interoceptive exposure) and situations (*in vivo* exposure), and allow their anxiety to dissipate while acquiring a sense of control in the presence of these stimuli. The behavioral and cognitive techniques used in CBT for different forms of anxiety disorders are comparable, but the concrete content (or protocol) is adapted and tailored to the specific model of the core fears in each disorder. For example, whereas patients with panic disorder may fear health-related consequences from physical sensations ("My heart is racing—I must be having a heart attack"), persons suffering from social phobia may fear social consequences ("My heart is racing—everyone will see how anxious I am").

Panic Disorder

Psychological treatments using cognitive and behavioral techniques have consistently demonstrated efficacy in the treatment of panic disorder with or without agoraphobia (Gould, Otto, & Pollack, 1995). In Gould and colleagues' (1995) meta-analysis, 43 controlled studies were evaluated; CBT showed the largest effect sizes and the smallest rate of patient attrition, compared to drug treatment or to approaches that combined psychological and drug treatments. Studies using interoceptive exposure not only provided the largest effect sizes, but

showed an incremental increase in the quality of life for patients (e.g., Telch, Schmidt, Jaimez, Jacquin, & Harrington, 1995).

In a recent multicenter study (Barlow, Gorman, Shear, & Woods, 2000), the largest combined treatment study to date (n = 312 patients with panic disorder), patients with mild to moderate agoraphobia were randomly assigned to receive imipramine, CBT, CBT plus placebo, pill placebo only, or CBT plus imipramine. All four active treatments resulted in marked acute improvements that were significantly greater than those observed for the pill placebo condition. No differences were observed between imipramine and CBT; the combination treatment did outperform CBT on several measures, but failed to outperform CBT plus placebo. These data indicate that that the increased efficacy of adding imipramine to CBT at the acute treatment outcome was accounted for by the nonspecific effects associated with pill taking. Furthermore, the outcome of combined treatment tended to suffer once medication was withdrawn, relative to CBT alone (see also Marks et al., 1993). This suggests the importance of CBT for long-term maintenance of symptom improvement.

Social Phobia

Psychological treatments for social phobia typically involve cognitive restructuring, various forms of exposure, social skills training (e.g., Heimberg et al., 1990), or a combination of these approaches. Cognitive restructuring and exposure to feared social stimuli both within and between sessions are aimed to correct maladaptive beliefs about the self and others, particularly beliefs that exaggerate the probability and consequence of negative social evaluation (Clark & Wells, 1995; Rapee & Heimberg, 1997). Group therapy for social phobia provides sufferers with the opportunity for exposure to feared social situations (e.g., Heimberg et al., 1990, 1998; Hofmann, 2004; Hofmann, Moscovitch, Kim, & Taylor, 2004).

Meta-analytic findings provide consistent support for the overall effectiveness of CBT interventions. In a recent meta-analytic review of treatments for social phobia, however, no clear superiority for specific interventions was found. Fedoroff and Taylor (2001), for example, found no significant differences in effect sizes for either exposure therapy alone, cognitive therapy alone, or combined exposure and cognitive therapy, while the majority of others (e.g., Gould, Pollack, Otto, & Yap, 1997) concluded that exposure therapy either alone or in combination with cognitive restructuring is somewhat more effective than cognitive restructuring alone. Repeated and prolonged exposure to social cues in the absence of avoidance strategies (e.g., distraction or safety behavior) is believed to extinguish learned alarm responses and anxious apprehension (self-focused attention).

Specific Phobia

Consensus about the treatment of choice for specific phobia is very strong and coherent: *In vivo* exposure to the feared object or situation is perceived as both necessary and sufficient for the vast majority of patients suffering from various forms of specific phobia (e.g., phobias of spiders, snakes, heights, flying).

Considerable variation in exposure-based treatment duration, context, and frequency of exposure practices has been observed, yet with little variation in the overall positive outcome. In fact, identifying specific predictors of response has been difficult; this suggests the importance of treatment administration rather than a specific patient's profile (e.g., age of onset, comorbidity, family history) for positive outcomes (Hellström & Öst, 1996). Studies on specific approaches during exposure (degree of perceived control, massed vs. expanding spaced exposure, same vs. different context, same stimulus vs. varied stimulus, and degree of distraction) yielded mixed outcomes, complicating general guidelines for

exposure. For example, whereas Rowe and Craske (1998a) showed that massed exposure for patients with spider phobia yielded better acute fear reduction, expanding spaced exposure showed more prolonged benefits in terms of return of fear after treatment. Similarly, the exposure to the same spider as compared to different spiders showed greater differential acute but not prolonged effects on fear reduction (Rowe & Craske, 1998b). Presenting the feared object (e.g., a spider) in multiple contexts (various situations and locations), however, does improve fear reduction both acutely and at follow-up (Mystkowski, Craske, & Echiverri, 2002). Use of distraction and safety aids during exposure has been found to impair fear reduction (Kamphuis & Telch, 2000; Powers, Smits, & Telch, 2004). Changes in anxious cognitions are believed to occur along with fear reduction during exposure—a finding that challenges the additive benefit of this component (e.g., Booth & Rachman, 1992).

Generalized Anxiety Disorder

In contrast to specific phobia, external triggers in GAD are harder to identify, and therefore the applicability of exposure-based treatment is reducted (Borkovec & Whisman, 1996). Consequently, psychological treatments for GAD have included a variety of techniques, including progressive muscle relaxation, self-monitoring imaginal exposure, and/or cognitive restructuring (e.g. Borkovec & Costello, 1993, Clark et al., 2003). Meta-analytic studies (Borkovec & Whisman, 1996; Gould et al., 1997; Weston & Morrison, 2001) strongly support the effectiveness of combined CBT interventions, compared to individual components (cognitive or behavioral approaches alone), for GAD. No significant advantage of combined treatment with CBT plus diazepam as compared to CBT alone was found, but CBT (alone or in combination) appeared superior to diazepam alone (Power, Simpson, Swanson, & Wallace, 1990).

CBT for GAD leads to lower estimates of end-state functioning than do extant psychological treatments for other anxiety disorders. Studies assessing predictive factors for outcome found a negative correlation between reports of interpersonal problems prior to and following therapy and measures of high end-state functioning (Borkovec, Newman, Pincus, & Lytle, 2002). As a result, acceptance-based or mindfulness-based treatments for GAD are currently under investigation (e.g., Hayes, Strosahl, & Wilson, 1999; Linehan, 1993; Roemer & Orsillo, 2002). Such therapies are thought to help patients reduce anxiety by teaching them to focuse on the present moment ("present-moment experience"), rather than on nonexistent perceived threats (Borkovec, Hazlett-Stevens, & Diaz, 1999).

Obsessive–Compulsive Disorder

Behavioral procedures (including exposure to feared situations while blocking compulsive rituals), as well as cognitive approaches (e.g., rational-emotive therapy, cognitive therapy) have demonstrated substantial success in patients suffering from OCD. One of the most successful treatment approaches is exposure and response prevention (ERP; Meyer, 1966)—a technique that uses prolonged exposure procedures (e.g., touching dirty surfaces) while preventing compulsive responses (e.g. washing hands) until fear and discomfort subsides. Standard ERP treatment has also been shown to alter patients' irrational appraisals and beliefs, which are targeted more intensively in cognitive therapy. Identifying and challenging beliefs that support OCD behavior, as well as using a wide variety of additional cognitive challenge strategies to correct problematic beliefs, are the key elements of the cognitive approach.

Meta-analytic reviews of OCD treatment studies (Abramowitz, 1997; Van Balkom et al., 1994) indicate overall that treatments involving behavioral procedures, particularly ERP, are more effective than cognitive therapy. However, procedural overlap between the

two types of approaches impedes a direct comparison between cognitive and behavioral therapy approaches.

A combined CBT (ERP) and pharmacotherapy (clomipramine) study by Franklin, Abramowitz, Kozak, Levitt, and Foa (2000) revealed no advantage of ERP alone over the combination treatment (ERP plus clomipramine). However, all active treatments (ERP alone, clomipramine alone, ERP plus clomipramine) outperformed placebo. ERP, alone or in combination, was superior to clomipramine alone and placebo.

Posttraumatic Stress Disorder

Exposure, cognitive restructuring, and anxiety management skills are typically used in psychotherapy programs for PTSD. Whereas exposure-based treatments emphasize confrontations with fear-evoking memories of the traumatic event (i.e., imaginal exposure) and avoided situations or stimuli (i.e., *in vivo* exposure), cognitive interventions address anxiety symptoms and challenge maladaptive beliefs. A more recent, yet controversial (e.g., Lilienfeld, 1996), approach to treating PTSD is eye movement desensitization and reprocessing (EMDR; Shapiro, 2001).

Meta-analytic studies (Sherman, 1998; Van Etten & Taylor, 1998) comparing several treatment approaches (e.g., behavior therapy, EMDR, supportive counseling, hypnosis, stress inoculation training) conclude that forms of CBT are highly effective in reducing PTSD symptoms. As in meta-analytic studies in OCD, testing the efficacy of cognitive versus behavioral procedures separately is complicated by procedural overlap.

In sum, CBT interventions for anxiety disorders have documented success, and many of their fundamental strategies are currently undergoing further refinement. However, we still know relatively little about the active ingredients of CBT packages. Marks and Dar (2000) have therefore called for more research to identify therapy components that reduce—alone or simultaneously—each facet of fear (cognitive, behavioral, and physiological). In addition, it appears that certain components of the CBT package may be useful for only certain anxiety disorders. Further empirical evidence for benefits or disadvantages in the treatment of particular disorders awaits exploration (Antony, 2002).

Psychopharmacological Treatments

There is ample evidence that pharmacological treatments improve psychopathology in patients suffering from anxiety disorders (e.g., Lydiard, Brawman-Mintzer, & Ballenger, 1996). Selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), benzodiazepines, and beta-blockers are the major classes of medications used for various anxiety disorders; these are described below.

Selective Serotonin Reuptake Inhibitors

Fluoxetine, sertraline, fluvoxamine, paroxetine, and citalopram are among the SSRIs commonly prescribed for panic disorder, OCD, PTSD, and social phobia. SSRIs are often used to treat people who have panic disorder, OCD, social phobia, or depression. Venlafaxine, a drug closely related to the SSRIs, is useful for treating GAD. Other, newer antidepressants are under study in anxiety disorders, although one (bupropion) does not appear effective for treating these disorders.

Tricyclic Antidepressants

The tricyclic antidepressants are as effective as the SSRIs, but have been shown to cause more side effects (e.g., dizziness, drowsiness, dry mouth, and weight gain). Tricyclic antidepressants may be particularly potent in treating people with co-occurring anxiety disorders and depression. Clomipramine, the only antidepressant in its class prescribed for OCD, and imipramine, prescribed for panic disorder and GAD, are examples of tricyclics.

Monoamine Oxidase Inhibitors

The most commonly prescribed MAOI is phenelzine, which is prescribed for people with panic disorder and social phobia (Stein, Vythilingum, & Seedat, 2004); however, it requires a restrictive diet, due to its dangerous interaction with some foods and beverages containing tyramine. Furthermore, MAOIs can interact with medications such as SSRIs, causing dangerous elevations in blood pressure or other potentially life-threatening reactions.

Benzodiazepine

Benzodiazepines relieve symptoms of acute fear quickly; however, development of tolerance and dependency is a serious issue, particularly in patients with a past or present history of drug or alcohol abuse. Examples of benzodiazepines include clonazepam, which is used for social phobia and GAD; alprazolam, which can be helpful for panic disorder and GAD; and lorazepam, which is also used for panic disorder. Buspirone—a newer antianxiety medication that is not a benzodiazepine, but shares some properties of these drugs—is used in the treatment of GAD, but it has to be taken consistently for at least 2 weeks to achieve an antianxiety effect.

Beta-Blockers

Often used to treat heart conditions, beta-blockers (e.g., propranolol) have also been found to be helpful in certain anxiety disorders—particularly in social phobia, due to its overall parasympathetic effects (reduction in heart rate, shaking, and other prominent physical symptoms that may occur during confrontation with fearful stimuli).

In sum, while these medications exert their action by attenuating the anxiety elicited by the feared cues associated with each disorder, their effects often only last as long as the medications are continued (e.g., Noyes, Garvey, Cook, & Suelzer, 1991). In addition, their discontinuation can have possible deleterious effects on psychological approaches, as discussed earlier (e.g., Barlow et al., 2000). Furthermore, dependency, tolerance, side effects, and associated larger treatment dropout rates (e.g., Hofmann et al., 1998) and costs as compared to CBT (e.g., Otto, Pollack, & Maki., 2000) are associated with the administration of psychopharmacological drugs.

Summary and Conclusion

Studies on broad-based vulnerabilities such as negative affectivity and emotion regulation and their genetic and environmental contributions suggest the presence of these constructs confer an increase in the risk for all forms of anxiety disorder. Development and

maintenance of anxiety disorders are shaped by both genetic and partly environmental influences, in addition to the interaction between environment and biology. There is no convincing empirical evidence that suggests a specific "anxiety gene." Instead, there are many genes that contribute to a generalized biological vulnerability for the development of anxiety disorders. Progress in the understanding of the neural circuitry of anxiety and fear has come from a variety of sources, including animal, clinical, and, most recently, neuroimaging studies. Further investigation and application in this area will facilitate understanding of the underlying processes and mechanisms of antianxiety therapies.

In terms of treatment, cognitive-behavioral interventions for anxiety disorders have documented success. Findings from limited trials of combined therapies (cognitive-behavioral and pharmacological therapy) do not indicate that the combination of psychotropic medication and behavioral therapy is incrementally better than behavioral treatments alone; however, they do appear to be better than medication alone, especially for preventing relapse. Nevertheless, behavior therapy combined with medication can be useful to reduce severe discomfort and thus to enhance motivation for exposure elements of behavioral treatment. Further research is necessary to determine predictors of treatment outcome and long-term effectiveness of these multifaceted treatment strategies among patients suffering from anxiety disorders.

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9

DEPRESSIVE DISORDERS

DAWN H. S. REINEMANN
SUSAN M. SWEARER

Depressive disorders adversely affect a significant portion of the population, and rates appear to be increasing. This development is especially disturbing, given the deleterious effects that these disorders may have on individuals—including lost productivity, problematic interpersonal relationships, increased health problems, and potential mortality as a result of suicidal behaviors (see Gotlib & Hammen, 2002). As a result, a large body of research has accumulated regarding the onset, course, maintenance, and treatment of depressive disorders. In particular, the past decade has seen significant advances in our understanding of the biological and neurological underpinnings of these disorders, as well as empirical evidence regarding pharmacological and psychosocial treatment effectiveness. The current chapter reviews the state of the field of depression research, as well as directions for future investigation.

OVERVIEW OF DEPRESSION

Definitions

Symptom

The term "depression" has been used to describe various forms of affective disturbance, and these different uses have often led to confusion and misinterpretation of research findings. First, depression can be defined as a *symptom* of sad or dysphoric mood. When defined in this way, depression is common across the lifespan and may last for either a brief or a lengthy interval (Stark et al., 1997). The symptom of depression may or may not be indicative of a mood disorder (Cantwell, 1990).

Syndrome

Depression can also be used to describe a *syndrome*, or a constellation of behaviors and emotions that reliably co-occur (Stark et al., 1997). A depressive syndrome includes not only dysphoria, but also other cognitive, behavioral/motivational, emotional, and physiological/vegetative symptoms (Cantwell, 1990). A depressive syndrome is less common than

depressed mood (Cantwell, 1990). Furthermore, it may be viewed as the major problem; it may occur as a secondary disturbance associated with other psychological disorders or with medical conditions; or it may be a result of negative life events, such as loss (Cantwell, 1990).

Depressive Disorders

Third, clinical depression (a disorder) is described as a depressive syndrome that has an extended duration and involves impaired functioning (Cantwell, 1990). The *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR; American Psychiatric Association, 2000a) includes three diagnostic categories of unipolar depressive disorders: major depressive disorder (MDD), dysthymic disorder (DD), and depressive disorder not otherwise specified (DDNOS). The main differences among these disorders are in the number, severity, and duration of symptoms.

A diagnosis of MDD requires a clinical course consisting of one or more major depressive episodes (MDEs), without any history of manic, hypomanic, or mixed mood episodes. To be characterized as having an MDE, an individual must exhibit five or more symptoms over a 2-week period, including one symptom of either depressed mood or loss of interest or pleasure (anhedonia). For children, irritability can be used to meet this criterion. In addition, four other symptoms must be present, including (1) changes in weight; (2) sleep disturbance; (3) psychomotor agitation or retardation; (4) fatigue or loss of energy; (5) excessive feelings of worthlessness or guilt; (6) lack of concentration or indecisiveness; and (7) suicidal ideation, attempts, or plans (American Psychiatric Association, 2000a).

DD is a lower-grade, chronic mood disturbance consisting of depressed mood (or irritability in children) and two other depressive symptoms. These symptoms must be present for at least 2 years (1 year for youth) without more than 2 symptom-free months (American Psychiatric Association, 2000a). Finally, individuals who exhibit depressive symptomatology that does not meet the diagnostic criteria for either MDD or DD may receive a diagnosis of DDNOS. Although a detailed discussion is beyond the scope of this chapter, the DSM-IV-TR (American Psychiatric Association, 2000a) also includes four types of bipolar disorders (bipolar I disorder, bipolar II disorder, cyclothymic disorder, and bipolar disorder not otherwise specified), characterized by the presence of manic, mixed, or hypomanic episodes, and usually also accompanied by MDEs.

Prevalence

Major Depressive Disorder

Depressive disorders are increasingly being viewed as potentially chronic, recurrent conditions that often have their origin in youth. Epidemiological studies of depression vary in their methods of assessment, populations being studied, informants, age ranges of samples, and other factors, thus yielding different prevalence rates and limiting comparison across studies. Considering these limitations, it appears that depressive disorders are relatively uncommon in preadolescent children, ranging from 1% to 3% for lifetime episodes (for reviews, see Hammen & Rudolph, 2003; Stark, 1990). However, by adolescence, prevalence rates rise significantly. For example, one study found that 9.4% of a community sample of high school seniors met the diagnostic criteria for MDD (Reinherz, Giaconia, Lefkowitz, Pakiz, & Frost, 1993). Similarly, the National Comorbidity Study (NCS) examined a nationally represented community sample, which included adolescents ages 15–18, and found

a lifetime prevalence rate for major depression in this group of 14% (Kessler & Walters, 1998). A more recent 10-year longitudinal study that examined the emergence of depression from preadolescence to young adulthood (Hankin et al., 1998) found that between the ages of 11 and 15, lifetime prevalence rates of depression increased from 1% to 5.6%. Hankin and colleagues (1998) reported that by age 18, the lifetime prevalence rate had increased to 20.67%, while Lewinsohn, Rohde, and Seeley (1998) indicate that approximately 28% of adolescents will have developed MDD by age 19. Even higher prevalence rates have been found in child clinical populations, averaging 42% across published studies (Petersen et al., 1993).

Three major epidemiological examinations of prevalence rates of mood disorders (the term "mood disorders" will be used throughout the chapter to define what was formerly termed "affective disorders") in the U.S. population have been undertaken since 1980; all of these utilized diagnostic interviews to determine psychiatric status. Specifically, the Epidemiologic Catchment Area (ECA) study was conducted from 1980 to 1985 (Robins & Regier, 1991), and the NCS was conducted from 1990 to 1992 (Kessler et al., 1994). The National Center for Health Statistics and the Centers for Disease Control and Prevention conducted the Third National Health and Nutrition Examination Survey (NHANES III) from 1988 to 1994 (Jonas, Brody, Roper, & Narrow, 2003). Results from these three population-based studies are shown in Table 9.1. As can be seen, whereas the ECA study reported relatively low prevalence rates, the NCS and NHANES III indicated higher rates of mood disorders in the population—a fact that may be due to differences in diagnostic interviewing across these three national surveys. Additional explanations for the rise in prevalence rates over time include a possible increased risk for depression in recent cohorts, and reduced social stigma in endorsing depression (Kessler, 2002). Taken together, it seems reasonable to conclude that at least one out of every six adults in the U.S. population has met criteria for major depression at some point in his or her life (Kessler, 2002).

Dysthymic Disorder

Fewer studies have examined the prevalence rates of DD. It is important to examine DD as a separate entity, because research has indicated that DD is often a precursor to the development of an MDE (Garber, Kriss, Koch, & Lindholm, 1988). Prevalence rates of children currently experiencing DD have been reported at approximately 2.5% in the general population (see Stark, 1990, for a review), while results from the NHANES III indicated that 4.7% of 17- to 19-year-olds had a lifetime history of DD (Jonas et al., 2003).

TABLE 9.1. Lifetime Prevalence of Depressive Disorders, Based on Three Community Epidemiological Surveys

Study	Age group	Diagnosis	MDE	DD	Any mood disorder
ECA	18 and older	DSM-III/DIS	5.8	3.3	8.3
NCS	15–54	DSM-III-R/UM-CIDI	17.1	6.4	19.3
NHANES III	17–39	DSM-III/DIS	8.6	6.2	11.5

Note. Prevalence rates are per 100 persons. ECA, Epidemiologic Catchment Area study (Regier, Burke, & Burke, 1990); NCS, National Comorbidity Survey (Kessler et al., 1994); NHANES III, Third National Health and Nutrition Examination Survey (Jonas et al., 2003); DSM-III/DIS, diagnosis based on DSM-III criteria and made with the Diagnostic Interview Schedule; DSM-III-R/UM-CIDI, diagnosis based on DSM-III-R criteria and made with a modified version of the Composite International Diagnostic Interview; MDE, major depressive episode; DD, dysthymic disorder.

Rates of DD in adulthood range from approximately 3% to 6.4% (see Table 9.1). Thus, although DD is less prevalent than MDD, it also affects a significant number of individuals during the course of their lifetimes.

Gender Differences

It appears that prior to adolescence, the sex ratio of children with depressive disorders is about equal, with some studies finding slightly higher rates in boys than in girls (Nolen-Hoeksema, Girgus, & Seligman, 1991). However, by adolescence, females are more likely to be diagnosed with depression than males (Hankin et al., 1998; Kandel & Davies, 1982; Lewinsohn et al., 1998). Longitudinal investigations have found that the emergence of gender differences in depression seems to occur between ages 13 and 15 (e.g., Hankin et al., 1998) and extends into adulthood (Kandel & Davies, 1986; Petersen et al., 1993). In adulthood, females with depression outnumber males by a 2:1 ratio (see Nolen-Hoeksema, 2002, for a review).

Investigators have begun to explore possible biological, psychological, and social factors that may account for the increased rates of depression in women. Although an in-depth review of this literature is beyond the scope of this chapter, a brief summary of the major findings reveals little evidence that hormone levels or pubertal status can directly account for the observed gender differences in rates of depression (Nolen-Hoeksema, 2002). Nolen-Hoeksema (2002) points out that complex associations among gonadal hormones and brain neurotransmitters may affect mood in a minority of women who are genetically vulnerable to depressive disorders. However, for the vast majority of the female population, hormonal changes are not associated with changes in mood.

It does appear that women may have a stronger biological reactivity to stress, characterized by a dysregulated hypothalamic–pituitary–adrenal (HPA) axis response—in part because they are more likely to be exposed to traumatic life events, which are known to affect the HPA axis (Heim et al., 2000). For example, females are more likely to experience sexual victimization (Cutler & Nolen-Hoeksema, 1991), which increases the risk for depression as well as posttraumatic stress disorder (Cutler & Nolen-Hoeksema, 1991; Widom, 1999).

Moreover, exposure to negative life events of an interpersonal nature may pose a particular risk for females, due to their greater affiliative needs and emphasis on social relationships (Nolen-Hoeksema, 2002; Rudolph, 2002). This exposure, combined with a cognitive style characterized by excessive rumination, dysfunctional attitudes, and a pessimistic explanatory style, appears to contribute to higher rates of mood disorders in women (Hankin & Abramson, 2001; Nolen-Hoeksema, 2002). All of the variables discussed above probably interact to increase the risk for depression in women. Thus researchers are beginning to develop integrated models that take into account various biological, psychological, and social factors in order to provide a more comprehensive explanation of the gender difference phenomenon (e.g., Hankin & Abramson, 2001; Nolen-Hoeksema, 2002).

Ethnic, Cultural, and Socioeconomic Differences

Until recently, little research has examined depression across different cultures. However, within the last decade, researchers have taken an increased interest in the prevalence and unique manifestations of depression in different cultural contexts. Although depression is known to exist throughout the world, important variations across cultures have been elucidated (Gotlib & Hammen, 2002). One of the most consistent findings that has been re-

ported across the epidemiological literature is that prevalence rates of depression are lower in Asian cultures (e.g., Japan, China, Taiwan) than in Western cultures (U.S., Canada, Germany, New Zealand) (Bland, 1997; Hwu, Chang, Yeh, Chang, & Yeh, 1996; Simon, Von Korff, Picvinelli, Fullerton, & Ormel, 1999). According to Tsai and Chentsova-Dutton (2002), this pattern is probably due to a number of factors, including cultural variation in the way in which mental illness is conceptualized, differences in the stigma associated with psychopathology, and varying levels of social support across cultures.

Epidemiological studies of depression in the United States have also examined whether prevalence rates of depression differ across various culturally and ethnically diverse groups. For example, all three of the national surveys described earlier (i.e., the ECA, NCS, and NHANES III) reported lower rates of MDD in black than in white individuals (Jonas et al., 2003; Kessler et al., 1994; Weissman, Bruce, Leaf, Florio, & Holzer, 1991). However, there have been conflicting data when the prevalence rates of Hispanic and white non-Hispanic individuals have been compared. Whereas the ECA and NHANES III reported lower rates of lifetime major depression in Hispanic versus white non-Hispanic populations (Jonas et al., 2003; Weissman et al., 1991), the NCS failed to find significant differences in lifetime rates of any mood disorders, and additionally noted that Hispanics exhibited higher rates of current (12-month) mood disorders than white non-Hispanic individuals (Kessler et al., 1994). Examination of other ethnic groups was not possible in these national surveys, due to limited sample sizes. However, smaller investigations suggest that prevalence rates of depression are elevated in Native American adolescents (see Petersen et al., 1993). Furthermore, gay, lesbian, and bisexual individuals are at greater risk for depression and suicide (Anhalt & Morris, 1998). Finally, higher rates of mood disorders have been noted in both children (Reinherz et al., 1993) and adults (Jonas et al., 2003; Kessler et al., 1994) of lower socioeconomic status.

Comorbidity

Substantial comorbidity exists among those who evidence depression. For example, Lewinsohn and colleagues (1998) concluded from their research that 43% of adolescents with MDD have a lifetime comorbid psychiatric disorder. Anxiety disorders are the most common co-occurring conditions with depression (Angold, Costello, & Erkanli, 1999; Fleming & Offord, 1990). According to Kovacs (1990), conservative estimates suggest that from 30% to 50% of youngsters with a depressive disorder also evidence an anxiety disorder. Furthermore, it appears that for the majority of youth, anxiety disorders precede the development of depression (Brady & Kendall, 1992; Kovacs, Gatsonis, Paulauskas, & Richards, 1989). Depressed children and adolescents also often experience comorbid disruptive behavior disorders, attention-deficit/hyperactivity disorder (ADHD), and substance abuse (Angold et al., 1999; Bird, Gould, & Staghezza, 1993; Fleming & Offord, 1990; Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993; Lewinsohn et al., 1998; Petersen et al., 1993). For example, Kovacs, Paulauskas, Gatsonis, and Richards (1988) found that one-third of their sample of depressed youth also had been diagnosed with conduct disorder at some point in their lifetimes, while Petersen and colleagues (1993) reported that 10–35% of adolescents experience comorbid depression and conduct disorder. Nottelmann and Jensen (1995) summarized the existing data and found that depression co-occurs with conduct disorder, oppositional defiant disorder, or ADHD in approximately 25% of youth. Of note, Lewinsohn and colleagues (1998) reported that when such comorbidity occurred, MDD developed following the other condition in 80% of their cases.

In the adult depression literature, comorbidity also appears commonplace, and is estimated to be between 56% and 60% (e.g., Blazer, Kessler, McGonagle, & Swartz, 1994). The ECA study found that 75% of individuals with lifetime major depression were also diagnosed with at least one other form of psychopathology (Robins, Locke, & Regier, 1991). Data from the NCS indicate that 27% of all respondents evidenced two or more lifetime psychiatric disorders. Furthermore, "only 21% of all the lifetime disorders occurred in respondents with a lifetime history of just one disorder. This means that the *vast majority* of lifetime disorders in this sample (79%) were comorbid disorders" (Kessler et al., 1994, p. 11; emphasis in original). As in youth, anxiety disorders appear to have the strongest lifetime comorbidities with depression (see Maser & Cloninger, 1990). MDD is also associated with a wide variety of other comorbid conditions, including substance abuse, personality disorders, and poor physical health (Jonas et al., 2003; Kessler, 2002). Again, it appears that first onset of depression follows the onset of other comorbid disorders (Kessler, 2002).

In addition, a significant number of individuals may experience "double depression," defined as the presence of comorbid MDD and DD. In one large-scale study conducted in the United States, approximately 25% of a clinical sample met criteria for double depression (Keller, Lavori, Endicott, Coryell, & Klerman, 1983). General population samples have reported lifetime rates of double depression ranging from 1.6% (Regier, Burke, & Burke, 1990) to 3.4% (Jonas et al., 2003). In the ECA study, almost one-half (48%) of those diagnosed with DD also had a lifetime diagnosis of MDD (Regier et al., 1990), while Jonas and colleagues (2003) found that among those persons with DD, 54.8% were also diagnosed with severe MDD. Thus MDD and DD co-occur at greater than chance levels.

The implications of comorbidity for prognosis and outcomes are substantial. In general, comorbidity appears to lead to more negative outcomes than does the experience of a single disorder. In particular, youth and adults who experience comorbidity tend to evidence more severe problems and to have a more complex symptom picture (Rohde, Lewinsohn, & Seeley, 1991). Research indicates that children and adolescents with comorbid depression and conduct disorder have a poorer prognosis than youth who evidence only one of these disorders (Cole & Carpentieri, 1990; Kovacs et al., 1988). In addition, research has shown that a diagnosis of comorbid depression and conduct disorder significantly increases the likelihood of suicide attempts (Kovacs, Goldston, & Gatsonis, 1993). Likewise, comorbid depression and substance use disorders appear to increase the risk of suicide in both adolescents (Lewinsohn et al., 1998) and adults (Mueller et al., 1994). Comorbidity also predicts treatment utilization; those diagnosed with more than one disorder are more likely to receive treatment (Kessler et al., 1994; Lewinsohn et al., 1998).

In sum, high rates of comorbidity exist in those who suffer from depressive disorders. Though some have argued that rates of comorbidity may be artificially elevated as a result of referral bias, in which those with multiple disorders are more likely to be referred for assessment and treatment (Caron & Rutter, 1991), recent community-based epidemiological studies of the general population also report a significant amount of comorbidity. It should be noted that elevated rates of comorbidity may also in part reflect problems associated with the current nosological system (i.e., the DSM), in which there is symptom overlap across disorders and increased division of diagnostic categories (Caron & Rutter, 1991). Regardless of the issues surrounding the study of comorbidity, the complexity of, and adverse outcomes associated with, multiple diagnoses behoove researchers and practitioners alike to continue to address comorbidity's occurrence in the population.

Course and Prognosis

Age of Onset

Adult depression is now being viewed mainly as a recurrent disorder that begins during adolescence (Hammen & Rudolph, 2003). For example, a longitudinal investigation found that the average age of onset for MDD in a child clinical sample was approximately 11 years, with DD appearing somewhat earlier (Kovacs, Feinberg, Crouse-Novak, Paulauskas, & Finkelstein, 1984a). Lewinsohn and colleagues (1998) have reported the age of onset for MDD in a community sample of youth participating in the Oregon Adolescent Depression Project at 14.9 years. As noted above, it appears that during ages 11–15, a sharp increase in depression emerges and continues into early adulthood (Hankin et al., 1998; Lewinsohn et al., 1998). Earlier onset of depression seems to predicts a longer duration and more severe course in youngsters (Kovacs et al., 1984a; Lewinsohn et al., 1998), and in adults (Hammen, Davila, Brown, Gitlin, & Ellicott, 1992). It also increases the risk for future MDEs (Kovacs et al., 1984b).

Duration

The average duration of episodes of MDD in clinical samples of youth is reported to be between 32 and 36 weeks (Kovacs et al., 1984a), while Lewinsohn and colleagues (1998) reported a mean duration of 26 weeks, with a range of 2 to 250 weeks, in a community sample of adolescents. By its very nature, dysthymia has a longer duration, averaging approximately 3 years in youth (Kovacs et al., 1984a). Length of adult MDD appears similar to the figures reported in youth (Coryell et al., 1994). Others have found that over 90% of adult cases of MDD remitted by 1 year (McLeod, Kessler, & Landis, 1992). However, even after remission, subsyndromal levels of symptoms often persist, along with impairment in functioning in both children (Kovacs & Goldston, 1991) and adults (Judd et al., 2000).

Recurrence

Depression tends to reoccur in both youth and adults. Recent follow-up studies of depressed adolescents suggest that recurrences in adulthood are commonplace (Harrington, Fudge, Rutter, Pickles, & Hill, 1990; Lewinsohn, Rohde, Klein, & Seeley, 1999). Research on adults has revealed that approximately 40% of individuals have a recurrence of MDD within 2 years, and over 80% experience another episode within 5–7 years (Coryell et al., 1994). Likewise, results from a 10-year follow-up of participants in the Zurich Cohort Study (a prospective community-based epidemiological cohort study of young adults ages 19–20 at initial assessment), indicated that 75% experienced one or more recurrent MDEs (Angst, 1992). Boland and Keller (2002) reported that factors increasing the risk for recurrent MDEs include (1) prior multiple MDEs, (2) double depression, (3) onset after age 60, (4) longer duration of MDEs, (5) a family history of mood disorders, and (6) continuing to experience symptoms during continuation therapy. Lewinsohn, Rohde, Seeley, Klein, and Gotlib (2000) found that female gender, multiple MDEs in adolescence, higher proportion of family members with recurrent MDD, borderline personality features, and conflict with parents (for female participants) predicted recurrence of MDD in young adulthood (ages 19–23) in a community sample of formerly depressed adolescents.

Continuity across the Lifespan

According to Hammen and Rudolph (2003), there is preliminary evidence to support the continuity of childhood depression into adulthood. For examples, Weissman and colleagues (1999) followed depressed children into adulthood and found that a subgroup of 108 clinical youths experienced MDD as adults, although the majority of youngsters in the study did not evidence adult depression. Likewise, Harrington, Fudge, Rutter, Pickles, and Hill (1991) found continuity for depression from childhood to adulthood for those who solely evidenced childhood depression, while those with comorbid depression and conduct disorder, although considerably impaired as adults, were less likely to have adult MDD. Thus it appears that a subgroup of children characterized by a family history of depressive disorders, less comorbidity, and recurrent MDEs, may be particularly at risk for continuity of depression into adulthood (Hammen & Rudolph, 2003). Research on the continuity of depression from adolescence to adulthood also reveals substantial stability over time (Lewinsohn et al., 1999; Weissman et al., 1999).

In addition, evidence supports the continuity of depression across the adult lifespan. For example, in their follow-up of participants in the Zurich Cohort Study, Merikangas and colleagues (2003) reported that very few of their respondents had time-limited depression. Instead, they continued to evidence impairment throughout their lives. Likewise, Keller and Boland (1998) concluded that most clinically depressed adults will suffer from a recurrent MDE within 5 years, and that the rate of recurrences increases with the passage of time.

Impairment

Youth and adults who suffer from depressive disorders have impaired, social, emotional, behavioral, and academic/occupational functioning. In childhood, research suggests that depressed youngsters have significantly lower academic achievement than that of their nondepressed peers (Puig-Antich et al., 1985), and are at increased risk for dropping out of high school (Kessler, Foster, Saunders, & Stang, 1995). Childhood depression is also associated with low self-esteem (Kaslow, Brown, & Mee, 1994), as well as suicidal ideation and attempts in adolescence (Lewinsohn et al., 1999). In addition, investigators have noted that compared to their nondepressed counterparts, depressed school children are rated by peers and adults as less attractive and likeable (Mullins, Peterson, Wonderlich, & Reaven, 1986). They also tend to be more socially isolated and to view others as being less friendly (Larson, Raffaelli, Richards, Ham, & Jewell, 1990).

Prospective investigations of adolescents followed into early adulthood have shown that adolescent depression predicts adverse outcomes. Specifically, adolescent depression increased the likelihood of early marriage for young women (Gotlib, Lewinsohn, & Seeley, 1998). It also predicted marital dissatisfaction and, for males, increased marital conflicts (Gotlib, Lewinsohn, & Seeley, 1998). Other investigators have reported higher rates of divorce among those suffering from depressive disorders (Wade & Cairney, 2000). Moreover, in a follow-up investigation of a clinical sample of depressed children and adolescents, researchers found that adolescent depression was associated with increased risk for adult suicide and interpersonal relationship problems (both love relationships and friendships) (Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001). Of note, those individuals who evidenced comorbid MDD and conduct disorder in adolescence proved the most impaired in adulthood, exhibiting the highest rates of suicide, criminal offenses, and social dysfunction (Fombonne et al., 2001). Young adults who experienced MDD in ado-

lescence were also found to exhibit impaired occupational performance, interpersonal functioning, quality of life, and physical well-being (Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2003). However, when covariates such as adolescent comorbidity and psychosocial functioning, adult psychopathology, and current (adult) depression were included in analyses, the relationships between adolescent MDD and adult functioning became nonsignificant (Lewinsohn et al., 2003). Thus Lewinsohn and colleagues (2003) suggest that such variables may mediate the relationship between adolescent MDD and subsequent adult functioning, and they call for continued research in this area. Finally, a growing number of investigations have reported an adverse impact of depression on the physical and social–emotional well-being of older adults (see Powers, Thompson, Futterman, & Gallagher-Thompson, 2002, for a review).

ETIOLOGY

It appears that multiple causal pathways lead to the development of depressive disorders, and that no singular genetic or environmental factor can explain their occurrence. Although different theoretical models tend to emphasize a limited number of etiological factors, there has been a growing recognition of the need to include biological, cognitive, and behavioral/interpersonal variables in a more comprehensive and integrative model of depression. Therefore, as the research on etiological variables is examined, it is important to consider how these variables may interact over time and lead to a developmental trajectory characterized by affective disturbance.

Biological Aspects of Depression

Genetic Research

Research has confirmed that there are significant genetic influences in unipolar depression (see Wallace, Schneider, & McGuffin, 2002, for a review). Most of this work has consisted of studies examining rates of depression among family members/relatives, as well as twin studies. First, family aggregation studies investigate whether depression occurs more frequently among the relatives of those who are depressed than among the relatives of control subjects who do not evidence a depressive disorder. Research conducted with depressed children and their families has shown that if one parent has MDD or if there is a family history of MDD, the risk that children in that family will develop depression is approximately 15% (Goodwin, 1982). If both parents have a history of MDD, the risk increases to 40% for any child in that family (Goodwin, 1982). In their review of the literature, Downey and Coyne (1990) also reported that children of depressed parents were more likely to receive a depressive disorder diagnosis than control children. In fact, the rate of any mood disorder was three times higher in children of depressed parents than in control youngsters (Downey & Coyne, 1990). Furthermore, these children appeared to be at specific risk for MDD, as their rate of MDD was six times that of the control youth (Downey & Coyne, 1990). Similarly, studies that have investigated samples of adult probands have also found higher rates of depression in relatives of depressed probands than in relatives of control participants (Sullivan, Neale, & Kendler, 2000). In their meta-analysis, Sullivan and colleagues (2000) found that all five family studies included in their review confirmed a family aggregation of MDD in the first-degree relatives of probands with MDD compared to controls, with an odds ratio across the studies of 2.84 (95%

confidence interval [CI] = 2.31–3.49). Thus results of family investigations not only support the notion that depression runs in families, but imply a genetic contribution to depressive disorders. However, it must be stated that family aggregation studies cannot *prove* a genetic basis for depression, as they do not control for possible environmental sources of transmission (Wallace et al., 2002).

As a result, research designs that utilize twin samples have been undertaken in an effort to discern possible genetic contributions to depression more clearly. In twin studies, monozygotic (MZ) twins, who share all of their genetic makeup, are compared to dizygotic twins (DZ), who share half of their genes. It is generally assumed that MZ and DZ twins are similar in terms of shared environment; therefore, any differences in concordance rates of depressive disorders are assumed to be due primarily to genetic determinants. Results of twin studies generally support a heritable component to depression (Lyons et al., 1998; McGuffin, Katz, Watkins, & Rutherford, 1996; Sullivan et al., 2000). For example, McGuffin and colleagues (1996) examined 177 adult probands with MDD and their same-sex cotwins and found that the concordance rate for MDD in MZ twins was 46%, while the concordance rate for MDD in DZ twins was 20%. In addition, the investigators found that certain proband characteristics led to a higher MZ concordance rate, including having more than two MDEs, having a longest MDE of 13 months or less, and having an endogenous pattern of symptoms. Lyons and colleagues (1998) assessed 1,874 MZ and 1,498 DZ pairs of adult male twins from the Vietnam Era Twin Registry. Results of this large-scale study showed that MZ twins were significantly more likely to be concordant for MDD than DZ twins, with a 22.5% MZ concordance rate compared to a 14% DZ concordance rate. When DD was examined, concordance rates were lower for both MZ and DZ probands (7.4% and 8.7% respectively), and no significant differences between twin types were found. In addition, Lyons and colleagues reported that severity of MDD was associated with a heavier genetic loading, as MZ twins had significantly higher concordance rates for severe/psychotic MDD than DZ twins. Moreover, there was a greater MZ than DZ concordance rate for early-onset MDD, implying that early-onset and severe MDD may be more heritable conditions. Lyons and colleagues summarize their findings by indicating that both genetic and nonshared/unique environmental factors contributed to MDD, whereas shared/family environmental factors did not appear to play a role. In contrast, DD diagnosis was affected by family and unique environmental factors, but not by genetics. Likewise, Sullivan and colleagues (2000) included five twin studies in their meta-analysis and reported that family aggregation of MDD was due to an additive effect of genetics (point estimate of heritability of liability = 37%, 95% CI = 31–42%), and unique/nonshared environmental factors (point estimate = 63%, 95% CI = 58–67%), while shared family environment of siblings made little contribution (point estimate = 0%, 95% CI = 0–5%). Meta-analytic results further indicated that the genetic contribution to depression was similar for both genders.

These, results suggest substantial heritability for MDD. However, there are limitations to twin studies, including questionable generalizability to other populations, potential problems in determining zygosity, and difficulty in obtaining representative samples of all available twins in a given population (Wallace et al., 2002). Although it is not possible to prove definitively that results of these studies are not substantially influenced by such limitations, there is currently no reason to question the validity of twin study findings (Sullivan et al., 2000). In sum, twin studies provide some of the strongest evidence that both genetics and unique environmental factors contribute to the development of depressive disorders (Wallace et al., 2002).

Given these data, attempts are underway to identify possible candidate genes that may be responsible for depression. A number of candidate genes have been targets for study, especially those associated with neurotransmitter systems, such as the serotonin transporter (5-HTT) gene located on chromosome 17 (Morley, Hall, & Carter, 2004; Wallace et al., 2002). Studies of 5-HTT gene polymorphism have provided some preliminary evidence that this gene variant may result in some phenotypic effect (Wallace et al., 2002). For example, after controlling for family history of suicide, Joiner, Johnson, Soderstrom, and Brown (2003) found that individuals with polymorphism in the 5-HTT gene were significantly more likely to have two or more first-degree relatives with a history of depression than those without the gene variant. In a longitudinal investigation, Caspi and colleagues (2003) reported that polymorphism in the 5–HTT gene moderated the impact of stressful life events on depression. Other candidate genes have been less well examined. Furthermore, replication of findings is needed, as well as the creation of additional technologies that will allow a more comprehensive analysis of genetic contributions to mood disorders (Wallace et al., 2002). The Human Genome Project has great potential to advance our knowledge of the genetic basis for depression in the coming decades (Wallace et al., 2002).

Neurobiological Research

Studies of the neurobiology of depression have examined possible neurochemical and neuroanatomical abnormalities. Neurochemical theories of depression emphasize dysfunction of one or more neurotransmitter systems in the brain. The neurotransmitters implicated in depression include the monoamines norepinephrine, serotonin (5-HT), and dopamine (American Psychiatric Association, 2000a; McKim, 1997; Stark, Laurent, Livingston, Boswell, & Swearer, 1999). These monoamine neurotransmitters are involved in the regulation of behaviors that are associated with problems during depression, such as sleep and appetite disturbances, psychomotor agitation or retardation, and others. (Thase, Jindal, & Howland, 2002). According to neurochemical models, a reduction or depletion of these neurotransmitters is associated with depressive disturbances. How does this occur? According to Thase and colleagues (2002), prolonged exposure to stress in genetically vulnerable individuals is believed to affect vital areas of the brain, ultimately leading to reduced levels of monoamines and subsequent characteristic symptoms of depression. More specifically, perception of stress is relayed from the cerebral cortex to the locus coeruleus via the thalamus and hypothalamus, leading to release of norepinephrine and cortisol (Thase et al., 2002). As the locus coeruleus neurons continue to fire in response to chronic stress, and norepinephrine is released, a number of counterregulatory processes attempt to help the organism regain homeostasis. These processes include a reduction and down-regulation of receptor sites, as well as activation of inhibitory 5-HT neurons (Thase et al., 2002). However, if elevated stress continues, eventually norepinephrine stores will become depleted and the system becomes dysregulated.

5-HT pathways in the brain are colocalized with the norepinephrine pathways described above, and act to counterbalance norepinephrine activity (Thase et al., 2002). 5-HT is involved in the regulation of appetite, the sleep–wake cycle, and body temperature. Low levels of 5-HT have been associated with aggression, suicide, and violence (Mann, Brent, & Arango, 2001). As in the case of norepinephrine, stress has been found to lead to the down-regulation of 5-HT_{1A} receptors, eventually leading to abnormally low levels of 5-HT stores (Thase et al., 2002). In an analogous manner, chronic stress also reduces dopamine, a monoamine neurotransmitter whose neural pathways begin in the ventral tegmentum and extend to the

mesolimbic system (McKim, 1997). Dopamine is involved in emotional expression, goal-directed behavior, motivation, and executive functioning (Thase et al., 2002). Dysfunction of the serotonergic system also appears to impact the dopaminergic system, highlighting the complex and interactive nature of neurochemical systems of the brain (Thase et al., 2002). Evidence in support of neurotransmitter deficits in depression comes from psychopharmacological treatment studies, which show that medications increasing neurotransmission lead to a reduction in depressive symptomatology (see Gitlin, 2002). Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) block the reuptake of norepinephrine and/or 5-HT at the presynaptic terminal, allowing more of each neurotransmitter to be available to neurons (Gitlin, 2002; McKim, 1997).

Given the important role that stress plays in altering monoamine functioning, it is imperative to discuss the relationships among stress, abnormalities in the HPA axis, and depression (Plotsky, Owens, & Nemeroff, 1998). 5-HT and norepinephrine help modulate the secretion of hormones by the HPA system. Stress also activates the HPA axis, culminating in the synthesis and hypersecretion of adrenocortical steroids (Plotsky et al., 1998). This includes production of corticotropin-releasing hormone, which stimulates the production of adrenocorticotropic hormone (ACTH) by the pituitary. ACTH leads to the production of cortisol by the adrenal glands (Plotsky et al., 1998). Such increased activity is revealed in elevated urinary free cortisol concentrations or nonsuppression of plasma cortisol (Plotsky et al., 1998; Thase et al., 1996). The dexamethasone suppression test (DST) has been used as a method of assessing cortisol secretion in depressed individuals (Yaylayan, Weller, & Weller, 1992). During the DST, a dose of dexamethasone (a synthetic steroid) is given, and cortisol levels are subsequently measured. The failure of dexamethasone to reduce cortisol secretion after its administration results in a positive DST (Yaylayan et al., 1992). The reaction to the DST determines whether dysregulation is occurring in the HPA axis. According to Yaylayan and colleagues (1992), cortisol hypersecretion has been found in about 50% of adults with endogenous depression. Thus depressive disorders appear related to hypothalamic dysfunction and related deficits in monoamine neurotransmitters.

In addition, the hypothalamic–thyroid system may contribute to depression. Hypothyroidism is associated with depression, and thyroid hormone replacement therapy has been found to alleviate depressive symptoms in adults, while similar results of thyroid hormone replacement have not been found in prepubertal depressed children (Burke & Puig-Antich, 1990), suggesting possible age mediation (Stark et al., 1997).

Next, abnormalities in growth hormone (GH), secreted by cells in the anterior pituitary, have been reported in depressed adults (Thase & Howland, 1995; Yaylayan et al., 1992). Blunted GH secretion has been found following sleep onset or in response to antidepressant medications (Thase et al., 2002). Likewise, recent investigations of depressed youth have reported low responses to GH-releasing hormone, with continued blunted responses following remission of the depressive episode (Dahl et al., 2000); this implies that abnormal GH secretion may be a "marker" of depression (Thase et al., 2002).

Another biological system implicated in depression is the sleep–wake cycle. Depressed individuals often manifest sleep disturbances, and electroencephalographic (EEG) studies have been undertaken to determine the underlying nature of sleep abnormalities. Research conducted with depressed adults has identified a number of disturbances in sleep patterns, including reduced slow-wave sleep; increased rapid-eye-movement (REM) density in early REM periods during the night; short REM latency; and various discontinuities in sleep, such as initial, middle, and terminal insomnia (Thase et al., 2002; Yaylayan et al., 1992). Severity of depression has been found to be related to inefficient sleep and wakefulness, as well as an increase in the intensity of phasic REM sleep (Thase et al., 2002). It seems that

the sleep difficulties manifested by those with depression may be a result of dysregulation of 5-HT, norepinephrine, and/or acetylcholine neurotransmitter systems (Thase & Howland, 1995). It should be noted that the abnormalities in sleep patterns found in adults have not been replicated in EEG studies of children; this again points to the importance of examining biological aspects of depression from a developmental, lifespan perspective (Burke & Puig-Antich, 1990; Thase et al., 2002).

In addition to research into the neurochemical systems involved in depression, investigators have studied the neuroanatomy of individuals with depressive disorders. This research has included postmortem studies of brain structures; it also uses imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and functional MRI (fMRI), as well as examinations of cerebral metabolism via positron emission tomography (PET) scans. Results of these investigations reveal that a number of abnormalities characterize adults who suffer from unipolar depression. To begin, several EEG studies of adolescents and adults have reported brain asymmetries in those with depression, including higher right and lower left frontal brain activity (Davidson, Pizzagalli, & Nitschke, 2002; Gotlib, Ranganathand, & Rosenfeld, 1998; Miller et al., 2002). According to Davidson and colleagues (2002), left frontal brain regions appear more active during approach-related (positive) experiences of emotion, while the right frontal regions seem to be more active during withdrawal-related (negative) emotions. Thus asymmetries in brain activation in which there is left hypoactivation appear to lead to reduced ability to experience positive emotions and an increased responsivity to negative stimuli—the hallmark characteristics of those who suffer from depression (Davidson et al., 2002; Gotlib, Ranganathand, & Rosenfeld, 1998). Congruent with these notions, Gotlib, Ranganathand, and Rosenfeld (1998) examined a sample of currently depressed, previously depressed, and never-depressed females, and found that both the currently and previously depressed groups evidenced left frontal lobe hypoactivation in comparison to control participants. In another investigation, Miller and colleagues (2002) found gender differences in brain activation of young adults with a childhood history of depression. In particular, women with childhood depression, but not men with similar histories, showed higher right and lower left frontal brain activity. Miller and colleagues surmise from these findings that men and women may differ in their biological predispositions for emotion regulation, and they call for additional research in this area. In addition, investigations of infants and toddlers of depressed mothers reveal similar left frontal hypoactivation in these youngsters, implying that brain activation abnormalities may be genetically transmitted, acquired prenatally, or acquired during early stressful mother–child interactions (Dawson, 1994). Taken together, these investigations provide support for the notion that left frontal hypoactivation may be a stable marker of vulnerability to depression (Davidson et al., 2002; Gotlib, Ranganathand, & Rosenfeld, 1998).

In addition to left frontal lobe hypoactivation, researchers have reported anatomical differences between depressed individuals and their nondepressed counterparts. In one such study, Coffey and colleagues (1993) used MRI and found that the mean total frontal lobe volume was 7% smaller in the severely depressed adult inpatients than in a comparison group of nondepressed individuals. They also reported that the patients with depression had a significantly higher frequency of subcortical hyperintensity in the periventricular white matter (Coffey et al., 1993). Likewise, in their review of neuroimaging studies, Soares and Mann (1997a) found evidence for reduced frontal lobe volume, as well as smaller basal ganglia and cerebellum volume, in those with unipolar depression. Rajkowska (2000) has examined anatomical abnormalities in postmortem brains and found altered numbers of neurons and glial cells in those with mood disorders, possibly leading to the volume

reductions and metabolic changes observed in those with depression. These alterations included cell loss in the subgenual prefrontal region, cell atrophy in the dorsolateral prefrontal cortex and orbitofrontal cortex, and increased numbers of cells in the hypothalamus and dorsal raphe nucleus.

fMRI and PET studies also indicate that individuals with depression appear to have regional cerebral blood flow and glucose metabolism deficits (see Davidson et al., 2002; Soares & Mann, 1997b). In particular, depressed individuals exhibit decreased blood flow and metabolism in the prefrontal cortex, as well as in the basal ganglia (Soares & Mann, 1997b). The prefrontal cortex is thought to play an important role in volition, working memory, inhibition, motivation, and regulation of emotion. Therefore, dysfunction of the prefrontal cortex appears to be an area of importance in the pathophysiology of depression (Soares & Mann, 1997b). Since the prefrontal cortex is also involved in cognitive functions (attention, concentration, etc.), dysfunction in this brain region may underlie the cognitive impairments common in depressed persons (Livingston, Stark, Haak, & Jennings, 1996; Soares & Mann, 1997b). Other brain abnormalities associated with depression include reduced anterior cingulate cortex activation, and hyperactivation of the amygdala, in a subgroup of depressed persons with familial pure depressive disease (Drevets, 2001).

There has been conflicting evidence regarding abnormalities in the temporal lobe of unipolar depressed individuals, with most studies failing to find abnormalities in glucose metabolism, while most blood flow studies point to abnormalities (Soares & Mann, 1997b). Likewise, there have been inconsistent findings regarding abnormalities in the hippocampus of those who are depressed; it has been suggested that variables such as age, severity, and gender may serve as moderators (Davidson et al., 2002). According to Soares and Mann (1997b), genetic and environmental factors probably interact with these brain structures to influence the development of depression. However, longitudinal investigations of at-risk individuals are needed in order to determine which brain dysfunctions and abnormalities found in depressed individuals are etiological determinants, and which arise secondary to dysfunctions that initially occur in other areas (Davidson et al., 2002; Drevets, 2001).

Cognitive Diathesis–Stress Models

Cognitive diathesis–stress models propose that depressive disorders develop as a result of a disturbance in cognition that becomes activated by vulnerabilities to stressful life events (Stark et al., 1999). Two major cognitive models of depression have received considerable attention in the literature (i.e., Abramson, Metalsky, & Alloy, 1989; Beck, 1967). According to Beck's (1967) cognitive theory, exposure to stressful, negative life events activates maladaptive schemas that serve as a filter, guiding the processing of information in a negatively distorted manner. As a result, individuals engage in biased information processing, which leads them to hold negative views about the self, world, and future (Beck's "cognitive triad"). The self-schema, in particular, plays a crucial role in depression and contains cognitive content that is unrealistically negative and characterized by a sense of loss, unlovability, and/or inadequacy. When activated, this schema leads persons to seek out and incorporate environmental stimuli that confirm their negative self-view, and to ignore or distort contradictory evidence. Thus schema-driven, biased information processing leads to reinforcement of the negative self-schema and cognitive triad, producing and maintaining depression through a circular feedback loop (Beck, 1967). Beck proposes that maladaptive cognitive schemas develop early in life in response to stress, which may be related to real or perceived loss. Furthermore, Beck (1987) believes that this cognitive model applies

mainly to a subgroup of depressive persons who evidence nonendogenous, unipolar affective illness.

Similarly, Abramson and colleagues (1989) have proposed a cognitive diathesis–stress theory called the "hopelessness theory" of depression. This theory stipulates that a subtype of depression, "hopelessness depression," exists; it includes a number of cognitive, behavioral, affective, and motivation symptoms, such as sadness, retarded initiation of voluntary responses, lack of energy, apathy, psychomotor retardation, suicidal ideation and attempts, sleep disturbance, concentration problems, and mood-exacerbated negative cognitions (Abramson et al., 1989). According to Abramson and colleagues, hopelessness depression develops as a result of expectations that highly desired outcomes will not occur or that undesired outcomes will occur, and that no possible response will change the likelihood of these outcomes. In this theory, negative life events are the "occasion setters" for the development of hopelessness and subsequent depression. Abramson and colleagues argue that three kinds of conclusions about negative events contribute to the development of hopelessness: causal attributions, inferred consequences, and inferred characteristics about the self. Specifically, individuals are likely to develop hopelessness and subsequent depression when they attribute important negative life events to stable (over time) and global (affecting many areas of life) causes. Second, if individuals believe that adverse consequences of these events are important, are not amenable to change, or are likely to lead to other negative consequences, they will be prone to experience hopelessness depression. Third, Abramson and colleagues highlight the importance of the impact that these negative life events have on individuals' beliefs about the self, such as worth, abilities, and personality.

Abramson and colleagues (1989) believe that stress alone is insufficient to trigger a depressive episode. Rather, some individuals are susceptible to the depressogenic effects of stress. Specifically, vulnerability to depression following exposure to negative life events (the stress) stems from a general style of explaining the causes of life events, known as a "depressogenic" attributional or explanatory style (the diathesis). Individuals who characteristically attribute negative events to stable and global factors, and who view negative events as important, are likely to develop hopelessness upon exposure to stress. If negative events do not occur, or if positive events take place, the depressogenic attributional style will not become activated, and hopelessness depression will not develop. Thus cognitive style serves as a vulnerability factor when persons experience negative life events (stress).

Research has examined several tenets of Beck's (1967) and Abramson and colleagues' (1989) cognitive theories of depression. Cross-sectional studies that examined the cognitive products of depressed versus nondepressed individuals confirmed that those with depression exhibited more negative thoughts about the self, world, and future; had more dysfunctional attitudes; and evidenced a depressogenic attributional style for positive and negative events (Beck, 1967; Gladstone & Kaslow, 1995; Gotlib, 1984; Gotlib, Lewinsohn, Seeley, Rohde, & Render, 1993; Stark, Schmidt, & Joiner, 1996). However, more sophisticated research designs and a more comprehensive examination of diathesis–stress theories were needed. Therefore, prospective studies were conducted with both youngsters (Nolen-Hoeksema, Girgus, & Seligman, 1992; Robinson, Garber, & Hilsman, 1995) and adults (Reilly-Harrington, Alloy, Fresco, & Whitehouse, 1999), and revealed that those who evidenced depressogenic cognitive styles were more likely to develop subsequent depressive symptoms after experiencing negative life events than those who did not evidence the cognitive diathesis. Likewise, prospective studies of Beck's (1967) theory found that the negative cognitive triad and/or dysfunctional attitudes interacted with negative life events

to predict increases in depressive symptoms over time in adults (Joiner, Metalsky, Lew, & Klocek, 1999) and youth (Reinemann, Eckert, Brodigan, & Ellison, 2004).

Other tests of the cognitive theories of depression have employed "behavioral high-risk" designs. These studies have examined individuals who were at risk for developing depressive disorders due to a depressogenic cognitive style, but who currently were not depressed. These individuals have been compared to their low-risk counterparts on their likelihood of experiencing depressive disorders both in the past (retrospectively) and in the future (prospectively) (Abramson et al., 2002). One such project utilizing this design has been the Cognitive Vulnerability to Depression project, conducted collaboratively at Temple University and the University of Wisconsin–Madison (Alloy & Abramson, 1999; Alloy et al., 1999, 2000). Using a retrospective behavioral high-risk design, Alloy and colleagues (2000) found that those individuals classified as high risk due to their depressogenic cognitive styles and dysfunctional attitudes had higher lifetime prevalence rates of MDD, hopelessness depression, and minor depressive disorder than their low-risk counterparts. In fact, the lifetime risk of MDD was triple for the high-risk group. Likewise, Alloy and colleagues (1999), in a prospective high-risk design, reported that high-risk participants were more likely to develop subsequent MDD (17% vs. 1%), hopelessness depression (41% vs. 5%), or minor depressive disorder (39% vs. 6%) during the first 2½ years of follow-up than were those at low cognitive risk. Thus a large body of research has provided support for cognitive diathesis–stress vulnerability models of depression. However, more attention is needed regarding the mechanisms through which a cognitive diathesis for depression develops.

Behavioral/Interpersonal Aspects of Depression

Early behavioral/interpersonal models conceptualized the development of depression as an overgeneralized response to a stimulus (negative life event) (Gotlib & Hammen, 1992). For example, Lewinsohn (1975) proposed that depression develops as a result of low rates of response-contingent positive reinforcement and/or high rates of aversive experiences in important areas of life. The lack of positive reinforcement may occur as a result of within-person social skills deficits, an environment that lacks positive reinforcement or contains negative life experiences, or an individual's inability to enjoy positive reinforcement (anhedonia) and/or increased sensitivity to stress (Lewinsohn, 1975). Coyne (1976) expanded on behavioral models and proposed an interpersonal theory stipulating that depressed individuals elicit a pattern of rejection in others, which reinforces the depression. Thus individuals create negative social environments in which their increasingly symptomatic behavior, in an effort to elicit support, becomes aversive; this leads to rejection, avoidance, and reinforcement of the affective disturbance. Behavioral/interpersonal theories have recently received new attention and have been expanded to explain another possible pathway to the development of depression. According to Joiner, Coyne, and Blalock (1999), these new efforts have converged around the notion that "interpersonal experience, especially involving significant others (e.g., parents), affects mood outcomes by laying down a negative and stable view of the interpersonal world" (p. 13). Thus new theories are integrating cognitive, behavioral, and interpersonal components into their explanations of the etiology of depression.

Research on interpersonal risk factors for depression has focused on social skills deficits, interpersonal dependency, and inhibition (Joiner, 2002). For example, in a meta-analytic review, Segrin (1990) examined the evidence that social skills impairment is related

to the development of depression. Results suggested only moderate support for this notion, and support primarily came from studies that used self-reports to measure social skills. Likewise, Joiner (2002) reported little evidence for a main effect of social skills deficits on later depression. However, social skills may serve as a diathesis for depression when activated by some other moderator variable such as stress, although few studies have tested this notion (Joiner, 2002). Research has found a relationship between a specific type of social skills problem, that being seeking negative feedback, and depression. Specifically, Giesler, Josephs, and Swann (1996) reported that 82% of depressed individuals in their sample sought out information that confirmed their negative self-views, and also failed to seek out positive evaluations from others. Thus, as Beck (1967) proposed, once the negative self-schema is activated, it biases information processing so that a depressed individual assimilates negative information congruent with this schema, while discounting incongruent, positive information.

Various depression researchers have also identified interpersonal dependency as a risk factor for depression (Blatt, 2004; Schmidt, Schmidt, & Young, 1999). According to Schmidt and colleagues (1999) perception of stress leads to reassurance-seeking behaviors. However, information-processing biases in those with cognitive risk will have an impact on this process. Specifically, Schmidt and colleagues state that maladaptive, negative schemas lead to increased detection of social stressors, lead to more negative interpretations of stressors, lead to greater reassurance seeking when schema-relevant stressors occur, produce ineffective reassurance-seeking behaviors, and produce more negative and ambiguous perceptions of interpersonal feedback; together, these factors ultimately lead to depression. Congruent with this model, Joiner and Schmidt (1998) have found that excessive reassurance seeking prospectively predicted depressive reactions to stress in college students.

Moreover, excessive need for and concern about interpersonal attachment are believed to lead to behaviors that contribute and maintain depression (Joiner, 2002). Congruent with this hypothesis, investigators examined interpersonal attachment cognitions (i.e., the ability to be close to and depend on others, and anxiety about rejection/abandonment) in the prediction of depression in adult women (Hammen et al., 1995). Results indicated that following interpersonal stress, interpersonal attachment cognitions had direct or interactive effects on the prediction of depression and other psychological symptoms 1 year later. Likewise, Stark and colleagues (1999) have integrated attachment theory into their model of childhood depressive disorders. According to these researchers, perceived negative parental messages about the self, world, and future, as well as punitive parent–child interchanges, contribute to a negative affective home atmosphere and an insecure parent–child attachment relationship. If this occurs, the child will develop an internal working model characterized as full of contradictions, leading to the development of a dysfunctional schema about relationships and a negative core self-schema. When the child is exposed to stressors, these schemas begin to guide information processing and subsequent behavior. As a result, the child begins to act in ways that elicit rejection and isolation, further solidifying the negative self-view and producing and maintaining depression (Stark et al., 1999). Research has shown that negative messages directed at the child from parents are related to the child's developing schemas and symptomatology (Stark et al., 1996).

Finally, it has been suggested that interpersonal inhibition (e.g., avoidance, shyness, withdrawal) may serve as a risk factor for depression, although few investigations have addressed this possibility (Joiner, 2002). In one such study, Joiner (1997) examined college undergraduates and found that those who were shy and unsupported were more likely to experience increases in depressive symptoms and decreases in positive affect over time than those who were not inhibited. Furthermore, Joiner found that loneliness partially

mediated the relationship between inhibition and subsequent depression. These results lend support to the notion that interpersonal inhibition may serve as a vulnerability factor for depression that operates through increased loneliness/isolation.

In summary, a cognitive and behavioral/interpersonal framework for explaining the etiology of depression posits that stress exposure and maladaptive schemas arising out of dysfunctional parent–child attachment relationships lead to interpersonal dysfunction. Over time, a pattern of aversive interpersonal interactions develops; this serves to isolate the individual from social support, inhibits the development of prosocial behaviors, and solidifies the negative self-schema, culminating in the development and maintenance of depressive symptomatology. Although various aspects of the model have been empirically examined, additional prospective research is needed in order to fully test the model and its applicability across the lifespan.

ASSESSMENT OF DEPRESSIVE DISORDERS

Issues in Clinical Assessment

Given that depression has been described as one of the world's most serious diseases (Gotlib & Hammen, 2002; Murray & Lopez, 1997), accurate assessment of this ubiquitous problem is paramount. In addition, since research has demonstrated the continuity between childhood depressive disorders and adult depressive disorders (Zeitlin, 2000), reliable and thorough assessment of depressive symptomatology is vital for improving the course and prognosis for depressed individuals. Although the interplay between depressive disorders and physical illness in adults is frequently seen by primary care physicians, many such physicians do not feel adequately trained to address depressive symptomatology (Schulberg, Schulz, Miller, & Rollman, 2000). In older adults, the presence of a depressive disorder may be overlooked in favor of a medical diagnosis. Conversely, a medical condition may appear to manifest as a depressive disorder. Furthermore, depression in older adult patients may be a response to the physical illness and/or disability occurring in the aging process. The etiology of adult depression is thus an important component of the assessment process. It is vital to assess the temporal presentation of physical illness and depressive disorders in the adult patient.

Clinical assessment should include a complete mental status examination of the depressed patient, with questions about age of onset, frequency of symptom recurrence, and family history of mood disorders. For an adult patient, a complete medical exam should also be conducted, to rule out any organic cause of the depressive symptomatology. Certain illnesses, such as cancer, cardiovascular disease, multiple sclerosis, diabetes mellitus, and hypothyroidism, are among the most common diseases with concomitant depressed mood (Schulberg et al., 2000). Fortunately, many assessment tools, including both pencil-and-paper and interview formats, are available for accurate assessment of depressive symptomatology.

Diagnostic Interviews

There are several well-known clinician-administered interviews that can be used for deriving DSM-IV-TR depressive disorder diagnoses. One major advantage of diagnostic interviews is that they also assess comorbid DSM conditions. Three of the most widely used and psychometrically sound diagnostic interviews are the Schedule for Affective Disorders

and Schizophrenia (Endicott & Spitzer, 1978); the Diagnostic Interview Schedule—IV (Robins et al., 2000); and the Structured Clinical Interview for DSM-IV Axis I Disorders (First, Spitzer, Gibbon, & Williams, 1997). Though all three interviews are time-intensive, they provide a reliable assessment of depressive disorders.

Rating Scales

There are many self-report rating scales that can be used to assess the symptomatology of a depressed patient (see Table 9.2). In a review of the *Mental Measurement Yearbooks* from 1985 to 2003, 14 psychometrically sound self-report rating scales for adults were identified. For a more comprehensive review of each self-report measure, the reader is encouraged to read the *Mental Measurements Yearbooks* (Impara & Plake, 1998; Kramer & Conoley, 1992; Mitchell, 1985; Plake & Impara, 2001; Plake, Impara, & Spies, 2003).

TREATMENT AND PROGNOSIS

Antidepressant medications have historically been the front-line treatments for depressive disorders in adults. There are over 24 antidepressant agents (for a complete review, see Gitlin, 2002). This section begins with an overview of typical pharmacological therapies. Although it is beyond the scope of this chapter to include a review of all antidepressant medications, the goal is to familiarize the reader with the array of pharmacological choices for use with depressed adults. While pharmacotherapy is often the first choice of treatment for depressed adults, clinicians and physicians must be aware that other medications can produce dysphoric affect. For example, antihypertensive medication, corticosteroids, and sedative/hypnotic medications have been found to produce depressed mood (Schulberg et al., 2000). A complete medical history, including a thorough medication history, should be a part of a clinical assessment for depressed adults. Following the overview of pharmacotherapy, we review the leading psychosocial therapies for depression.

Pharmacotherapy

Selective Serotonin Reuptake Inhibitors

The SSRIs are the most commonly prescribed antidepressant medications and have demonstrated effectiveness in treating depression in adults (Morishita & Arita, 2003). These antidepressants have relatively few side effects and are easy to administer, with once-daily dosing. The SSRIs block the presynaptic reuptake of 5-HT, and a similar new class of drugs, the serotonin and norepinephrine reuptake inhibitors (SNRIs), inhibit the reuptake of both 5-HT and norepinephrine. Although both the SSRIs and the SNRIs are effective in treating depression in adults (Puech, Montgomery, Prost, Solles, & Briley, 1997), the onset of action may differ. In a study comparing the effectiveness of fluvoxamine (Luvox), paroxetine (Paxil), and milnacipran (Ixel), researchers found that the onset of action for milnacipran (an SNRI) was 2 weeks faster than the onset of action for the other two drugs (Morishita & Arita, 2003). Results suggest that if a patient does not respond within 6 weeks to fluvoxamine and paroxetine or within 4 weeks to milnacipran, the treatment protocol should be altered. SSRIs have also been found to be effective in elderly patients (mean age of 70 years old). In a placebo-controlled, flexible-dose, double-blind, randomized trial, both

TABLE 9.2. Self-Report Measures for Adult Depression

Name	Publisher	Ages; number of items	Language(s)
Beck Depression Inventory–II	Psychological Corporation	13 to adult; 21 items	English, Spanish
Brief Symptom Inventory	Pearson NCS	18 to adult; 18 items	English
Carroll Depression Scales	Multi-Health Systems	18 to adult; 61 items and a 12-item brief scale	English, French Canadian
Clinical Assessment Scales for the Elderly	Psychological Assessment Resources	Ages 55–90; 300 items; 100 items (short form)	English
College Adjustment Scales	Psychological Assessment Resources	College and university students; 108 items	English
Hamilton Depression Inventory	Psychological Assessment Resources	Adults; 38 items	English
Hospital Anxiety and Depression Scale	NFER–Nelson	Adults, ages 18–89; 14 items	English
Millon Clinical Multiaxial Inventory–III	Pearson NCS	18 to adult; 175 items	English, Spanish
Minnesota Multiphasic Personality Inventory–2	University of Minnesota Press; distributed by Pearson NCS	18 to adult; 567 items	English
Multiscore Depression Inventory	Western Psychological Services	13 to adult; 118 items	English
Revised Hamilton Rating Scale for Depression	Western Psychological Services	Depressed individuals; 76 items and clinician rating form	English
Reynolds Depression Screening Inventory	Psychological Assessment Resources	18–89; 19 items	English
Symptom Checklist 90—Revised	Pearson NCS	13 to adult; 90 items	English
State–Trait Depression Adjective Checklists	Psychological Assessment Resources	14 to adult; 2 forms, 34 state-mood items, 34 trait-mood items.	English

controlled-release paroxetine (Paxil CR) and immediate-release paroxetine (Paxil IR) were effective in treating MDD in elderly adults (Rapaport, Schneider, Dunner, Davies, & Pitts, 2003).

Tricyclic Antidepressants

The tricyclic antidepressants are the oldest class of antidepressants and have significant side effects, which make them less desirable than the SSRIs and SNRIs. Age and gender studies have typically not found a differential treatment response pattern to any class of

antidepressant medications (Scheibe, Preuschhof, Cristi, & Bagby, 2002). Both males and females appear to respond equally well to SSRIs and tricyclics (Parker, Parker, Austin, Mitchell, & Brotchie, 2003; Powers et al., 2002).

Monoamine Inhibitors

The monoamine inhibitors (MAOIs) not only have significant side effects, but their use also stipulates significant dietary restrictions. Individuals taking MAOIs need to monitor their diets carefully, due to increased risk of hypertension. Thus MAOIs are typically the third- or fourth-line antidepressants (Gitlin, 2002).

There are many factors to consider in choosing a path of treatment for depression. First, treatment adherence factors need to be considered. Would medication, psychosocial treatment, or both medication and therapy be the best front-line treatment? If medication is chosen, what are the side effects, ease of administration, medication history, and patient's compliance? If psychosocial treatments are pursued, which form of treatment would be best in terms of efficacy and presenting issues? Life circumstances, age, physical health, depressive subtype, side effect profile, support systems, history of past response, family history, and treatment cost are other issues to explore in pursuing a course of treatment for depression. Therefore, the depressed patient, the patient's family, and clinician(s) must work together to formulate an effective treatment plan.

Psychosocial Treatments

Cognitive-Behavioral Treatment

In over 80 controlled research trials, cognitive-behavioral interventions for depression have been shown to be effective forms of treatment (American Psychiatric Association, 2000b). Since Aaron Beck pioneered the use of cognitive therapy for depressive disorders (Beck, Rush, Shaw, & Emery, 1979), many other researchers and clinicians have expanded upon this seminal work. An impressive array of theory-driven research supports the use of cognitive-behavioral interventions in the treatment of depression (DeRubeis & Crits-Christoph, 1998). Cognitive theory suggests that changes in cognition are vital for positive changes in depressive symptomatology (Beck et al., 1979). Changes in cognitive functioning are connected to positive treatment outcome. Findings from a controlled trial (patients randomly assigned to an antidepressant and clinical management condition or to an antidepressant, clinical management, and cognitive therapy condition) suggest that cognitive therapy alters dichotomous, absolutist, negativistic thinking, which reduces relapse rates (Teasdale et al., 2001). Relatedly, few changes in cognitive content and rigid negative thinking are associated with shorter duration to time of recurrence of depressive symptoms (Beevers, Keitner, Ryan, & Miller, 2003). Thus both theory and empirical work support the vital connection between cognitive restructuring and positive treatment outcome for depressed patients.

Interpersonal Psychotherapy

Interpersonal psychotherapy (IPT) has over a 30-year track record of effectively reducing depressive symptomatology. It is one of the American Psychiatric Association's recommended therapies for adults with depressive disorders (Weissman & Markowitz, 2002). The focus of IPT is on the patient's present functioning and on making significant, positive life changes. In addition, IPT conceptualizes depression as a medical illness that is a treatable problem.

The hallmark of IPT is helping the depressed patient achieve his or her interpersonal goals (for a complete description of IPT, see Weissman, Markowitz, & Klerman, 2000).

Couple and Family Therapy

Given the interpersonal factors in the etiology and maintenance of depressive disorders (Joiner & Coyne, 1999), the relational contexts in which depressed individuals function can also be the target for effective intervention. Marital discord has been clearly linked to depressive disorders, and marital therapy has been found to reduce depressive symptomatology in depressed patients (Anderson, Beach, & Kaslow, 1999). Several couple and family therapies that have demonstrated effectiveness in depressed individuals include behavioral marital therapy, IPT conjoint marital therapy, behavioral family intervention, and cognitive-behavioral family intervention (Beach & Jones, 2002). Thus depressed individuals and their families may choose from a number of therapy modalities that have evidence in support of their effectiveness.

SUMMARY

Depressive disorders adversely affect a substantial number of individuals during the course of their lives. Researchers have made important strides in uncovering the multiple pathways leading to the development of these disorders, including biological, cognitive, and behavioral/interpersonal determinants. Armed with this information, pharmacological and psychosocial treatments have been created and continue to undergo empirical evaluation. However, additional research is needed utilizing a comprehensive, integrative theory of depression to examine the onset and maintenance of depressive disorders across the lifespan. In addition, continued empirical validation of treatments is needed—especially research that focuses on optimal length of treatment, specific treatment components that appear to be the "salient ingredients" involved in clinical change, increased collection of follow-up data to examine longer-term treatment outcomes, and potential moderators of treatment effectiveness (i.e., participant characteristics, treatment characteristics, type, source and target of outcomes assessed, etc.). Continued research in the next decade should offer answers to some of these important questions.

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10

AUTISTIC SPECTRUM DISORDERS

ELAINE CLARK
WILLIAM R. JENSON
JUDITH N. MILLER

Autism was first described in the literature in 1943 by Leo Kanner. The article, which appeared in the journal *Nervous Child*, described 11 children who had what Kanner observed to be an innate "disturbance of affective contact" (Kanner, 1943).This group of children were distinct from other children in psychiatric treatment at John Hopkins Hospital in a number of ways—including the degree to which the children were socially isolated and lacked awareness of people, as well as their very limited communication and unusual stereotyped behaviors. Basically, the children displayed the core features of the disorder now known as autism, and when Kanner (1971) followed up on them 28 years later, they had very similar symptoms and problems with activities of daily living. Relatively little was published on adult outcomes in the two or more decades that followed; in fact, only in recent years have researchers focused attention on adult outcomes (not just outcomes in elementary and middle school).

The recent interest in adults is not surprising, given the fact that children who were first diagnosed with autism after the enactment of the Education for All Handicapped Children Act of 1975 and the inclusion of "infantile autism" as a distinct category in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III; American Psychiatric Association [APA], 1980) are now adults in need of services. Although a lot has been learned about the service needs of adults with autism and related disorders (e.g., vocational counseling and skills training), relatively little is known about the best ways to provide these services and to increase the chances that adults will be more self-reliant and less dependent on their families and communities for support.

PREDICTING ADULT OUTCOMES

Predicting outcomes into adulthood for individuals with autism spectrum disorders (ASDs) has been difficult, in part because of the lack of structured services and agencies specifically responsible for addressing these individuals' needs. Although staff members in state departments of vocational rehabilitation occasionally come in contact with adults who have

high-functioning autism (HFA), the numbers have not been as great as those with other disability conditions (e.g., adults with traumatic brain injuries). What is known about adults with ASDs (even HFA), however, is that they have very significant problems with work. Kanner found this in his 1971 follow-up study, and others have provided similar data to support the view that much more needs to be done to include individuals with ASDs in the workplace and make the experience successful for them. Similarly, more information is needed to determine better ways to help adults with ASDs live in the community, and not just in their family homes. A consistent finding across time and studies has been the poor likelihood that adults with autism and related disorders will be able to live on their own, or to have employment that pays them a reasonable rate and provides them with opportunities to build self-esteem and live self-determined lives.

Sample of Outcome Studies over Time

The first systematic outcome study was performed by Rutter and Lockyer in the 1960s, but did not examine adult outcomes (Lockyer & Rutter, 1969, 1970; Rutter & Lockyer, 1967). What these researchers investigated was the adolescent status of 38 children who had been identified as having autism when they were very young children. The majority of the participants (who on average were 16 years of age) had not held any job; in fact, only 3 of the 38 had ever had a job. Fifty-nine percent were living in extended care hospital settings or residential facilities, and another 18% were living at home with their parents. The researchers judged the outcomes as being "poor" for 61% of the participants, "fair" for 25%, and "good" for only 14%.

When Kanner (1971) conducted his follow-up study a short time later, he found similar results—that is, poor outcomes for the vast majority of adults. Since he only had nine participants, it is difficult to compare his data directly to those of Rutter and Lockyer; however, Kanner reported that only three had reasonably good outcomes, meaning that two had regular employment (i.e., one worked as a duplication machine operator and the other as a bank teller), and one worked with his mother in a nursing home she happened to own (this man, however, had never developed language skills and was mute). The majority of participants in Kanner's study had also spent the majority of their lives living in institutional settings.

Poor outcomes for adults with autism have also been found in other cultures, including China (Clark & Zhou, 2005) and Japan (Kobayaski, Murata, & Yashinaga, 1992). According to Kobayaski and his colleagues' study of 201 Japanese autistic adults (ages 18–33), 46% were reported to be doing "poorly," and only 27% were described as having either a "fair" or "good" outcome. Although 20% of the Japanese adults were employed at the time of the study, most of them worked in the food service industry and were receiving minimal pay. As in studies of autistic adults from other cultures, the majority were living at home with family members, and none had married. Perhaps most notable in these studies over time has been the degree to which adults with autism remain dependent on families and society for their livelihood and social support. This is also true of the most recent investigations.

Recent Follow-Ups

The most recent follow-up study in the literature to date was conducted by Howlin, Goode, Hutton, and Rutter (2004). These researchers examined the outcomes for 68 individuals

between the ages of 21 and 48. Similar to the investigators of the 1960s and 1970s, Howlin and her colleagues found that outcomes for 58% of the participants were rated as being either "poor" or "very poor," and only 22% "good" or "very good." What was unique about this study, however, was the inclusion of many more individuals with higher intellectual abilities. All of the participants, in fact, had obtained (during childhood) IQ scores of 50 or higher, with the mean Performance IQ (PIQ) being 80.21 (with a standard deviation of 19.28), and the mean Verbal IQ (VIQ) being 61.49 (with a standard deviation of 21.26).

The researchers demonstrated that verbal ability as reflected by VIQ changed over time, but that PIQ was more stable. However, both variables together provided the best predictive utility. In general, IQs above 70 were required for the possibility of a good outcome, but were not sufficient. Only 5 of the 11 individuals with both VIQ and PIQ above 70 had a "good" or "very good" outcome. Howlin and her colleagues concluded that it was easier to predict poor outcomes than good ones. Only 3 of the 68 participants were living on their own; the rest depended on families and other caregivers for support. Although a third had some type of job, only 12% had regular, paying jobs, and 25% were employed in supported (structured) employment settings.

The adults who had IQ scores above 70 also struggled with academic tasks, including reading and spelling. In fact, only about half scored at the fifth- or sixth-grade level on achievement tests, and 78% had quit school without any academic credentials. Interestingly, Howlin and her colleagues found that many of the adults in the study attributed their functional problems as adults to "autistic-type" behaviors—that is, restrictive, repetitive, stereotyped activities and interests that consumed excessive amounts of time (time that might have otherwise been spent on studies or work). Only 12% reported not having any problems with these behaviors (e.g., rituals, routines, and preoccupations), whereas 42% reported mild interference and 46% reported moderate to severe interference. Although some researchers have indicated that these "autistic-type" behaviors improve with age (e.g., Seltzer, Krauss, Shattuck, Orsmond, & Lord, 2003), it appears from the Howlin and colleagues (2004) study that the behaviors remain sufficiently problematic to interfere with adult tasks (e.g., work).

CLINICAL MANIFESTATION AND DIAGNOSIS IN ADULTS

Researchers have consistently found that the single most defining feature of ASDs, at any age, is social impairment. Although adults with these disorders have been described as being more interested than children in social interactions, and some researchers have even found that they are more socially skilled (e.g., Szatmari, Bryson, Boyle, Streiner, & Duku, 2003), problems with establishing and maintaining friendships have been shown to be lifelong. In fact, Howlin and her colleagues (2004) found that 56% of the adults they studied had no friends or acquaintances. Social problems appear to be related to a number of factors, including some of the fundamental problems associated with ASDs: lack of social reciprocity, inflexibility, and poor adaptability (Powell & Jordan, 1996); problems with being able to understand another's perspective and understand their thoughts and feelings (i.e., problems with the theory of mind; Frith & Happe, 1999; Landa, 2000); tendencies to become overly focused on details; inability to distinguish relevant from irrelevant information; misinterpreting sarcasm and humor; approaching conversations in a rigid way (e.g., ignoring social greetings, being blunt, and using formalized speech); and missing important social cues. For example, a man with autism may talk for several minutes or more about

an idiosyncratic topic he is interested in, such as vacuum cleaners, without noticing that the person he is talking to has been looking at her watch the entire time and is edging away from him in an effort to leave. Such communication problems are common in individuals with ASDs, and they may end up being perceived as egocentric, self-absorbed, eccentric, or odd. Baltaxe (1977) found that even if individuals are capable of a reciprocal conversation, they often have problems with recognizing whether another person understands what they are saying, as well as problems in clarifying information for others. For example, when asked in an experimental study to clarify information, individuals with ASDs generally used restatements, whereas individuals without ASDs were able to make a significant change in their content.

Making the diagnosis of an ASD for the first time in adulthood is often more difficult than it is during childhood. Not only is there an increase in the heterogeneity of symptoms (Seltzer et al., 2003); there is often more limited information about early developmental history available. As a result, adults often end up with diagnoses such as schizoid personality disorder or schizoaffective disorder, not an ASD. The diagnostic criteria, however, are the same for adults as they are for children, and professionals continue to rely on one of two classification systems: the 10th revision of the *International Classification of Diseases* (ICD-10), published by the World Health Organization (2003), or the DSM-IV-TR, published by the APA (2000). Other than a few minor differences in nomenclature, such as the DSM-IV-TR description of autism as "autistic disorder" and the ICD-10 description as "autism/autistic [child] [infantile]," both systems employ similar diagnostic criteria. In addition, both have modified the criteria for ASDs from one revision to the next. When the DSM-III (a precursor to the DSM-IV-TR) was published, the concept of autism was defined more broadly than it had been before, and received criticism for being overly inclusive. With the publication of the fourth edition, the definitions for ASDs were narrowed; apparently, for some commentators, they became too narrow and too restrictive to capture the essence of a condition (e.g., Asperger disorder) (Miller & Ozonoff, 2000; Szatmari et al., 2003).

Below, we describe the DSM-IV-TR criteria for autistic disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified (PDD NOS), the disorders typically considered in the autistic spectrum. Although childhood disintegrative disorder and Rett disorder are included in the DSM-IV-TR category of pervasive developmental disorders (PDDs), these two conditions are considered nonautistic. For this reason—and also because both are characterized by a specific pattern of regression and degeneration, and are typically associated with severe to profound mental retardation—they are not described in this chapter.

Autistic Disorder

The criteria for autistic disorder in the DSM-IV-TR (APA, 2000) specify that an individual must have qualitatively impaired social interaction and communication, as well as limited, repetitive, and stereotyped behaviors. In order to meet the criteria for impaired social interaction, individuals must display two or more of the following: notable impairment in the use of nonverbal behaviors (e.g., eye gaze, facial expression, body gestures); no development of appropriate peer relationships; absence of spontaneous sharing of enjoyment; and absence of social or emotional reciprocity. The DSM-IV-TR criteria for communication impairment state that individuals must have one or more of the following: delay or lack of appropriate expressive language; if verbal, notable impairment in the ability to begin

or sustain conversations; repetitive and stereotyped use of language or idiosyncratic speech; and absence of varied and spontaneous imaginative or socially imitative play. For the limited, repetitive, and stereotyped patterns of behavior, interests, and activities, according to the DSM-IV-TR, an individual must manifest one of the following: pervasive preoccupation with restricted and stereotyped patterns of interest that are abnormal in focus or intensity; inflexible adherence to nonfunctional rituals or routines; repetitive and stereotyped motor mannerisms (e.g., hand flapping); and continuing preoccupation with parts of objects (APA, 2000). In addition to meeting these criteria, an individual must manifest the delays or abnormal functioning in at least one area (i.e., social interaction, language used for social communication, and symbolic or imaginative play) by the age of 3 years.

Asperger Disorder

Hans Asperger, an Austrian psychiatrist, first identified the condition that bears his name in 1944. However, his description was not read widely until it was translated into English in the early 1980s, after Wing (1981) published a review of 34 cases of Asperger disorder in *Psychological Medicine*. It is widely accepted that Asperger disorder is a mild form of autism, but arguments persist about its validity as a distinct disorder. Although it is characterized by an absence of significant delay in cognitive or language development, individuals with Asperger disorder have the same "severe and sustained impairment in social interaction . . . and the development of restricted, repetitive patterns of behaviors, interests, and activities" that hinder their ability to function in their daily lives as seen in autism (APA, 2000, p. 80). The DSM-IV-TR criteria for Asperger (or Asperger's, as the manual calls it) disorder includes the same qualitative impairment of social interaction as in autistic disorder, manifested by at least two of the same four characteristics as those described for autistic disorder. The criteria also include the same limited, repetitive, and stereotyped patterns of behavior, interests, and activities as in autistic disorder, as manifested by at least one of the same four phenomena as those described for autism. Like individuals with autism, individuals with Asperger disorder often devote considerable time to gathering information about circumscribed interests and topics—an activity that is often all-encompassing.

In order to be diagnosed with Asperger disorder, individuals must also have significant impairment in social, occupational, or other areas of functioning. The criteria exclude children who have delays in language development or cognitive ability in the first years of life (e.g., who fail to use single words by 2 or phrases by 3). Though the other communication impairments seen in autism are not included in the diagnostic criteria, many individuals with Asperger disorder show the same difficulties in reciprocal conversation, imaginary play, or unusual and repetitive language as seen in autism (Miller & Ozonoff, 1997).

Some have suggested that individuals who meet criteria for Asperger disorder may have more social interest than individuals with HFA (i.e., individuals with borderline, average, or higher intellectual functioning, but significant language/communication delays as children). Some have also suggested that individuals with Asperger disorder have more motor skill problems and are more clumsy than those with HFA (Klin, Sparrow, Marans, Carter, & Volkmar, 2000). However, comparisons between groups have not consistently found meaningful differences between the two conditions (Asperger disorder and HFA) (Klin et al., 2000; Mayes, Calhoun, & Crites, 2001; Miller & Ozonoff, 2000). What is known is that individuals diagnosed as having either HFA or Asperger disorder are often socially ostracized and have problems in adapting to environments (including school and

work), due to their unusual and sometimes eccentric behaviors (e.g., pedantic speech patterns, verbosity, and preoccupation with circumscribed interests). This finding has been shown in studies of children as well as adults (Howlin et al., 2004). Many individuals with HFA or Asperger disorder have a previous diagnosis of attention-deficit/hyperactivity disorder, oppositional defiant disorder, or an anxiety disorder. The diagnosis of Asperger disorder is often delayed, because the social problems sometimes do not become apparent until a child enters school and is forced to interact with peers (Ozonoff & McMahon-Griffith, 2000), In adults, the diagnosis may be missed or mistaken for other psychiatric disorders (e.g., schizoid personality disorder, schizoaffective disorder) (Lainhart, 1999).

Pervasive Developmental Disorder Not Otherwise Specified

The PDD NOS diagnosis is given to individuals who do not meet the full criteria for a specific PDD (i.e., autistic disorder, Asperger disorder, childhood disintegrative disorder, or Rett disorder). Often this means that an individual displays atypical autistic symptoms, or does not meet the required threshold of number and type of symptoms for a diagnosis of autistic disorder or Asperger disorder, and/or fails to meet the age-of-onset criterion. In order to receive a PDD NOS diagnosis, however, the person must have "severe and pervasive impairment in the development of reciprocal social interaction" (APA, 2000, p. 84), and must have either communication deficits (verbal or nonverbal) or stereotyped, rigid patterns of behaviors, interests, or activities (Buitelaar, Van der Gaag, Klin, & Volkmar, 1999).

Relatively few studies have tried to distinguish PDD NOS from other ASDs. Allen and colleagues (2001) examined potential differences between children with PDD NOS and children with autism in language and adaptive skills. The researchers found that scores on language and adaptive measures for individuals with PDD NOS fell between those of nondisabled controls and the children with autistic disorder. The children diagnosed with PDD NOS also displayed more anxiety, psychosis, and aggression than did their peers with a diagnosis of autistic disorder. Research indicates that, like children diagnosed with the other ASDs, children who are given the diagnosis of PDD NOS also display significant social and emotional problems. Unfortunately, due to the nature of classification, the PDD NOS diagnosis is used for a variety of purposes: as a provisional diagnosis for very young children before the full developmental course is clear; as a provisional diagnosis until an individual can be evaluated by a specialist; or as a final diagnosis for individuals too mildly affected to meet criteria for autism or Asperger disorder. As a result, it has been a difficult disorder to categorize reliably (Stone et al., 1999).

PSYCHOLOGICAL PROFILES OF INDIVIDUALS WITH ASDs AND THEIR FAMILIES

Individuals with ASDs have been found to be at increased risk for a number of other psychiatric disorders, including major depression, anxiety, and psychosis (Lainhart, 1999). Although the literature on adults has grown over the years, there is still a tremendous need for information about various comorbid psychiatric conditions that might warrant treatment. Professionals and families alike would also benefit from information about the personality styles of adults with ASD. Unfortunately, many individuals with ASDs, including high-functioning adults such as those with HFA or Asperger disorder, are not evaluated for psychiatric conditions, and they are rarely given personality tests. Instead, the behav-

iors and adjustment problems of adults are often attributed to the core features of ASDs, not to associated psychiatric disorders or personality features.

Psychiatric Disorders

Psychosis

Researchers have found that individuals with ASDs may have an increased risk for psychosis, particularly schizophrenia (Klin & Volkmar, 1997). In a study that compared adults with schizophrenia to adults with ASDs, it was found that more of the adults diagnosed with ASDs displayed "negative" features of schizophrenia than adults diagnosed with schizophrenia (Konstantareas & Hewitt, 2001). These features included minimal social interactions, minimal facial expressions, and flat emotional affect. Adults with ASDs, however, have also been found to have some of the "positive" features of schizophrenia, including disturbed thinking and perceptual distortions (the latter are consistent with impaired reality testing; Lainhart, 1999). However, these symptoms resemble the cognitive and communication difficulties experienced by adults with ASDs that have been previously described, including problems in understanding abstract concepts, literal interpretations of situations, and idiosyncratic and tangential speech (Lainhart, 1999). The concrete nature and often socially irrelevant characteristics of the speech of these adults, and their intense and unusual interests and preoccupations (e.g., wanting to act and dress like celebrities with whom the individuals are preoccupied), can also lead to diagnostic confusion between ASDs and schizophrenia (Perlman, 2000). Some individuals with ASDs also feel that they have unique relationships with certain people, even when this interest is not reciprocated. Hypersensitivity to criticism, and misinterpretation of comments as critical, are also characteristic of ASDs; these can lead to strong irrational reactions that may be confused with paranoid and/or psychotic behavior. Tendencies toward verbal perseveration (some of which may be highly inappropriate) on topics of special interest, as well as behavioral eccentricities, can lead to an erroneous conclusion that these adults suffer from a schizophrenic spectrum disorder. In some cases, however, schizophrenia has been found to coexist with ASDs (Dekeyzer, 204; Lainhart, 1999).

Depression and Anxiety

In a comprehensive review of the literature, Lainhart (1999) found rates of depression in individuals with autism to range from a low of 4.4% to a high of 57.6%. Although such a wide range probably reflects some of the heterogeneity in the population, it also reflects the different ways that the depressive conditions manifest themselves, as well as different reporting styles. Lainhart found that adults with ASDs and depression often sought psychiatric or psychological treatment more for the behavioral changes accompanying the mood disorder than for the experience of low mood itself. In fact, researchers who have studied depression in children with ASDs indicate that they more often complain about changes in behavioral patterns, such as intensity of circumscribed interests, than about sadness or low mood (Ghaziuddin, Alessi, & Greden, 1995). Studies have nonetheless found that individuals with ASDs who are depressed often show increased irritability and aggression, including self-injury, as well as social withdrawal and disturbances in sleep and appetite (Howlin, 1997; Lainhart & Folstein, 1994). In addition, Lainhart found that the symptoms of individuals with both ASDs and bipolar illness often include reduced need for sleep, inappropriate laughter, excessive verbalizations, irritability, and wide fluctuation in mood.

Although Lainhart (1999) has suggested that anxiety occurs so often in individuals with ASDs that a separate diagnosis of an anxiety disorder is often not necessary, her research suggested incidence rates ranging from 7% to 84% in the population. Social phobia has been found to be the most common anxiety disorder among individuals with ASDs, also occurring in 22.4% of those individuals who have a comorbid diagnosis of depression (Kessler, Nelson, & McGonagle, 1996). Understanding social rules and protocols, reading social cues and solving social problems, and adapting to new situations can all be perplexing and anxiety-provoking at times for adults with ASDs (Landa, 2000; Powell & Jordan, 1996). Their lack of social connectedness, difficulties in understanding the feelings of others, and problems that arise from not knowing at times what is appropriate in certain social situations all lead to a lack of reinforcement from social engagement with others and isolation from peers (Klin & Volkmar, 2000). It is not surprising that individuals with ASDs begin to avoid social contacts and to be perceived as uninterested in social interactions and relationships (Ozonoff, Dawson, & McPartland, 2002).

Personality Features

Research in the area of personality has lagged behind that of studies examining cognitive and social-behavioral features of ASDs. Because a disproportionately high number of individuals with ASDs have been found to have limited personal awareness and insight into their internal states, impaired ability to think abstractly and communicate effectively, reduced motivation, and intellectual and academic skill deficits, researchers have questioned whether these individuals can complete standard self-report personality measures such as the Minnesota Multiphasic Personality Inventory–2 (MMPI-2) and the Millon Clinical Multiaxial Inventory–III (Garcia, 2003; Lainhart, 1999). In one study, however, adolescents and adults with Asperger disorder did not show significant differences on a measure of "private self-consciousness"—that is, the ability to attend to the private aspects of oneself, such as feelings and motives (Blackshaw, Kinderman, Hare, & Hatton, 2001). Autobiographical writings of adults with Asperger disorder have also shown awareness of their social and emotional difficulties (e.g., Spicer, 1998).

Results from a recent study at the University of Utah suggest that adults with ASDs may be mixed in their ability to self-report as well as typically developing adults (Garcia, 2003). Adults with ASDs and their mothers were each asked to complete the MMPI-2—the adults with ASDs about themselves, and the mothers about their adult children with ASDs. The individuals with ASD showed significantly higher scores on the Lie scale, suggesting a lack of personal insight, or a tendency to deny common faults and report unrealistically positive traits. However, on clinical scales, the researcher found that the ratings of the adults with ASDs were highly similar to the mothers' reports about their children. Both the self- and parent-completed MMPI-2s yielded scores on the Depression and Social Introversion scales three to four times higher than those for either the normative sample or the control group. Furthermore, the Social Introversion score was more than twice as likely to be one of the two highest scores on the MMPI-2 for the group with ASDs. Although Blackshaw and colleagues (2001) found significantly elevated scores on the MMPI-2 Paranoia scale for their group with ASDs, this finding was not replicated by Garcia (2003).

Soderstrom, Rastam, and Gillberg (2002) also examined personality characteristics of adults with ASDs, using the Temperament and Character Inventory (TCI). In this study, the researchers found that adults with Asperger disorder had significantly more idiosyncratic responses and also scored significantly higher on measures of harm avoidance. These

adults also scored significantly lower on the TCI measures of cooperation, self-directedness, reward dependence, and novelty seeking.

Family Personalities and Psychiatric Histories

Although relatively few studies of personality have been conducted on individuals with ASDs, several studies have examined personality traits of family members (e.g., Murphy et al., 2000; Piven, Palmer, Jacobi, Childress, & Arrndt, 1997; Piven, Palmer, Landa, et al., 1997b). Particular attention has been given to family members who have subclinical features of autism, or the "broader autism phenotype" (BAP). The BAP has been estimated to occur in 15–45% of families with autism (Bailey, Palferman, Heavey, & LeCouteur, 1998). This phenotype is often manifested by such features as a lack of empathy, failure to respond to another's emotions and needs, hypersensitivity to criticism, circumscribed interests, and communication problems (Bailey, Phillips, & Rutter, 1996; Piven, Palmer, Jacobi, et al., 1997). Studies have shown that the communication style of individuals with the BAP is often guarded, and that they have difficulty with the pragmatics of speech (Piven, Palmer, Jacobi, et al., 1997). The Piven and colleagues research suggests that these communication problems are more common among mothers of individuals with ASDs. Both mothers and fathers, however, have been shown to have high rates of social deficits and restricted, repetitive patterns of behaviors, interests, and activities. Research on siblings of individuals with ASDs has found that they have subclinical deficits in all three domains (socialization, communication, and restricted/stereotyped behaviors). Some investigators have also shown that families of individuals with HFA or Asperger disorder are more likely to have autistic features than families of lower-functioning individuals (DeLong & Dwyer, 1988).

Research on affected families has also shown an increased rate of psychiatric problems when compared to the general population. DeLong and Nohiria (1994) and Piven and colleagues (1991) showed a significant increase in mood disorders, particularly bipolar disorder, in families of individuals with ASDs. According to Piven and colleagues, parents had an increased frequency of anxiety (24%), major depressive disorder (MDD; 27%), and alcoholism (12%). Similar results were found in research by Ghaziuddin and Greden (1998), who observed that 77% of individuals with ASDs who also had MDD had positive family histories for a mood disorder. Although some have questioned whether findings of high rates of psychiatric problems are due to other genetic factors, when Smalley, McCracken, and Tanguay (1995) compared parents of individuals with ASDs to parents of persons with tuberous sclerosis, they found that the former group of parents had significantly higher rates of psychiatric disorders (i.e., MDD, social phobia, and substance abuse). Other psychiatric conditions that have been found to be present at higher-than-expected levels in families include panic disorder, obsessive–compulsive disorder, and schizophrenia (e.g., Bolton, Pickles, Murphy, & Rutter, 1998; Dekeyzer, 2004).

CONDUCTING ASSESSMENTS OF ASDs IN ADULTHOOD

For an adult who is being referred for the first time for a suspected ASD, it is important to conduct a good clinical interview and gather a thorough developmental and family history. However, historical information may be difficult to obtain if the adult cannot provide information about his or her own early development, and if it is not possible to gather the information from the parents. Educational transcripts and employment records can be

requested, so that the individual's performance in school and on the job can be assessed. If the adult is working, an interview with the employer can add invaluable information to the assessment (e.g., the extent and quality of interactions with coworkers and supervisors, work skills, communication capability, and the presence or absence of autistic behaviors). A variety of diagnostic and standardized tests can also be helpful in the evaluation process, as reviewed below.

Diagnostic and Screening Instruments

The Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 2003) and the Autism Diagnostic Interview—Revised (ADI-R; Rutter, LeCouteur, & Lord, 2002) are the current "gold standard" instruments for diagnosing ASDs. The ADOS is a standardized interaction/observation, and the ADI-R is a standardized developmental history. Both were originally designed for research purposes; however, they are gaining popularity as clinical tools. They have both been shown to have excellent diagnostic validity. The ADOS has modules specifically designed for every age (very young children through adults) as well as every functioning level (from very low to very high). The ADI-R gathers both current and lifetime information, which provides a systematic way to record whether all characteristics have been present throughout life. Both the ADOS and ADI-R require a rather significant investment in the training needed to administer and score them correctly, as well as in the time required to administer them. The ADOS takes approximately 25–45 minutes to administer, and the ADI-R takes 2–3 hours to administer.

A variety of new screening tools have been developed, generally geared at children rather than adults. None have proved equal or superior to a comprehensive developmental history and observation by clinicians experienced in ASDs. As in assessment for any disorder, caution should be used with any screening measure, and the relative costs of false negatives and false positives must be weighed for the setting in which a screening tool is to be used. Relying on parents to rate an adult child's development in the preschool years is problematic for obvious reasons. However, an interview between a parent and a skilled clinician about the adult child's early functioning can elicit extremely valuable information. The use of screening questionnaires by adults themselves is also problematic, as much more research needs to be done to determine how adults with ASDs would rate their own social experiences, interests and hobbies, and communication with others. Furthermore, it is unlikely that even typically developing adults could reliably provide information about their own early history and development, much less the types of early difficulties associated with ASDs.

Other Psychological Tests

IQ profiles and neuropsychological testing have not been found to be helpful in making a diagnosis of an ASD, but can be very helpful for other purposes. Previous research suggested that lower-functioning individuals with ASDs (i.e., not those with HFA or Asperger disorder) have a significantly lower VIQ than PIQ (e.g., Green, Fein, Joy, & Waterhouse, 1995). However, more recent research, including more research on higher-functioning individuals, indicates that there is no IQ profile specific to ASDs. Miller and Ozonoff (2000) found that 40% of individuals with Asperger disorder had no significant VIQ–PIQ discrepancy, 40% had a VIQ greater than PIQ, and 20% had a PIQ greater than VIQ.

Although IQ profiles have not been shown to be helpful in diagnosing ASDs, information from standardized intelligence tests can certainly be helpful in identifying strengths and weaknesses. Neuropsychological tests can also be helpful in this way. Researchers have shown that adults with ASDs often have deficits in executive functioning, processing speed, attention, memory, language, learning, abstract ability, and cognitive flexibility (e.g., Dawson, 1996; Happe & Frith, 1996; Ozonoff, 1995). These same studies have found that motor skills, visual–spatial skills, and sensory perceptual abilities are often spared. In a study by Minshew, Goldstein, and Siegel (1997), however, the researchers found that when these same domains were assessed but the complexity of the tasks were varied (from simple to complex), adults with ASDs performed differently. According to Minshew and her colleagues, the adults with ASDs did poorly across domains when tasks were complex, regardless of the type of stimuli (visual or auditory). The researchers found that specific problems were evidenced on tests that involved concept formation, higher-order language ability, working memory, and cognitive flexibility. Assessing these abilities may be critical in determining what type of education or job might be most appropriate for an individual, and what training could assist the person to achieve his or her goals (e.g., improving motor skills for manual labor jobs, providing support for limited organizational skills).

Adults with ASDs can benefit from assessments of adaptive behavior. The abilities of lower-functioning individuals may be adequately assessed by scales typically used in the assessment of individuals with developmental delays, such as the Vineland Adaptive Behavior Scales, Second Edition (Sparrow, Cicchetti, & Balla, 2004) and the Scales of Independent Behavior—Revised (Bruininks, Woodcock, Weatherman, & Hill, 1996). Many individuals with ASDs demonstrate significantly lower adaptive skill functioning than their intellectual functioning would predict. Many times, such individuals need to be specifically taught individual skills of daily living, just as they must be taught other discrete skills.

Individuals with ASDs can also benefit from vocational assessment. Although formal vocational assessments can be obtained (e.g., from state departments of vocational rehabilitation), for lower-functioning individuals, the Adolescent and Adult Psychoeducational Profile–IV (Mesibov, Schopler, Schaffer, & Landrus, 1988) can be used to provide helpful information. This profile assesses a variety of work skills and behaviors that may be appropriate in sheltered workshops or supervised assembly-level jobs. Results can be used to match the individual to the appropriate job, as well as to create treatment programs centered around teaching higher-level work skills. For higher-functioning individuals, vocational assessments are best conducted by vocational specialists, such as those employed by agencies designed to provide vocational rehabilitation services. For some individuals with ASDs, the vocational assessment can be further informed by a neuropsychological assessment to obtain a more comprehensive picture of the individuals' strengths, weaknesses, and interests.

Mood and anxiety inventories (e.g., the Beck scales) and personality measures (e.g., the MMPI-2 and the NEO Personality Inventory—Revised) can also be helpful at times. However, since only preliminary research has been conducted to study the reporting styles and personality characteristics of adults with ASDs, caution must be used in the interpretation of these and other scales that have not included populations with ASDs in their normative studies.

ESTIMATING THE PREVALENCE OF ASDs IN ADULTS

Just as it is more difficult to diagnose ASDs in adulthood, it is more difficult to estimate their prevalence. Epidemiological data on ASD are limited in general, and the few studies

available are usually confined to children. However, since ASDs (excluding the neurodegenerative PDDs) are considered by most to be lifelong conditions, but not life-threatening, it may be appropriate to use data collected on children for minimum estimates. It may be that the true prevalence is higher for adults than for children, considering that some higher-functioning adults are not identified during childhood. Furthermore, the prevalence may increase due to increased awareness of HFA and the clinical manifestations in adulthood, and increased ability to make differential diagnoses (i.e., to distinguish ASDs from other developmental disorders and psychiatric conditions). Research on children, for example, has shown that as the rate of "mental retardation" has decreased (from 28.8 in 10,000 to 19.5), the rate of autism has increased (from 5.8 in 10,000 to 14.9) (Yeargin-Allsopp et al., 2003)—presumably due to differences in diagnostic patterns. Ultimately, however, it remains an empirical question whether the prevalence changes with age, as it is not currently known whether adults with ASDs may have a shorter life expectancy (because of increased injuries or accidents, etc.).

Recent data from the Centers for Disease Control and Prevention (CDC) indicate that the rate of autism in children has risen dramatically over the past decade. In fact, it is estimated that between 1994 and 2000, the rate increased by 189%. Whereas some of this change has been attributed to more accurate diagnoses (e.g., misidentifying children as having intellectual disabilities rather than autism), increases have also been attributed to changes in diagnostic criteria (e.g., DSM and ICD) over the years, the inclusion of more individuals with HFA, and changes in the methods of epidemiological data collection. As more settings are studied and data tapped for potential cases of ASDs, rates can be expected to fluctuate for adults, just as they have for children. Yeargin-Allsopp and her colleagues (2003) found that when schools were used as data collection sites, far more African American children were identified as having autism. The same may be true for adults when residential centers for individuals with developmental disabilities and state hospital settings are tapped for their data.

As for current estimates of the prevalence of autism in the United States, the CDC data suggest that the rate is 3.4 per 1,000 (Yeargin-Allsopp et al., 2003). However, data collected by the CDC for the state of New Jersey give rates ranging from 4.0 to 6.7 in 1,000, depending on the definition used for autism (Bertrand et al., 2001). It is estimated that for ASDs of all degrees of severity, including HFA or Asperger disorder, a more accurate estimate is approximately 6 in 1,000 (Yeargin-Allsopp et al., 2003). This is reasonable, given data showing that certain conditions (e.g., PDD NOS) are estimated to occur at a rate 1½ times higher than that of autistic disorder (Fombonne, 2002).

GENETICS AND NEUROBIOLOGY

Today's adults with ASDs are of the generation whose mothers were erroneously told that they were emotionally cold and rejecting "refrigerator mothers." Since that time, it has become abundantly clear that ASDs are biological disorders. Research into the genetics and neurological bases of these disorders have increased significantly, and it is likely that they have multiple causes, some of which involve complex genetic interactions.

Autism has been associated with a variety of genetic syndromes, medical disorders, and chromosomal abnormalities. Such "syndromic" forms of autism are now being distinguished from "idiopathic" cases, where this is no definable medical condition that might account for the autism symptomatology. The most frequent causes of syndromic autism

include tuberous sclerosis, fragile *X*, and 15q duplication, but other factors (e.g., cytomegalovirus, thalidomide, valproic acic, inherited metabolic disorders, etc.) can also be considered causes. It should be noted that not all individuals with these syndromic causes demonstrate symptoms of ASDs, but in general syndromic autism is associated with lower functioning (for a helpful review, see Hansen & Hagerman, 2003).

One of the first links between autism and brain abnormalities was the finding that individuals with autism are at increased risk for seizures compared to the general population. Unfortunately, there is no one type of seizure most commonly associated with autism, and all seizure types have been reported. Research suggests that there may be two peak onsets of seizures—one in childhood (before age 10), and one in early adolescence (Rossi, Posar, & Parmegiani, 2000). In general, seizures appear to be more common in lower-functioning individuals.

That autism is a brain-based disorder is no longer in question, but as yet no visible brain abnormality that could be used as a marker for diagnosis has been discovered. Group comparisons of magnetic resonance imaging scans have found volumetric differences in various structures, suggesting that individuals with autism may have a different pattern of brain growth than their typically developing counterparts do. One recently described growth pattern is rapid acceleration before age 2, followed by a slowing in growth that results in average brain size in adulthood (Courchesne, Carper, & Akshoomoff, 2004). If this important finding is replicated with larger samples, it may help increase our understanding of the disorder; however, it is probably not specific enough on its own to help with diagnosis, as macrocephaly occurs in a variety of diseases as well as in normal development (Lainhart, 2003).

Without a universal finding of structural abnormalities in autism, the contribution of functional neuroimaging work to research on information processing in autism becomes clear. High-functioning adults have been critical for this work, as these studies require the participants to perform certain mental tasks under the scanner. Results have shown differences in regional brain activation for adults with ASDs compared to controls, with underactivation of some areas and overactivation of others. For example, regions associated with social cognition in typically developing individuals are frequently underactivated in those with ASDs during social cognition tasks, while atypical regions are overactivated (see DiMartino & Castellanos, 2003, for a review). Studies of facial processing show an underactivation of the right fusiform gyrus (typically associated with facial processing), accompanied by an overactivation of either the inferior temporal gyrus (which typically processes objects); the frontal, occipital, and anterior fusiform gyrus; or the primary auditory and visual cortex (Critchley et al., 2000; Pierce, Muller, Ambrose, Allen, & Courchesne, 2001; Schultz et al., 2000). This suggests that individuals with ASDs do not process faces in the same manner as typically developing individuals do, and may interpret them more like objects than like social stimuli. As this research is extended to younger and more impaired individuals with ASDs, it will become clearer whether these are primary or acquired differences, and whether they are amenable to intervention.

INTERVENTIONS

Clearly, much needs to be done to provide effective supports and interventions for adults with ASDs, both now and in the future. Although there is an obvious interest in identifying ways to cure or prevent ASDs, there is currently no proven "cure" (see Ozonoff, Rogers,

& Hendren, 2003, for a review). Thus it is most likely that interventions to teach specific skills, provide support when necessary, and address specific behavior problems are going to be needed. In addition, interventions that help individuals with ASDs accommodate to their environment and remove barriers that interfere with performance will be required by the Americans with Disabilities Act and other legislation.

Medications are frequently used to reduce serious behavior or mood problems. For example, neuroleptic drugs and mood stabilizers have been used to reduce aggression, agitation, disruptive behaviors, and affective instability. Selective serotonin reuptake inhibitors are often used to treat repetitive behaviors and mood disorders. Sometimes, when mood disorders are addressed effectively, an improvement in some of the core symptoms of ASDs may also be seen. In general, however, there is no medication that eliminates the core symptoms of ASDs, especially the social problems that so aptly define these disorders (Des Portes, Hagerman, & Hendren, 2003).

Behavioral interventions are widely accepted as effective for teaching specific skills and reducing specific behavior problems. As is true for typically developing children as well as for children with a variety of developmental disabilities, learning principles (reinforcement, extinction, behavioral shaping, etc.) are effective teaching strategies. They are also effective strategies for adults, and are frequently used to teach specific self-help, vocational, and social skills. Since they are usually individualized, behavioral strategies can be applied to individuals of any age or functioning level and may be appropriate for teaching a wide variety of specific skills. They generally do not target cognitive skills per se, but may increase an individual's ability to demonstrate his or her abilities more effectively.

Although there are a few studies indicating that early, intensive behavioral intervention can significantly improve outcomes in childhood (Lovaas, 1987; Smith, Groen, & Wynn, 2000), it is not yet clear what the outcomes are into adulthood. It will be important to determine whether comprehensive behavioral intervention initiated during the preschool years and conducted intensively (i.e., 27 hours or more a week for 2 years or more) will have a significant impact on the functioning of adults with ASDs. Furthermore, given the finding of Howlin and colleagues (2004) that a higher IQ did not guarantee a better outcome for adults, it is not clear to what extent changes in IQ brought about by early intervention will be maintained into adulthood, or whether these will differ from the outcomes for relatively high-IQ individuals who do not receive early intervention.

Interventions geared toward employment and independent living are desperately needed. Fullerton and Coyne (1999) describe a program to help young adults with autism to develop skills and concepts to aid them in the process of becoming more self-determined and having more enriching lives. The program includes education about autism (e.g., knowledge about communication and learning styles, social interactions, and self-awareness), goal setting, organizational skills, decision making, and practice in life skills. Division TEACCH (Mesibov & Handlan, 1997) has long been aware of the need to provide environmental supports for individuals with autism, which typically result in an increased level of independence within that environment. The TEACCH program includes both vocational and residential programs, and provides individualized instruction and individualized intervention (individualization is especially important, given the heterogeneity of the adult population with ASDs).

Increased research into the prevalence of ASDs in adults and the needs of these adults is certainly essential. In addition, research into effective interventions, and wider dissemination of effective strategies, will help the larger community address the needs of adults with ASDs, improving outcomes and overall quality of life.

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11

SUBSTANCE USE AND ABUSE

ARTHUR MACNEILL HORTON, JR.
ARTHUR MACNEILL HORTON, III

Perhaps the oldest reference to substance abuse is in the Biblical story of Noah's becoming drunk on wine he fermented from grapes he planted after the great flood ended. Still, Noah was probably not the first to abuse substances, and he surely hasn't been the last. The use of substances to modify moods, behaviors, and perceptions has been part of human history since earliest recorded time. For thousands of years, human beings have used alcohol and other naturally derived substances, such as peyote and opium, for their psychoactive effects. In more recent times, science provided new methods to produce heroin, cocaine, LSD, PCP, Ecstasy, designer drugs, and "ice," among others. In the coming years, it is almost certain that additional new substances that can be abused will be developed.

Abuse of substances is an important issue, but it is also a controversial one, particularly with respect to prohibition of substance use. What are currently prohibited substances were not always prohibited. For example, tobacco use in England in the early 1600s was discouraged by the government of King James I, but this was not effective in curtailing use. Indeed, a major reason for England's North American colonies at that time was tobacco cultivation in Virginia and North Carolina. Also, chocolate, the popular candy ingredient that can be bought in any grocery or convenience store today, was illegal in England in the early 1700s. In addition, among the most shameful chapters in the history of the British Empire were the two wars that were fought with China to allow opium to be sold in China in the 1700s and 1800s. The Chinese Emperor attempted to forbid importation of opium, but the British merchants were making so much money from the opium trade that they encouraged the British government to intervene. The British Royal Colony of Hong Kong, it might be noted, was annexed by treaty for 99 years by England after one of the opium wars, for the simple reason of having a safe and secure harbor next to the Chinese mainland through which to import opium to mainland China. In today's terms, this would be like the country of Colombia fighting a war with the United States and annexing Miami, Florida, or New Orleans, Louisiana. The United States, of course, prohibited alcohol use in the 1920s, but this effort was a complete and utter failure, and a constitutional amendment in 1933 reversed this prohibition. In short, prohibition of substance use is easier advocated than accomplished (Horton, 1996)!

Although the negative effects—indeed, the pathology—of substance abuse are the aspects most often discussed in today's newspapers and talk shows, it is important to realize

that the use of psychoactive substances to modify moods and behaviors may be also regarded as normal and appropriate in some circumstances. Social norms, of course, can influence society's decisions as to whether the use of a psychoactive drug is pathological or appropriate. Native Americans tribes in the southwestern United States, for example, have used peyote in religious rites for centuries. The majority of adults in the United States have used caffeine in the form of coffee, tea, or cola drinks at one time or another. The very limited use of marijuana, with a medical doctor's prescription, for a number of medical diseases has been allowed by legal authorities, in certain states, for selected individuals. Indeed, many western states have been moving fairly recently toward substantial decriminalization of marijuana use. In the state of Nevada, to cite a very remarkable example, a ballot initiative to make the use of marijuana legal and to make its sale a state monopoly was narrowly defeated in recent years. Narcotics are routinely used for the alleviation of pain in medically ill individuals when a physician's prescription has been obtained.

Therefore, society's views regarding the use of addictive substances are actually not immutable; rather, they change with social change. Many substances abused today, for example, were first employed for therapeutic medical purposes. Early in his illustrious career, Sigmund Freud, the famous discoverer of psychoanalysis, advocated the use of cocaine as an anesthetic. After a colleague became addicted to cocaine, Freud realized the abuse liability of cocaine and turned his efforts to other therapeutic modalities.

PREVALENCE AND NEGATIVE EFFECTS: AN OVERVIEW

Substance use and abuse are very prevalent in the United States, as a recent survey by the Substance Abuse and Mental Health Services Administration (SAMHSA, 2003) demonstrates. For example, the SAMHSA data indicate that in 2002, 19.5 million Americans, or 8.3% of the U.S. population age 12 or older, used illicit drugs. The most commonly used illicit drug in this survey was marijuana, with 14.6 million people (6.2% of the population) using it within the past month in 2002. In addition, 2.0 million persons (0.9%) used cocaine, 1.2 million used hallucinogens, 676,000 used Ecstasy, 166,000 used heroin, and 6.2 million (2.6%) used psychotherapeutic drugs nonmedically. In regard to prescription drugs, the SAMHSA survey found that 4.4 million used pain relievers, 1.8 million used tranquilizers, 1.2 million used stimulants, and 0.4 million used sedatives.

Alcohol use in the United States is also high, according to the SAMHSA data. In 2002, 120 million Americans age 12 or older (51.0% of the population) currently drank alcohol. Their alcohol use differed by drinking pattern: 54 million (22.9%) drank in monthly binges, and another 15.9 million (6.7%) drank heavily more often.

Simple raw numbers fail to capture the damage to society caused by substances of abuse. Substance abuse has been estimated as costing the United States at least $275 billion a year, in 1992 dollars (Harwood et al., 1998). Its negative impacts on society include greatly increased health costs, as well as costs from the results of domestic violence, traffic accidents, crime, and lost time from work (Hubbard et al., 1989). In addition, the social and emotional negative effects on those who abuse substances and on their immediate and extended families may last for generations (Allen & Landis, 1998).

It is important for all Americans to be aware of the dimensions of America's serious substance abuse problem, as they will be involved in the decisions about which substances should be prohibited and which should be made legal. The neurotoxic effects of substances of abuse on the human brain should be considered in making these decisions, among other

factors. The purpose of the remainder of this chapter is to review what is currently known about substances of abuse and the etiology of substance abuse, as well as to discuss approaches to treatment and prognosis after treatment.

BRAIN STRUCTURES AND PROCESSES UNDERLYING ADDICTIVE BEHAVIORS

Brain structures are the physical basis of the underlying addictive behaviors in those individuals who suffer from substance abuse. Addiction as a neurological process develops as a result of changes to the reward pathway of the brain (see Figure 11.1) when individuals are repeatedly exposed to psychoactive drugs, such as cocaine, heroin, and marijuana. The brain's reward pathway subserves how behaviors precipitate the experience of pleasure. The brain structures connect behaviors to positive feelings, with the effect that behaviors will again be performed to elicit the positive feelings. Neurophysiology underlies the circuits of pleasure (Horton & Horton, in press).

To understand how the reward pathway works, some background discussion of brain structures and processes may be helpful. (This discussion is based on Horton & Horton, in press, and on a National Institute on Drug Abuse [NIDA, 1998] online publication, from which the figures are reprinted.) The brain is composed of billions and billions of cells and neurons that function as an integrated whole. Communications within the brain occur via chemical and electrical means (see Figure 11.2). Individual structures perform different tasks relevant to the transmission of information. More specifically, information in the brain is received at the dendrites and somata, and this initiates chemical processes in the neurons (see Figure 11.3). A neuron's membrane regulates the internal chemical environment of the cell. The membrane maintains an electrical potential that is the difference in the electrical charge between the inside of the neuron and the outside. The difference results from concentrations of positively and negatively charged ions on each side of the membrane.

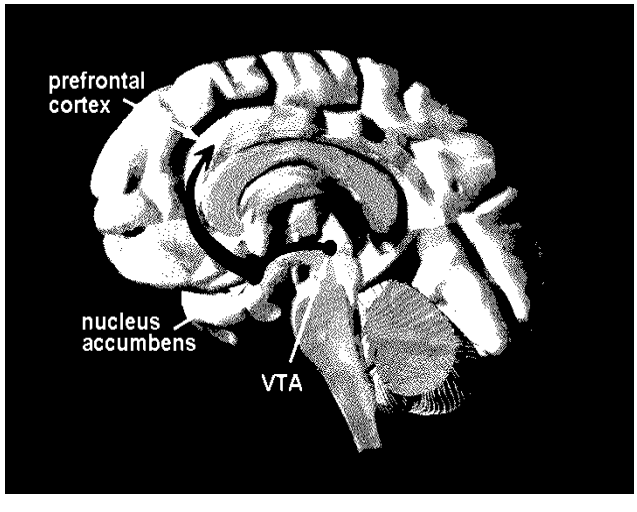

FIGURE 11.1. The reward pathway, consisting of three brain structures—the ventral tegmental area (VTA), nucleus accumbens, and prefrontal cortex—and the connections between the parts. From NIDA (1998).

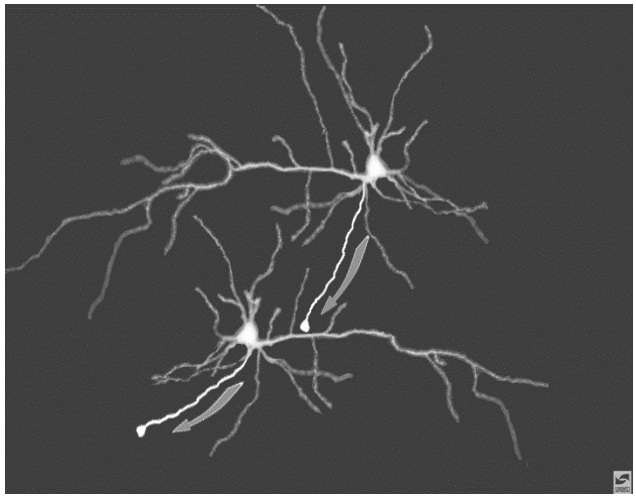

FIGURE 11.2. The path of a message sent from one brain cell to another brain cell, shown by the arrows. From NIDA (1998).

Prior to receiving signals from other neurons, a neuron is at resting potential. Membranes of dendrites and somata contain receptors that bind with specific chemical signals sent between neurons, known as neurotransmitters. Specific neurotransmitters may cause changes in the electrical potential by opening and closing ion channels nearby. Signals from surrounding neurons may depolarize the neuron and produce an action potential. In short, electrical currents travel from the dendrites and/or somata to the axon of the neuron as ion channels sensitive to electrical charge open. The cascading effect of

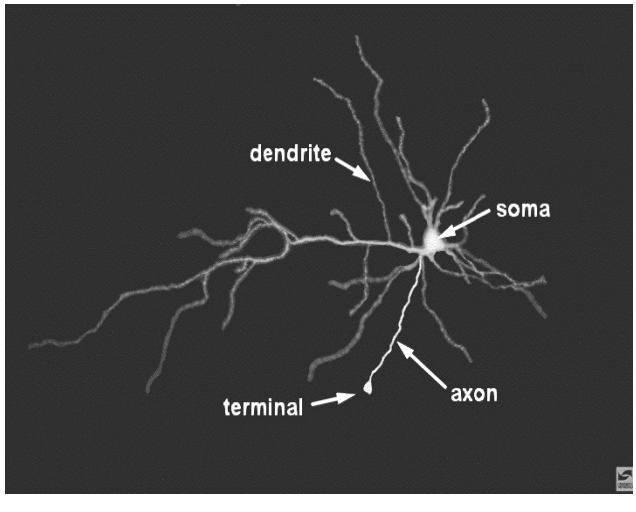

FIGURE 11.3. The characteristic parts of a neuron involved in its ability to receive and send messages. From NIDA (1998).

the flow of ions forces the electrical potential to go through the equilibrium. Electrical current generated goes to the end of the axon at the terminal. Stored neurotransmitters fuse with the neuron's membrane, causing the release of the contained neurotransmitters into the external cellular substance.

The membrane at the terminal is referred to as the presynaptic membrane. The space between the two neurons is the synaptic cleft. This space is bridged by the neurotransmitters. When the synaptic cleft is crossed, the neurotransmitters will attach to receptors on the postsynaptic membrane. The occupation of a receptor will depend both on the specific neurotransmitter and on the type of receptor. Neurotransmitters are then removed from the synaptic cleft by uptake pumps on the terminal of the presynaptic membrane (see Figure 11.4), or by enzymes that deactivate neurotransmitters by breaking them apart so that they can no longer link up to receptors. These neurophysiological processes happen repeatedly as chemicals move through the brain. The neurotransmitter dopamine is perhaps the prototypical example of a neurotransmitter that interacts with the reward pathway's brain structures and subserves addictive processes in human beings.

As Figure 11.1 has illustrated, the brain structures underlying the reward pathway progress from the ventral tegmental area (VTA) to the nucleus accumbens to the prefrontal cortex. The reward pathway is activated when positive reinforcement occurs following a certain behavior. All species can be positively conditioned through rewards. In humans, it is clear that stimulation of the nucleus accumbens and VTA with various psychoactive substances (e.g., cocaine) can activate the brain's reward pathway. Addictive substances produce strong relationships between intense feelings of pleasure and the substance-taking behavior by activation of the reward pathway. Changes in brain function resulting from the substance–brain interaction can be seen through the examples of cocaine, heroin, and marijuana; other psychoactive substances affect the brain similarly to these three examples.

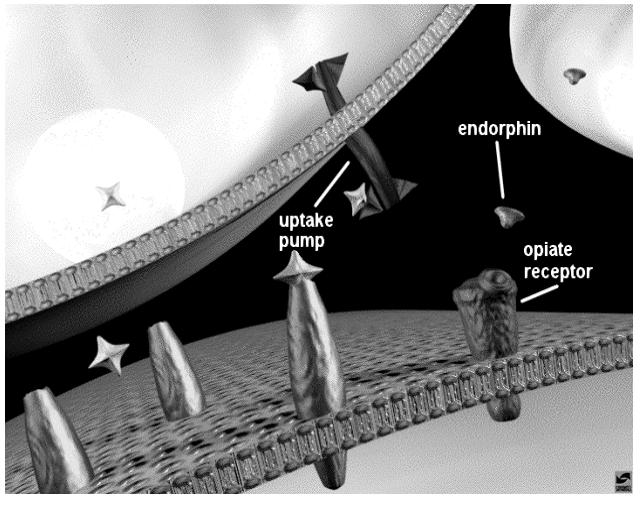

FIGURE 11.4. The activity in a synapse when chemical signals are being sent between neurons. From NIDA (1998).

In normal brain functioning, the binding of dopamine and its receptors attracts a specific protein, called the G protein. This protein, with the inclusion of an enzyme, forms a dopamine receptor–G protein–adenylate cyclase complex. The enzyme is turned on and produces cyclic adenosine monophosphate (cAMP) molecules, which regulate a neuron's ability to generate action potentials, as well as many other important functions (see Figure 11.5).

When cocaine is used, synaptic dopamine levels rise, and dopamine receptors become more highly activated (see Figure 11.6). Specifically, cocaine increases cAMP in the postsynaptic neuron, causing increased activation of the reward pathway (see Figure 11.7). The use of cocaine becomes linked with the experience of intense pleasure. In order to continue the pleasure, further use is encouraged. These types of effects on the brain's reward pathway are primarily responsible for the addictiveness of all psychoactive substances: The substances concentrate in the VTA and nucleus accumbens of the reward pathway, producing increased dopamine release.

In the case of heroin and other opiates, these substances (see Figure 11.8a) bind to opiate receptors, which are found on neither the presynaptic neuron nor the postsynaptic neuron, but rather another nearby neuron. This attachment sends signals to the dopamine terminals to release more dopamine. Higher levels of synaptic dopamine lead to more production of cAMP in the postsynaptic neuron. Otherwise, the effects on the reward pathway are the same.

Marijuana contains the active ingredient cannabinoids or delta-9-tetrahydrocannabinol (THC). Selected brain reward system structures contain concentrations of THC receptors (see Figure 11.8b). The reward pathway is activated by impulses sent from the nucleus accumbens to the prefrontal cortex, and, once again, increased dopamine release results (see Figure 11.9). Marijuana, like other psychoactive drugs, influences the reward pathway, and the use of the drug is associated with pleasure. The association of pleasure with drug-taking behavior serves to increase the behavior and thereby produces chronic patterns of substance abuse.

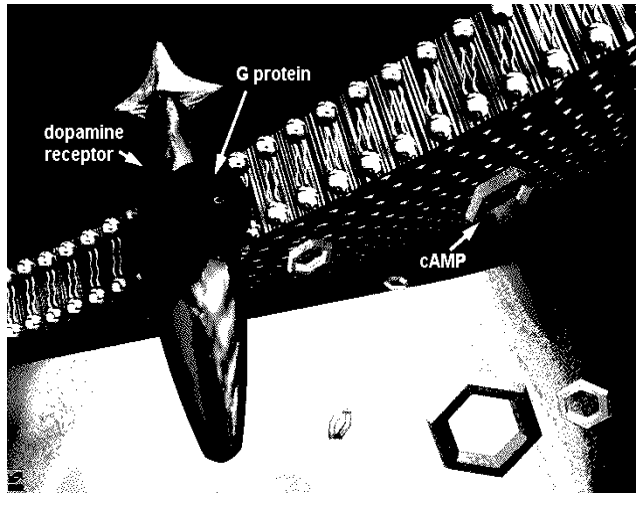

FIGURE 11.5. The normal effects of dopamine binding to a neuron, causing activities inside the neuron to change. From NIDA (1998).

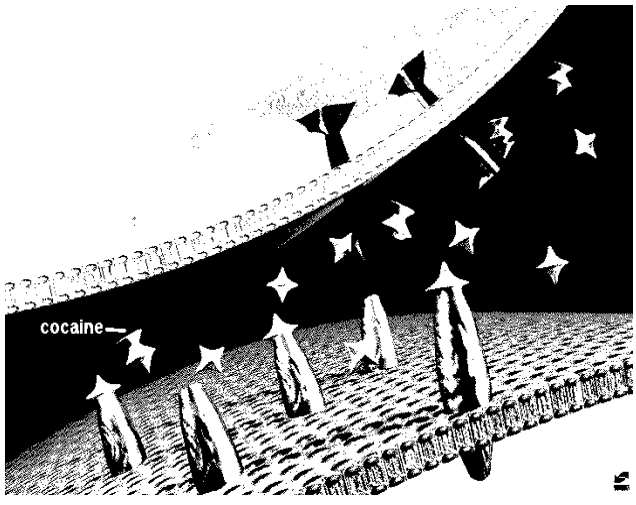

FIGURE 11.6. The way cocaine increases the amount of dopamine going between the neurons. From NIDA (1998).

ISSUES IN THE DIAGNOSIS AND ASSESSMENT OF PSYCHOACTIVE SUBSTANCE ABUSE

Methodological Difficulties

Before we discuss the diagnosis and assessment of substance abuse, some discussion of the many serious methodological difficulties involved with measuring residual substance abuse effects in human beings is appropriate. A prior review by Reed and Grant (1990) addressed many of these issues. For example, age, gender, and education as methodological confounds

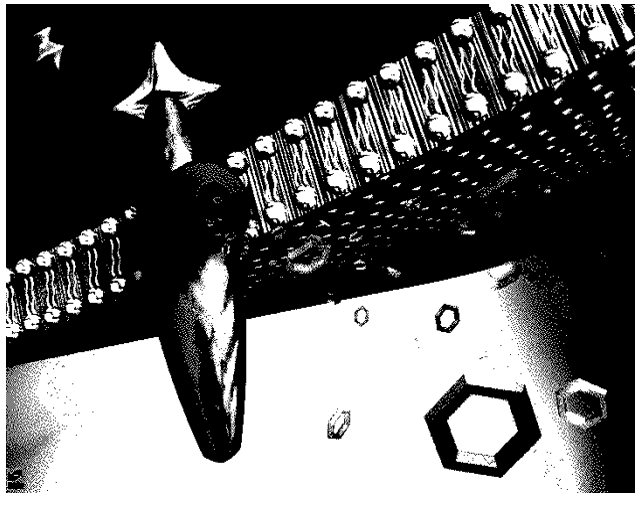

FIGURE 11.7. The change inside a neuron caused by the dopamine response to cocaine. Contrast with Figure 11.5 to see the difference in activity and production of cAMP. From NIDA (1998).

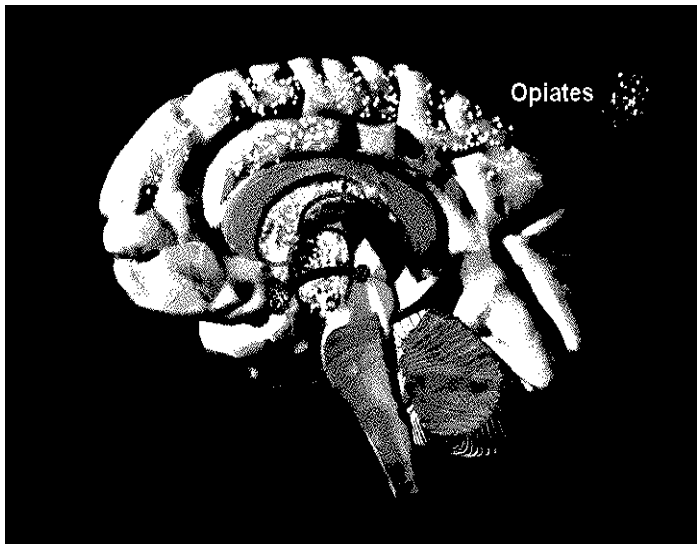

FIGURE 11.8a. A side view of the brain showing where opiates are found and active in the brain. From NIDA (1998).

are difficult issues to deal with. The results of many neuropsychological tests are correlated with age, gender, and education. Ideally, the recent availability of more accurate and comprehensive age and education norms for a number of neuropsychological tests should help in addressing this problem area (Heaton, Miller, Taylor, & Grant, 2004).

In addition, the issue of use of multiple substances is difficult to control in research investigations. Perhaps the majority of those addicted to substances engage in what is known as "garbage can" abuse. That is, they use a wide variety of psychoactive substances. Al-

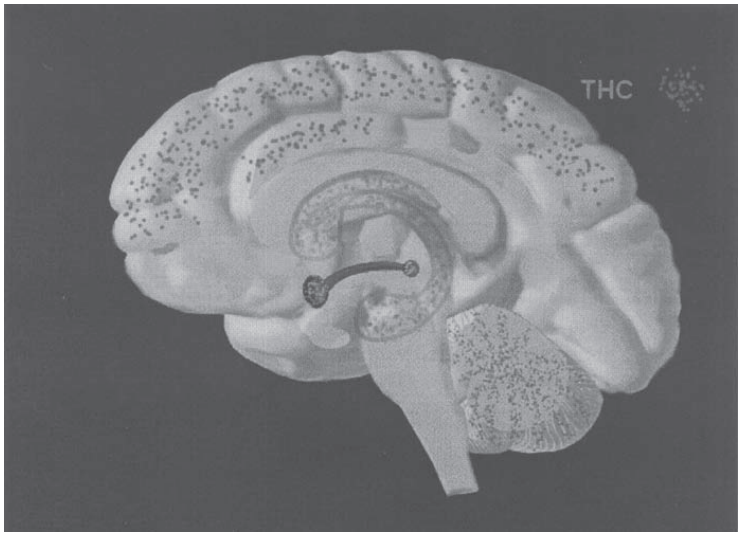

FIGURE 11.8b. Areas where THC is found and active in the brain. From NIDA (1998).

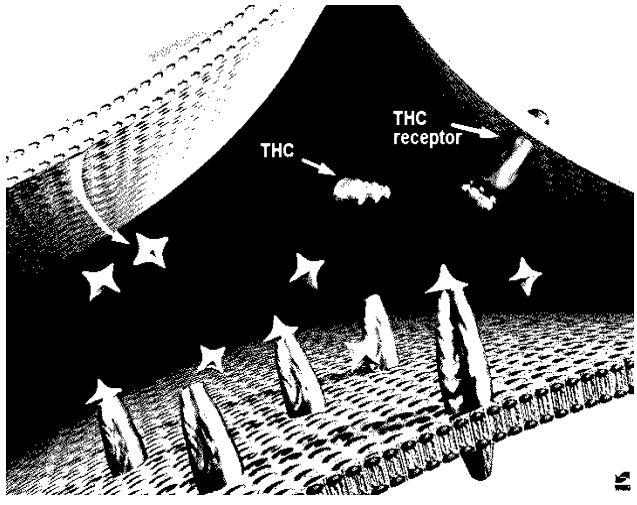

FIGURE 11.9. Increased dopamine levels resulting from the presence of THC. From NIDA (1998).

though in research such individuals may be characterized as having a preference for one substance, in reality their daily consumption of addictive substances is dependent primarily on which substances are most readily available. These are the substances most likely to be abused.

The amounts of substances consumed can also be difficult to measure. Research studies ask participants retrospectively how much of each substance they have abused. These self-reports may be solicited quite some time after the episode or episodes of substance abuse. Many individuals with substance abuse may have impaired short-term memory, and recall of what substances were abused can be confounded by the type and pattern of cognitive deficits (Spencer & Boren, 1990).

The methods for assessing residual substance effects based on the mode of consumption are poorly developed as well. That is, ingestion of drugs through needle injection, orally, or nasally produces different effects with respect to the action of the drug and possibly the residual neuropsychological impairment. Furthermore, premorbid and concurrent medical and psychiatric risk factors can be of great significance. Tarter and Edwards (1987) discuss a number of premorbid risk factors, such as learning disabilities and attention-deficit/hyperactivity disorder symptoms in childhood. Moreover, almost any psychiatric condition may be present along with substance abuse, and these mental disorders are difficult conditions to diagnose in an addicted population. Also, it has been clearly demonstrated that the lack of certain nutrients can play havoc with cognitive functioning. Finally, various organ systems can be impaired, and this impairment can have secondary effects on a person's mental ability. In short, multiple psychiatric, medical, and nutritional factors can obscure the diagnosis of substance abuse in human beings (Reed & Grant, 1990).

Diagnosis versus Assessment

Diagnosis and assessment are two separate undertakings. Horton and Wedding (1984) have noted that diagnosis places an individual in a recognized and/or defined category or class.

On the other hand, assessment describes multiple dimensions of an individual's adaptive and maladaptive functioning. The differences are similar to those between a photograph and a video. Reliable judgments regarding what is in a photograph can be determined straightforwardly, but reliable judgments regarding a video depend on watching similar sections of the video. In brief, multiple aspects can be considered and evaluated in assessment.

Diagnostic Guidelines

The *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR; American Psychiatric Association [APA], 2000), provides separate diagnoses for substance abuse and substance dependence. (Note that the term "substance abuse" is somewhat more narrowly defined by the APA than it is in common usage; elsewhere in this chapter, we have used the term in its broader, more general sense.) For a diagnosis of substance abuse, DSM-IV-TR requires recurrent, clinically impairing or distressing substance use that results in one or more of the following within a 12-month period:

1. Failure to meet major role obligations at school, work, or home.
2. Use in situations where use is physically hazardous (e.g., driving, operating machinery).
3. Recurring legal problems (e.g., arrests for disorderly conduct).
4. Recurrent social/interpersonal problems (e.g., physical fights, arguments with spouse or partner).

A DSM-IV-TR diagnosis of substance dependence requires a maladaptive pattern of substance use that is clinically impairing or distressing and includes three or more of the following within a 12-month period:

1. Development of physiological tolerance to the substance.
2. Development of a substance-specific withdrawal pattern.
3. Taking the substance in greater amounts or over a longer time than intended.
4. Persistent wish or unsuccessful efforts to reduce substance use.
5. Spending much time in activities needed to obtain or use the substance.
6. Giving up or reducing major social, recreational, or occupational activities because of substance use.
7. Continuing the substance use despite knowledge that it is causing a persistent physical or psychological problem.

In brief, the criteria for substance dependence include physical features such as tolerance and withdrawal (although a diagnosis with the qualifier "without physiological dependence" is possible), in addition to serious negative psychosocial consequences.

Assessment Procedures

Screening for substance abuse is important, so that treatment can be provided at an early state of addiction. The most widely used screening instrument for alcohol abuse is the CAGE (Mayfield, McLeod, & Hall, 1974), which is quite simple: It consists of four questions, and each letter of CAGE is used as a memory aid. The questions 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, an *Eye* opener, first thing in the morning to steady your nerves or to get rid of a hangover?

A newer measure, the RAFFT (Bastiaens, Riccardi, & Sakhrani, 2002), uses the same strategy as the CAGE, but the questions are reworded so that they apply to both drinking and illicit drug use. Screening measures for substance abuse are remarkably accurate, as long as patients are open about their problems. They do miss problems when patients wish to hide problems, which is often the case.

When more comprehensive assessment is required, the most widely used instrument is the Addiction Severity Index (ASI; McLellan et al., 1985). The ASI is a structured interview designed for use in clinical settings for patients with substance abuse problems. Areas covered include alcohol abuse, other drug abuse, medical status, psychiatric/psychological adjustment, legal problems, family/social problems, and employment/financial problems. Ratings of problem severity in each clinical area can be generated, which is a great advantage in developing treatment plans. The ASI is well validated and is possibly considered an "industry standard" for substance abuse assessment.

Many other assessment instruments for addictions are available. These range from other quick screening measures (the Drug Abuse Screening Test; Skinner, 1982) to long interview schedules (the Comprehensive International Diagnostic Interview—Substance Assessment Module; Robins, Cottler, & Babor, 1989). For a detailed review of instruments, please see the relevant chapters in the *Diagnostic Source Book on Drug Abuse Research and Treatment* (Rounsaville, Tims, Horton, & Sowder, 1993).

A model for neuropsychological screening of individuals who abuse substances (Horton, 1993) suggests that the Trail Making Test (TMT) may be of great value (Roberts & Horton, 2001). The TMT has previously been demonstrated to be very effective in general screening of brain-injured individuals (Norton, 1978; Mezzich & Moses, 1980). For fuller discussions of this issue, please see Horton (1996), Parson and Farr (1981), Benedict and Horton (1992), and Horton and Horton (in press).

ETIOLOGY

The etiology of substance abuse can be said to be determined by the interaction and combination of multiple factors that may have different timing, intensity, and duration (Tarter & Vanyukov, 1994). In addition, the factors that contribute to drug abuse may be grossly characterized as acting at different levels. One way of dividing these levels would be to posit an individual level; a family, school, and peer level; a neighborhood and community level; and a society and culture level. Other conceptual models could be devised, but would be likely to have similar elements. At the individual level, some of the factors might include genetic liability to substance abuse, temperament and personality traits, psychopathology, cognitive impairment, deficient coping, and interpersonal problem-solving deficits, among other factors. At the family, school, and peer level, some of the factors might include physical/sexual abuse and neglect, parental and peer models of substance use and behavior, style of parental and school discipline, family dysfunction, family socioeconomic status, and exposure to substance use, among others. Neighborhood and community factors might include the presence

of criminal activities, poverty, inadequate housing, substance accessibility, and lack of positive role models in the neighborhood, among other factors. Society and culture factors might include societal norms regarding substance use, media images of substance use, and cultural/social rituals that incorporate substance use, among others. In short, no single factor causes substance abuse; rather, the etiology is multidetermined, with multiple factors playing roles in causing drug abuse. The advantage of such a model of etiology is the identification of multiple targets for intervention and remediation.

TREATMENT

Defining substance abuse treatment is difficult, because such treatment is multifaceted and has been evolving considerably over time. One way of understanding what substance abuse treatment is may be to ask this important question: Does substance abuse treatment work? A better question would be this: What form of treatment, for what substance of abuse, works for what population and over what time period, as determined by what outcome measures? The answer may vary by the specific parameters of the question asked.

To oversimplify grossly, it is possible to divide substance abuse treatment into two types: treatments that are conceptualized as happening in an office versus treatments that are seen as happening in an office building. Put another way, some forms of psychotherapy, such as cognitive-behavioral treatment or supportive counseling, are conceptualized as being delivered face to face by one therapist to one or more patients in an office or group therapy room. The second type of treatment can be conceptualized as being delivered by a staff of treatment providers to multiple patients in a setting that includes multiple offices or therapy rooms.

The first type of substance abuse treatment is derived for the most part from previously developed therapeutic approaches for neurotic complaints that have been adapted for work with substance abuse. For the most part, these therapeutic methods were first used with neurotic complaints and then modified to address substance abuse, because individuals who abuse substances often have neurotic problems (and frequently character disorders as well). Treatment manuals have been developed for a number of these therapeutic approaches, and some of these can be downloaded from the NIDA website (www.nida.nih.gov or www.drugabuse.gov) for free.

The second type of treatment approaches may be seen as focused on the delivery of substance abuse treatment services in a programmatic format, rather than on individual or group psychotherapy. This is not to say that a substance abuse treatment program cannot include individual and/or group psychotherapy; rather, they are included as just one aspect of the substance abuse treatment program. To understand the existing modalities of substance abuse treatment programs, it helps to have a historical perspective. The primary program types are methadone programs, therapeutic communities, drug-free outpatient programs, and 28-day programs. Each type was developed to address a unique set of circumstances related to substance abuse.

Methadone programs arose in response to heroin abuse and dependence in the 1960s in large cities. Essentially, methadone is a medication that is cross-tolerant with heroin but not psychoactive in the same way (Dole & Nyswander, 1965). It is given to people addicted to heroin, in order to enable them to lead more normal lives and to help wean them off heroin. Heroin was the first major drug of abuse that mobilized the public will to fund public drug abuse treatment. Methadone programs were at first only dispensers of medi-

cation, but over time they added substance abuse counseling, group psychotherapy, medical care, and vocational placement services, among other services. Persons can be enrolled in methadone programs for years.

Therapeutic communities were developed as a reaction to the medical approach of methadone programs (DeLeon, 1985). Many people struggling with heroin addiction were averse to taking any drug, even a medication like methadone. These persons banded together in residential settings and used confrontational group therapy methods, structured living arrangements, and dramatic behavior sanctions to shape drug-free behavior. Typical stays are 6 months to a year or longer. Many therapeutic communities have developed small or midsize commercial businesses to support themselves.

Outpatient drug-free programs arose in response to the psychedelic drug epidemic of the 1970s. Many persons started to abuse LSD and other psychoactive drugs that did not require medically supervised detoxification. These people did need substance abuse treatment, however, and in community settings close to their places of residence. Outpatient drug-free programs typically have enrollment periods of several months and focus on psychoeducation about addictions, outpatient group therapy, and individual psychotherapy.

The 28-day treatment programs were actually 12-step alcoholism treatment programs that were augmented to treat a wider range of substance abuse during the cocaine epidemic of the late 1980s. The term often used to describe such programs is the "Minnesota model of treatment for alcoholism." Many inpatient alcoholism treatment programs in the 1980s had large enrollments of patients who abused both cocaine and alcohol, and sometimes other drugs as well. As a matter of simple necessity, patients went to 28-day programs because of the relative shortage of formal drug abuse treatment programs. With the advent of managed care, however, most of these programs no longer last a full 28 days.

Now that the modalities of substance abuse treatment have been described, it is possible to address the question of what works in substance abuse treatment. By way of preparation for the answer, some background should be given. To date, there have been three major national studies of substance abuse treatment sponsored by the U.S. federal government. The earliest of these studies was the Drug Abuse Reporting Program (DARP; Simpson & Sells, 1982). The DARP national data system was established by a contract between the National Institute of Mental Health, prior to the establishment of NIDA, and Texas Christian University in Fort Worth, Texas. Information was collected on 43,943 clients (primarily persons addicted to opioids) during the years 1969–1974 in 52 treatment programs, at admission, during treatment, and at discharge. DARP assessed treatment effectiveness on the basis of first-year posttreatment outcomes. Follow-ups of DARP have collected data for multiple years after admission (Simpson & Sells, 1990). Program modalities sampled included methadone maintenance, therapeutic communities, and outpatient drug-free programs, among others. The DARP data demonstrated that drug abuse treatment reduced drug use, and that amount of time in treatment was a major factor in treatment effectiveness (Simpson, 1981).

The next large national study was the Treatment Outcome Prospective Study (TOPS) (Hubbard et al., 1989). The TOPS was funded by NIDA through a contract to the Research Triangle Institute (RTI) in Raleigh, North Carolina. In TOPS, data were gathered on 11,750 clients from 41 agencies during 1979–1981 on admission, after 3 months, and at three follow-up points (1, 2, and 3½ years after treatment). Drug abuse treatment program modalities sampled included methadone maintenance, therapeutic communities, and outpatient drug-free programs, among others. The TOPS sample included individuals who abused other substances besides opioids, and participants showed multiple patterns of abuse

(including polysubstance abuse). Similar to DARP, TOPS demonstrated reduced drug use after treatment. However, TOPS demonstrated a need to look at other factors influencing substance use, such as cognitive impairment, criminality, and employment, among others.

The third major national federally sponsored study was the Drug Abuse Treatment Outcome Study (DATOS). DATOS was a naturalistic, prospective cohort study of adults enrolled in drug abuse treatment programs (Fletcher, Tims, & Brown, 1997; Horton, 1993); it was sponsored by NIDA and funded through a contract to RTI. DATOS collected data from 1991 to 1993 in 96 drug abuse programs in 11 cities in the United States. The DATOS intake cohort consisted of 10,010 subjects interviewed at admission to treatment (Flynn, Craddock, Hubbard, Anderson, & Etheridge, 1997). As the purpose of DATOS was to evaluate the effectiveness of drug abuse treatment in typical and stable community-based treatment programs, the data collection may have been skewed toward larger and more stable programs (Etheridge, Hubbard, Anderson, Craddock, & Flynn, 1997). Therefore, the DATOS data are most representative of subjects in the more established treatment programs in medium to large metropolitan areas in the United States. The specific cities from which subjects were drawn were Chicago, Houston, Miami, Minneapolis, Newark, New Orleans, New York, Phoenix, Pittsburgh, Portland (Oregon), and San José. The cities producing the largest numbers of subjects were Pittsburgh, New York, New Orleans, Chicago, and Miami. Of the entire sample, 66% of the subjects were male, 47% were African Americans, and 13% were Hispanic Americans. The average age of the sample was 32.6 years (Fletcher et al., 1997).

DATOS included various treatment modalities (methadone maintenance, therapeutic communities, drug-free outpatient programs, and chemical dependency programs) and included measures of social functioning, psychiatric status, cognitive impairment, vocational status, and health factors, among other data (Horton, 1993). The study demonstrated that length of time in drug abuse treatment was associated with better treatment outcomes, and that severity of psychosocial problems mediated treatment outcome (i.e., clients with less severe problems had better posttreatment outcomes) (Simpson, Joe, Fletcher, Hubbard, & Anglin, 1999). As in DARP and TOPS, drug abuse treatment was effective in reducing drug use after treatment. The various treatment modalities all appeared to be effective, and all seemed to be treating clients with problems at varying levels of severity (Hubbard, Craddock, Flynn, Anderson, & Etheridge, 1997). Since different modalities were treating essentially different types of clients and different levels of severity, cross-modality comparisons were more descriptive than evaluative. The bottom line from all three of the federally sponsored large-scale research studies, however, was that drug abuse treatment is effective in reducing drug use.

As the issue of drug abuse treatment services modalities has been addressed (albeit very cursorily), attention can be returned to the issue of psychotherapies to treat drug abuse. Generally speaking, the comparisons of therapy types (e.g., psychoanalytic and cognitive-behavioral therapies) have been disappointing, because no specific psychotherapy modality seems clearly better than any other modality, though all seem to be somewhat effective (Crits-Christoph et al., 1999; Project MATCH Research Group, 1997, 1998). The only exceptions are behavioral treatments that use behavior modification strategies such as positive reinforcement through a system of vouchers (Higgins et al., 1994). Essentially, a voucher system provides vouchers contingent on the accomplishment of such treatment goals such as clean urine samples. The vouchers can be used to obtain a variety of goods and services, much as in a standard token economy system. When compared to other drug abuse treatments, voucher systems seem to be the most effective single treatment approach (Higgins & Petry, 1999; Silverman et al., 1996).

A research-based guide that lists scientifically based approaches to drug addiction treatment has been published online by NIDA (1999). Treatment approaches that have

been found to be scientifically based and are described in the NIDA guide include the following:

- Relapse prevention
- The matrix model
- Supportive–expressive psychotherapy
- Individualized drug counseling
- Motivational enhancement therapy
- Behavioral therapy for adolescents
- Multidimensional family therapy for adolescents
- Multisystemic family therapy
- Combined behavioral and nicotine replacement therapy for nicotine dependence addiction
- Community reinforcement approach plus vouchers
- Voucher-based reinforcement therapy in methadone maintenance treatment
- Day treatment with abstinence contingencies and vouchers

Because of the lack of clear superiority for any single psychotherapy-based treatment, other than contingency management (i.e., vouchers), there has been a shift in interest from outcomes to the substance abuse treatment process (DiClemente, Schlundt, & Gemmell, 2004). That is, rather than focusing on treatment effectiveness, researchers are shifting to understanding how people with addictions change in substance abuse treatment. The idea is that through understanding the process of change, it will be possible to promote positive change in such persons. A key contribution has been the Prochaska and DiClemente (1994) transtheoretical approach to describing states of change involved in substance abuse treatment. An additional discussion of the special problems of elderly patients with addictions can be found in Horton and Fogelman (1991).

PROGNOSIS

The prognosis for clients with substance abuse is that they are likely to relapse. Two-thirds of the TOPS sample, for example, relapsed in the first 3 months (Hubbard et al., 1989). Although substance abuse treatment helps, the fact remains that such abuse is very difficult to treat. The expectation, however, is that relapses are common and should be planned for, and that multiple treatment episodes are likely to be needed before substance use will end. As mentioned above, important variables include the amount of time spent in treatment and the severity of psychosocial problems upon admission to a substance abuse treatment program. Factors that suggest a good prognosis for recovery include the following (Benson, 2004):

- Early treatment
- High level of patient motivation
- Existing social support network (housing, employment, intact family)
- Absence of antisocial personality traits (this indicates an ability to control impulses)
- Age (older patients are more successful)
- Adequate intelligence (the higher, the better)
- Good insight

SUMMARY

This chapter has briefly discussed the brain structures and processes underlying addictive behaviors, and has reviewed selected definitions of substance abuse and dependence. Difficulties involved in assessing the use and abuse of various psychoactive substances have been alluded to. Discussions of substance abuse etiology, treatment, and prognosis have been provided. The hope and expectation is that this chapter will contribute to the more effective treatment of persons with substance use and abuse problems.

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PART III

Disorders with Broader-Spectrum Effects

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12

TURNER SYNDROME

M. PAIGE POWELL
KIMBERLY R. SNAPP

Turner syndrome (TS) is one of the most widely known and examined chromosomal abnormality in females (White, 1994). It is characterized by extremely short stature; a lack of spontaneous development of secondary sexual characteristics, with accompanying infertility; a broad chest; a webbed neck; and a myriad of skeletal, renal, and cardiac abnormalities. Otto Ullrich (1930) gave the first definitive description of the disorder. Ullrich's report was followed by that of Henry H. Turner (1938), for whom the disorder was named after he described seven cases of it. TS is also referred to in the literature as "Ullrich–Turner syndrome," "monosomy X," and "gonadal dysgenesis" (45,X or X0). In 1959, Ford, Jones, Polani, de Almeida, and Briggs were able to identify the genetic abnormality associated with the syndrome, linking it with a loss of or an abnormality in one of the two X chromosomes present in females. This absence or irregularity of the X chromosome has been linked to a large number of physical, neuropsychological, and emotional sequelae for the affected girls and women.

ETIOLOGY

TS occurs in approximately 1 out of every 2,500 live births of female children (Elsheikh, Dunger, Conway, & Wass, 2002; Jones, 1988; Orten, 1990; Orten & Orten, 1992; Ross, 1990). However, the actual conception rate for TS is much higher, and it is estimated that only 1% of pregnancies with female fetuses with TS chromosomal abnormalities actually result in live births; the other 99% of the fetuses are spontaneously aborted (Jones, 1988; Temple & Carney, 1993). TS is found across all racial and ethnic groups (Rovet, 1995).

In order to understand the chromosomal abnormalities that lead to TS, it is important to understand the development of normal chromosomal patterns. After conception, the normally developing fetus has 46 chromosomes, each of which carries the inherited genetic information from the parents. The fetus receives 22 chromosomes from each parent, along with an X chromosome from the mother and either an X or a Y chromosome from the father, resulting in 46 chromosomes (23 pairs) in a normal fetus. If the fetus receives an X chromosome from the father, the child will be female (46,XX). If the fetus receives a Y chromosome from the father, the child will be male (46,XY). Each cell in a

person is supposed to contain exactly the same genetic information, except the egg cells or the sperm cells. TS occurs when there is an absence of or abnormality in the X chromosome, the sex chromosome, from either parent.

In the case of TS, a number of chromosomal abnormalities can result in the syndrome. The first identified, and most common, form of TS is referred to in the literature as "pure" TS (Jones, 1988; Temple & Carney, 1993). This is also referred to as 45,X0, indicating the absence of one of the X chromosomes that the fetus should have received from a parent—usually the paternal chromosome (Jones, 1988). Females with this form of TS have only one X chromosome. Approximately 50% of cases of TS have this genotype. The second most common form of TS is "mosaicism," which occurs in 30–40% of cases. In mosaicism, the cell division that replicates the chromosomes fails to replicate the genetic material completely, and some cells contain a slightly different set of chromosomal material. Mosaicism can occur in females with 45,X0 or in females with the normal chromosomal pattern of 46,XX. Other types of abnormalities occur less frequently; these include a partial deletion of one arm of the X chromosome, or a duplication of one arm of the X chromosome with the loss of the other arm (Jones, 1988; Temple & Carney, 1993). The chromosomal abnormality is thought to occur during the division of the sex cell of the parent, and there does not appear to be a significant maternal age factor (Jones, 1988).

CLINICAL PRESENTATION

Physical Manifestations

There are many physical abnormalities present with TS. These physical problems vary across clients and vary depending on the chromosomal abnormality present. The most obvious and common physical characteristic of TS is extremely short stature—often between 4 feet, 6 inches tall and 4 feet, 10 inches (Jones, 1988). Issues surrounding short stature are often dealt with through the administration of growth hormone (GH). GH therapy has been found to increase quality of life in most children and adolescents. It can also improve physical and psychological functioning (Bertelloni et al., 2003; Hull & Harvey, 2003). Siegel, Clopper, and Stabler (1998) found that the administration of GH therapy led to positive behavior changes in girls with TS.

Girls and women with TS have a wide variety of skeletal/bone abnormalities (Elsheikh et al., 2002; Lippe, 2001). In addition to the short stature, women with TS often have disproportionately short legs and an abnormal upper-body-to-lower-body ratio. This results in the appearance of a squarely shaped chest and widely spaced nipples. Scoliosis is also present in approximately 10% of the females with the disorder. The neck is often short due to cervical vertebral hypoplasia. In addition, cubitus valgus (i.e., an unusual carrying angle for the elbows) and short fourth or fifth metacarpals and/or metatarsals are often found with TS. Moreover, osteoporosis is common in women with TS. There is evidence of decreased bone mass in 25% of people with TS (Shore, Chesney, Mazess, Rose, & Bargman, 1982; Smith, Wilson, & Price, 1982). As a result, there is an increased risk of fracture for both girls and women (Davies, Gulekli, & Jacobs, 1995; Gravholt, Juul, Naeraa, & Hansen, 1998; Landin-Wilhelmsen, Bryman, Windh, & Wilhelmsen, 1998). Early estrogen replacement therapy and GH treatment, in combination, have been found to increase bone mass in women with TS (Elsheikh et al., 2002).

The skeletal malformations present in TS also lead to characteristic facies for females with TS. The first is micrognathia, or a small lower jaw. Other facial characteristics in-

clude a downward slope to the epicanthic folds, a high-arched palate, and low-set ears (Elsheikh et al., 2002).

Lymphedema, an abnormal accumulation of lymph in the tissues, can cause swelling in many places in the body. The lymphedema is thought to be responsible for the webbed neck that is often seen in TS. It may also result in other characteristic symptoms associated with TS, including ptosis (i.e., the drooping of the upper eyelid) and a low posterior hairline. Swelling in the hands and feet is also common and may result in the commonly seen nail dysplasia (pitting of the nails and lateral hyperconvexity) (Elsheikh et al., 2002).

Another central characteristic of TS is gonadal dysfunction. In TS, during the fetal stage of development and after birth, there is a massive loss of oocytes or egg cells (ovarian dysgenesis), which results in the lack of development of the ovaries. Because of this dysgenesis, most women with TS fail to develop secondary sexual characteristics, such as enlarged breasts and pubic hair (Jones, 1988). Most women with TS have either streak ovaries or ovaries that are too small to be seen on ultrasound. In women who have not received hormonal treatment, the uterus remains hypoplastic and prepubertal in size (Huber & Ranke, 1999; Massarano, Adams, Preece, & Brook, 1989). Most girls with TS do not enter puberty spontaneously. Studies have reported that only 12–16% of girls with TS will enter puberty spontaneously. This is most likely to occur when the genotype of the disorder is mosaicism (Elsheikh et al., 2002; Pasquino, Passeri, Pucarelli, Segni, & Municchi, 1997).

When puberty does not begin spontaneously, as in the majority of girls and women with TS, sex hormone replacement therapy is required. This therapy continues into adulthood. The long-term estrogen replacement has been found to decrease the risk of osteoporosis and atherosclerosis and may also improve aspects of cognitive functioning (Elsheikh et al., 2002).

In addition, spontaneous pregnancy is only found in about 5% of women with TS, so as they age, fertility issues become salient (Pasquino et al., 1997; Sybert, 1995). The outcomes of pregnancy for women with TS appear to be poor. Studies report that approximately 40% of pregnancies end in miscarriage or perinatal death of the fetus. When live births do occur, approximately 37% of the children will have some form of a chromosomal abnormality (most commonly Down syndrome or TS), or a congenital malformation such as a heart or neural tube defect (Kaneko, Kawagoe, & Hiroi, 1990; Tarani et al., 1998).

Most women with TS will be infertile. Although there are fertility options for these women (including oocyte donation and *in vitro* fertilization), there is a high occurrence of miscarriages, possibly due to uterine hypoplasia or ischemia. Often women with TS will require a cesarean section due to their small pelvic size (Foudila, Soderstrom-Antilla, & Hovatta, 1999; Kastgir et al., 1997). Finally, women with TS who do become pregnant should be considered to have high-risk pregnancies, due to the cardiovascular complications and hypertension associated with TS (Garvey, Elovitz, & Landsberger, 1998).

As just mentioned, cardiovascular disease is yet another area of concern for girls and women with TS. Heart defects are common and early death resulting from such defects has been reported in women with TS. Cardiac abnormalities include a bicuspid aortic valve and aortic coarction (narrowing). Aortic coarction can lead to dilation and dissection of the aorta. In addition, hypertension and ischemic heart disease are not uncommon in females with this disorder (Mazzanti & Cacciari, 1998; Sybert, 1998).

Still another area of concern for females with TS is otological disease. Because of the craniofacial abnormalities associated with TS, as well as problems with the eustachian tubes, ventilation of the middle ear, and inner-ear defects, middle-ear infections are very common in girls with TS (Hultcrantz & Sylven, 1997; Lippe, 1991; Sculerati, Lesdesma-Medina, Finegold, & Stool, 1990; Sybert, 1995). As they age, conductive hearing loss as the result of the recurrent

otitis media occurs. In addition, progressive sensory–neural hearing loss (changes in the nervous impulses in the ear) is common (Sculerati, Oddoux, Clayton, Lim, & Oster, 1996).

Finally, a myriad of other medical problems have been found to be associated with TS. These include obesity; renal or kidney problems (horseshoe kidney, double or cleft renal pelvis); Hashimoto thyroiditis; increased likelihood of gastrointestinal disorders; cataracts and other ophthalamic disease; arthritis; diabetes mellitus; and hyperlipidemia. In addition, an increased presence of pigmented moles or nevi is common. Finally, there appears to be an increase in the likelihood of certain malignancies, including endometrial carcinoma and gonadoblastoma (Elsheikh et al., 2002). There is evidence that females with the "pure" form of TS, the 45,X0 type, are likely to have more malformations than people with the mosaic or other forms of TS (Jones, 1988). The most common physical manifestations, with their relative percentages of occurrence, are reported in Table 12.1.

Previously, for most girls and women with TS, diagnosis was not typically made until late adolescence. A referral for a genetic evaluation was usually precipitated by the fact that a young woman had failed to begin puberty (Rovet, 1993). Because of the late diagnosis, many children and adults with TS have not received the appropriate medical, psychological, or educational intervention (Rovet, 1993). However, the diagnosis of TS is beginning to occur earlier, during infancy and early childhood (Mathiesen, Reilly, & Skuse, 1992); this allows children to receive appropriate intervention earlier.

Neuropsychological Manifestations

For many years after the discovery of the syndrome, it was widely believed and often reported (as late as Orten & Orten, 1992) that women with TS frequently have mental retardation. However, research has shown that this is not the case, and that girls and women with TS have Verbal IQ (VIQ) score distributions similar to those in the general popula-

TABLE 12.1. Common Physical Characteristics of TS, with Percentages of Occurrence

Characteristic	Percentage
Short stature	100
Ovarian dysgenesis	90
Lymphedema	80
Broad chest with widely spaced nipples	80
Prominent ears	80
Narrow palate	80
Low posterior hairline	80
Small mandible	70
Cubitus valgus	70
Hypoplastic nails	70
Knee anomalies	60
Kidney malformations	60
Webbed neck	50
Short fourth metacarpal/metatarsal	50
Bone dysplasia	50
Excessive pigmented nevi	50
Hearing loss	50

Note. Data from Jones (1988).

tion (Bender, Puck, Salbenblatt, & Robinson, 1984; Garron, 1977; Lewandowski, Costenbader, & Richman, 1984; McCauley, Ito, & Kay, 1986a; McCauley, Kay, Ito, & Treder, 1987; Money, 1963; Money & Alexander, 1966; Rovet, 1990; Rovet & Netley, 1982; Shaffer, 1962; Waber, 1979). However, the Performance IQ (PIQ) scores tend to be somewhat lower than VIQ scores in women with TS. These lower-than-expected scores on the Performance subtests of the Wechsler scales may result in lower Full Scale IQ (FSIQ) scores (Rovet, 1995). The lower PIQ scores found on the Wechsler scales are generally due to difficulties in tasks that require visual–spatial processing.

In 1962, Shaffer was the first researcher to suggest the presence of a specific cognitive profile for TS. His study found the pattern of VIQ scores higher than PIQ scores, which has since been consistently documented in the literature (Bender et al., 1984; Buckley, 1971; Downey et al., 1991; Garron, 1977; Lewandowski et al., 1984; McCauley, Ito, & Kay, 1986, 1987; Money, 1963; Money & Alexander, 1966; Pennington et al., 1985; Rovet, 1990; Rovet & Netley, 1982; Shaffer, 1962; Waber, 1979). FSIQ scores for females with TS have covered the full range of normal IQ (Temple & Carney, 1993). The differences between individuals appear to be related to familial influences rather than genotype (Haverkamp, Zerres, Rietz, Noeker, & Ruenger, 2004). Despite the consistent finding of lower PIQ than VIQ in most girls and women with TS, a homogenous cognitive profile across females with TS has not been documented (Rovet, 1990). However, a number of perceptual, motor, and cognitive deficits have been reported.

The Wechsler scales have been the assessment instruments most widely used in studying the neuropsychological aspects of TS. In the first study to examine the neuropsychological manifestations of TS (Shaffer, 1962), Verbal Comprehension was found to be high, with poor performance in tasks requiring perceptual organization (Block Design and Object Assembly) and freedom from distractibility (Arithmetic and Digit Span). These findings have been confirmed across the literature. Many studies have found Wechsler subtest deficits in women and girls with TS when compared to control subjects (Dellantonio, Lis, Saviolo, Rigon, & Tenconi, 1984; Downey et al., 1991; Lewandowski et al., 1984; Money, 1963, 1964; Romans, Stefanatos, Roeltgen, Kushner, & Ross, 1998; Rovet, 1993; Shucard, Shucard, Clopper, & Schachter, 1992; Temple & Carney, 1995).

Although the literature has been clear and consistent regarding the findings of deficiencies in nonverbal areas in TS, the literature has been less clear on the exact nature and cause of these deficits. Across studies, many different types of deficits have been noted. The most widely reported deficits are visual–spatial processing deficits (Cornoldi, Marconi, & Vecchi, 2001; Downey et al., 1991; Money, 1993; Murphy et al., 1994; Robinson et al., 1986; Romans et al., 1998; Rovet, 1993; Rovet & Netley, 1982; Temple & Carney, 1995). Other specific deficits that have been reported include problems with visual memory (Alexander & Money, 1966; Buchanan, Pavlovic, & Rovet, 1998; Downey et al., 1991; Haberecht et al., 2001; Lewandowski, 1985; Lewandowski et al., 1984), visual constructional skills (Downey et al., 1991; McCauley et al., 1987; Robinson et al., 1986; Temple & Carney, 1995), short- and long-term memory (McCauley et al., 1987; Pennington et al., 1985; Shaffer, 1962), word fluency (McCauley, Ito, & Kay, 1986; Money, 1993; Waber, 1979), facial expression recognition (Buchanan et al., 1998; McCauley et al., 1987), and arithmetic (Downey et al., 1991; Garron, 1977; Money & Alexander, 1966; Shaffer, 1962). The cognitive deficits that have been identified in TS do appear to continue across the lifespan (Downey et al., 1991; Garron, 1977).

Other studies have identified motor problems in girls and women with TS. Mathiesen and colleagues (1992) reported oral–motor feeding problems in infants with TS. Others have found reduced muscle tone and muscle strength. Finally, motor speed appears to be

affected (Bender, Linden, & Robinson, 1994; McGlone, 1985). Nijhuis-van der Sanden, Smits-Engelsmam, Eling, Nijhuis, and Van Galen (2002) have found that the motor problems are related mainly to motor execution and that they are present independently of visual–spatial problems. Interestingly, Collaer, Geffner, Kaufman, Buckingham, and Hines (2002) found that women with TS showed more cognitive and motor task deficits than controls on tasks that show sex differences (male-superior and female-superior measures) than on sex-neutral tasks. In addition, Romans and colleagues (1998) found that motor skill deficits improved as subjects moved from adolescence to adulthood.

Many studies have attempted to identify the actual area or areas of dysfunction within the brain that lead to the typical cognitive deficits seen with TS. Currently there are two theories with some empirical support. Both of these theories revolve around the issue of lateralization of the brain. The human brain has two hemispheres, left and right, each of which is believed to be responsible for certain cognitive tasks (i.e., the brain is lateralized). The left hemisphere is thought to be responsible for language and symbolic operations. The right hemisphere is thought to be responsible for nonverbal information processing (Watson, 1981).

The first theory regarding dysfunction within the brain and lateralization in TS is that women and girls with TS have generalized right-hemispheric dysfunction (Dellantonio et al., 1984; Kolb & Heaton, 1975; Rovet, 1995; Rovet & Netley, 1982; Shucard et al., 1992; Silbert, Wolff, & Lilienthal, 1977). This makes intuitive sense when one considers that women and girls with TS tend to have intact verbal skills (left hemisphere) and difficulties with nonverbal, visual–spatial tasks (right hemisphere).

The second theory suggests a lack of or failure in development of normal lateralization of the brain in people with TS. Rovet (1990) found that people with TS used the left hemisphere more than nondisabled controls did when processing nonverbal information. According to Rovet, this finding suggests that the left hemisphere is compensating for a weaker right hemisphere, resulting in a lack of normal brain lateralization.

Other differences in brain function that have been identified include abnormalities in the medial temporal and hippocampal structures of the brain (Murphy et al., 1994; Pennington et al., 1985). These areas of the brain are thought to have an impact on facial recognition and memory, which are areas of deficit identified in people with TS.

In recent years, studies of brain function through the use of magnetic resonance imaging (MRI), electroencephalography, and other technologies have been done. These studies have shown various dysfunctions to support the hypothesis of atypical hemispheric organization. They also provide evidence of other brain differences in women and girls with TS. Portellano-Perez, Bouthelier, and Monge (1996) found greater right-hemispheric activation for reading and greater left parietal activation for arithmetic in TS. Shucard and colleagues (1992) found electrophysiological evidence to support right-hemispheric abnormality. Studies using MRI have found reduction in gray and white matter in the right temporal and parietal and left parietal perisylvian regions of the brain (Reiss, Mazzocco, Greenlaw, Freund, & Ross, 1995), the cerebellum and the pons (Reiss et al., 1993), and the hippocampal lenticular nuclei and the thalmus (Murphy et al., 1994). Kesler and colleagues (2004) found activation deficits in the parietal–occipital and frontal areas of the brain in women with TS. Tamm, Menon, and Reiss (2003) found that subjects with TS tended to compensate for executive functioning problems by recruiting other prefrontal cortex areas. However, the studies have not found consistent major hemispheric differences in the anatomy of the frontal regions. It is believed that organizational deficits may be due to genetic malformation of the brain, while activation deficits may be related to hormonal insufficiency.

Psychoeducational Manifestations

Given the large number of neuropsychological deficits found with TS—specifically, difficulties with visual–spatial, visual–motor, and memory tasks—it is not surprising that there are also educational difficulties associated with TS. The most common learning problems for girls with TS are in the area of mathematics (Downey et al., 1991; Garron, 1977; Money & Alexander, 1966; Rovet, 1995; Shaffer, 1962). Rovet (1995) reported that the mathematics problems appear to be more related to the conceptual/factual area than to the actual computational area. She also reported that older girls were more likely to have a mathematics disability than younger girls, probably due to the fact that math becomes more conceptual and relies more on memory skills as children progress through school. In addition, Rovet reported that spelling and reading skills appeared to remain intact. However, some girls may experience difficulty with reading decoding skills, but not comprehension skills. Rovet (1993) found that reading disabilities at times coexist with the mathematics disabilities in TS, but reading disabilities have not been found to occur alone.

Correlations between Phenotype and Neuropsychological and Psychoeducational Deficits

As in the physical features associated with TS, there appears to be extensive heterogeneity in the neuropsychological deficits associated with TS. Several studies have examined the impact of phenotype (i.e., 45,X0 vs. mosaicism) on these deficits. As a rule, it has been found that subjects with the mosaic form of TS tend to have fewer cognitive and visual–spatial difficulties than girls with the "pure" form of TS (Bender et al., 1994; El Abd, Turk, & Hill, 1995; Rovet & Ireland, 1994; Temple & Carney, 1993). Murphy and colleagues (1994) reported that the neuroanatomical abnormalities found in TS are less severe in mosaic forms of TS than in pure forms of TS. They also found that, in general, mosaic TS leads to less impairment than pure TS. Females with mosaic TS have been found to have better verbal skills than those with pure TS. Within pure TS, Bishop and colleagues (2000) found that women with the maternal X chromosome missing tended to have more verbal memory problems, whereas women with the paternal X chromosome missing tended to have more visual memory problems.

Psychosocial Aspects

Over the past 25 years, increasing attention has been given to the psychosocial aspects of TS. Overall, research has found that girls and women with TS tend to have fewer severe mental disorders than those found in the general population of females. Women with TS seem less likely to experience the "positive" symptomatology of psychopathology, such as acting-out behaviors, suicidal ideation, and alcohol/drug use. However, they do appear to experience more of the "negative" symptomatology of psychopathology, such as a lack of emotional reactivity and few or poor relationships with peers and other intimates (Downey, Ehrhardt, Gruen, Bell, & Morishima, 1989). Other personality characteristics commonly associated with TS have included high stress tolerance, unassertiveness, overcompliance, and a lack of emotional maturity (Baekgaard, Nyborg, & Nielsen, 1978; Downey et al., 1989; Higurashi et al., 1986; McCauley, Ito, & Kay, 1986; McCauley,

Ross, Kushner, & Culter, 1995; McCauley, Sybert, & Ehrhardt, 1986; Nielsen, Nyborg, & Dahl, 1977).

Several major psychosocial areas of concern have been identified and studied in relationship to TS. The first of these is poor self-esteem. Across studies, girls with TS have been found to have low self-esteem (McCauley, Ito, & Kay, 1986, 1995; Perheentupa et al., 1974). Among the major sources contributing to a child's sense of self-worth are the child's interactions with others, especially peers and family. Any perceived differences in appearance—let alone major differences, such as short stature and the other physical anomalies associated with TS—can have a lasting impact on a developing child's sense of self and self-worth. Short children are often teased and bullied by peers at school, which may adversely affect their self-esteem (Skuse, 1987), and this appears to be a major problem for girls with TS (McCauley, Ito, & Kay, 1986). A child with TS, who may be less assertive than her peers (Skuse, 1987), may have greater difficulty in handling the teasing in a proactive manner. In addition, because children are often treated according to the age that they appear to be rather than their actual chronological age, an older child or adolescent with TS may experience the added burden of being treated like a child much younger and not having the behavioral expectations that would correspond to her chronological age (Alley, 1983). This again will set her apart from her peers and have an impact upon self-esteem. In addition, it has been found that in girls with TS, the greater the number of physical anomalies, the lower the self-esteem (El Abd et al., 1995). Finally, difficulties with motor coordination and hearing difficulties due to inner-ear abnormalities may affect self-esteem (El Abd et al., 1995).

As with the cognitive aspects of TS, many of the psychosocial difficulties reported in children with TS continue into adulthood. Women with TS have also been found to experience difficulties with self-esteem (McCauley, Sybert, & Ehrhardt, 1986; Pavlidis, McCauley, & Sybert, 1995). Delooz, Van der Berghe, Swillin, Kleczkowski, and Fryns (1993) found that 50% of the women in their study had poor self-image.

It has been found that the delay in the onset of puberty may further decrease the self-esteem of girls with TS during adolescence (Skuse, 1987). There has been some evidence to suggest that girls with TS have average self-esteem until puberty, at which time they begin to fall behind their peers both physically and socially, and their self-esteem decreases. As they fall behind, they begin to withdraw and are viewed as socially immature (Perheentupa et al., 1974). However, self-esteem and psychological well-being in general appear to be higher in women who started hormone replacement therapy before the age of 14 (Ross et al., 1996). This may be due to the estrogen itself or may be due to a decrease in some of the teasing that may occur when girls do not go through puberty with their peers.

The impaired development of secondary sexual characteristics, and the accompanying infertility, have also been found to contribute to the low self-esteem in adults with TS (El Abd et al., 1995; Pavlidis et al., 1995; Skuse, 1987). Psychosexual development in women with TS has also received some attention. Although typical heterosexual romantic fantasies have been reported in women with TS, their experiences of dating and sexual activity experience appear to be delayed or infrequent (McCauley, Sybert, & Ehrhardt, 1986; Money & Mittenthal, 1970; Nielsen et al., 1977; Pavlidis et al., 1995).

Despite the delayed or absent development of secondary sexual characteristics, it does appear that women with TS have a strong female gender identity (Ehrhardt, Greenberg, & Money, 1970; Money & Mittenthal, 1970). Despite this, they are less sexually active than average. They also report less interest in sexual relationships (Downey et al., 1989). Even with this lack of sexual activity, and maybe because of a lack of interest in sexual relation-

ships, women with TS reported moderate to high levels of sexual satisfaction in one study (Pavlidis et al., 1995). However, higher sexual satisfaction was associated with higher frequency of sexual intercourse and a better health status in this study. Raboch, Kobilkova, Horejsi, Starka, and Raboch (1987) have reported that women with TS have lower sexual desire, a reduced orgasmic capacity, and a lower amount of sexual activity in general. However, when a woman is in a relationship with a partner, some of these differences disappear. Raboch and colleagues hypothesized that the lower interest in sex may be related to lower sexual hormones.

A second area of concern in the literature consists of problems with social isolation and poor peer relations. These problems in children with TS are reported across studies (Nielsen et al., 1977; Rovet, 1993; Siegel et al., 1998; Skuse, 1987). As girls are teased for their physical abnormalities, including short stature, they may withdraw from peer interactions. Poor peer relations may also be due to hormonal deficits. As puberty is delayed, children with TS fail to go through the hormonal changes of adolescence and may be seen as emotionally immature as well as physically immature (Skuse, 1987). They may prefer to be with children younger than themselves (McCauley et al., 1995; Rovet & Ireland, 1994).

Women with TS may continue to be less emotionally mature and continue to experience poor or few peer relationships (Nielsen et al., 1977). Women with TS have been found to be less socially competent (i.e., to have fewer friends, to be less likely to have a romantic partner, and to be less likely to have had sexual experiences) than women in control groups (Downey et al., 1989). In addition, they are less likely to live independently of their parents, to be married or to live with a partner, or to be sexually active than women in control groups, despite having similar educational attainment and employment status (Nielsen et al., 1977; Taipale, Niittymaki, & Nevalainen, 1982).

Social difficulties may also be related to the visual–spatial processing problems associated with TS, because children with these difficulties often have problems with affective discrimination (i.e., understanding the social cues and facial expressions of others) (McCauley et al., 1987; Waber, 1979). This has also been found to be the case in women with TS (Lawrence, Kuntsi, Coleman, Campbell, & Skuse, 2003). Overall, the reasons for more social withdrawal and isolation for women with TS are unknown. Downey et al. (1989) have postulated that these reasons may include their having more medical problems, more obvious physical abnormalities, infertility, and hormonal deficiencies.

A third area that has been identified as problematic for children with TS consists of academic difficulties. Academic problems can lead to lowered self-esteem in children. There is a vast literature base examining the impact of a learning disability on the development of a child's self-esteem and feelings of self-worth (Shapiro, Church, & Lewis, 2002). The psychosocial problems that are evident in children with learning disabilities, such as poor task motivation, poor social skills, externalizing behaviors, depression, and somatic complaints, may continue in adulthood (Jorm, Share, Matthews, & Maclean, 1986).

Given the reported perceptual and educational problems associated with TS, a continuing area of concern for adults with TS is educational and occupational achievement. Despite the findings that the perceptual and educational difficulties found in childhood continue into adulthood (Garron, 1977; Nielsen & Stradiot, 1987), women with TS have been found to perform at an average or above-average level academically and to be gainfully employed in a wide variety of occupations (Nielsen et al., 1977; Nielsen & Stradiot, 1987; Orten & Orten, 1992). Often the women tend to choose the helping professions. Many studies have found that women with TS are more likely to attend college than the average female (Elsheikh et al., 2002; Okada, 1994; Sybert, 1995). It has also been found

that they are often employed in jobs for which they are overqualified (Sybert, 1995; Sylven, Hagenfeld, Brondum-Nielsen, & von Schoultz, 1991).

The fourth major psychosocial area of concern that has been discussed in the literature consists of the behavior problems/mental health problems associated with TS. A number of studies have found behavior problems in girls with TS. Most of these problems have to do with poor peer relationships, immaturity, poor attention skills, and hyperactivity (Rovet, 1990; Rovet & Ireland, 1994; Sonis, Levine-Ross, & Blue, 1983). These problems do appear to increase across childhood (Skuse, 1987). Siegel and colleagues (1998) also found that girls with TS are more vulnerable to psychological problems. They found that at least half of the participants in their study had at least one risk factor indicative of a need for clinical intervention. However, they found that the girls who received GH treatment had positive behavioral changes. Siegel and colleagues posited that these changes could have resulted from the improved body image and increased self-esteem accompanying increased height, and/or that they could have been caused by chemical changes in the brain as a result of GH treatment.

As reported above, children with TS may tend to be more hyperactive than their same-age peers (McCauley, Ito, & Kay, 1986; Rovet, 1986; Rovet & Ireland, 1994; Sonis et al., 1983); however, adults with TS may have *lower* levels of activity level than expected (Downey et al., 1989; Higurashi et al., 1986; Money & Mittenthal, 1970; Pavlidis et al., 1995; Rovet, 1995). The reason for this difference is not readily discernible. In addition, adult women with TS may be likely to experience mild symptoms of depression and anxiety. However, there does not appear to be a consistent pattern of psychological problems or an increase in the frequency of psychological problems over the general population (Money & Mittenthal, 1970; Shaffer, 1962). In addition, a study by Orten and Orten (1992) found that women with TS reported that they were satisfied with their lives and happy.

Fifthly, there have been reports of a connection between the occurrence of anorexia nervosa in adolescents and adults with TS and the advent of hormone therapy (Muhs & Lieberz, 1993; Taipale et al., 1982). This appears to be related to the onset of sexual development and anxiety caused by the new sexual feelings that occur. It is believed that the development of anorexia nervosa in subjects with TS who have begun hormonal treatment follows a similar etiology as in girls without TS (Muhs & Lieberz, 1993; Taipale et al., 1982). It has also been attributed to a distorted body image caused by a combination of the "stocky" body build normally associated with TS and the perceptual deficits that exist with TS (Darby, Garfinkel, Vale, Kirwan, & Brown, 1981).

Finally, health status appears to be significantly related to a number of psychosocial issues in adults with TS. As noted earlier, health compromise is common in women with TS, given the large number of potential medical complications associated with the disorder. Pavlidis and colleagues (1995) found that better health status was associated with higher self-esteem and greater sexual satisfaction.

Correlations between Phenotype and Psychosocial Problems

Again, as in physical manifestations and neuropsychological manifestations, there is a wide homogeneity in psychosocial difficulties. Again, too, these also appear to be related to phenotype. Children and adults with the mosaicism phenotype appear to have fewer behavioral difficulties than individuals with other forms of TS (Pasaro Mendez, Fernandez, Goyanes, & Mendez, 1994; Rovet & Ireland, 1994; Temple & Carney, 1993).

ASSESSMENT

Due to the myriad of problems associated with TS, and the fact that they have different effects at different developmental levels, assessment of females with TS should occur across the lifespan. Powell and Schulte (1999) provide an examination of the assessment issues during childhood. In addition to the assessment of females with TS in childhood and adolescence, assessment can be helpful during adulthood. Because of the possible sequelae of TS, a comprehensive battery may be most helpful. Assessment during adulthood can provide information for appropriate treatment planning by those working with a woman with TS. If the woman has not received an assessment of intelligence and achievement during childhood and adolescence, it will be important to include measures of intelligence and achievement. Assessment of nonverbal (especially visual perceptual) skills, memory, and personality will also be important. In addition to the areas listed above, assessment utilizing the traditional neuropsychological batteries—the Halstead–Reitan (Reitan & Wolfson, 1985), the Luria–Nebraska (Golden, Purisch, & Hammeke, 1988), and the Neuropsychological Assessment Battery (Stern & White, 2003)—may be useful to explore strengths and weaknesses. The following discussion is not intended to be a thorough examination of all possible instruments in these areas.

Cognitive Measures

Assessment for learning problems should always begin with an examination of the person's current intellectual abilities. A large number of studies involving children have utilized the Wechsler scales (Downey et al., 1991; Lewandowski et al., 1984; McCauley et al., 1995; Netley & Rovet, 1982; Pennington et al., 1985; Rovet, 1993; Rovet & Netley, 1982; Temple & Carney, 1993, 1995; Williams, 1994). All of the Wechsler scales have excellent reliability and validity. The Wechsler Adult Intelligence Scale—Third Edition (WAIS-III; Wechsler, 1997a) can be used to evaluate people ages 16 years, 0 months to 89 years, 11 months. The WAIS-III provides a VIQ score, a PIQ score, an FSIQ score, and several factor-analytic scores (Verbal Comprehension, Perceptual Organization, Working Memory, and Processing Speed), all of which can be helpful in diagnosing cognitive deficits in people with TS.

In addition to the Wechsler scales, other cognitive measures may prove helpful in evaluating people with TS. The Stanford–Binet Intelligence Scales, Fifth Edition (SB5; Roid, 2003) yields a Nonverbal IQ, Verbal IQ, and Abbreviated Battery IQ, as well as an FSIQ score. It also yields five factor scores: Fluid Reasoning, Knowledge, Quantitative Reasoning, Visual–Spatial Processing, and Working Memory. These scores can provide critical information for the assessment and remediation of people with TS. The SB5 measures cognitive abilities in people ages 2 years, 0 months to 85 years, 11 months.

Achievement Measures

Academic achievement is another critical area for assessment in TS. It is important that learning disabilities be diagnosed in order for appropriate interventions to occur. Given the likelihood of academic problems, especially in the area of mathematics, it is very important to obtain a thorough educational evaluation. Instruments of choice may include the Woodcock–Johnson III (Woodcock, McGrew, & Mather, 2001), the Wechsler Individual Achievement

Test—Second Edition (Wechsler, 2001), and the Wide Range Achievement Test—Third Edition (Wilkinson, 1993).

Visual Perceptual Measures

Given the variety of visual perceptual problems that people with TS may exhibit, it is important to conduct a broad-ranging assessment in this area. Visual perceptual instruments can be divided into a number of areas. The first area is visual perceptual or gestalt integration. The Benton Visual Retention Test—Fifth Edition (Benton, 1992), the Visual Object and Space Perception Battery (Warrington & James, 1991), the Rey Complex Figure Test and Recognition Trial (Meyers & Meyers, 1995), the Test of Visual Perceptual Skills (Nonmotor)—Revised (Gardner, 1996), and the Kent Visual Perceptual Test (Melamud, 2000) can be used to assess visual perceptual skills. The second area, visual–spatial skills, can be assessed with the Judgement of Line Orientation Test (Benton, 1983), the Raven Coloured Progressive Matrices (Raven, Court, & Raven, 1977), and the Trail Making Test (Reitan, 1992). There are numerous instruments designed to assess visual constructive or visual–motor skills, including the Grooved Pegboard Test (Trites, 1989), the Bender Visual–Motor Gestalt Test—Second Edition (Brannigan & Decker, 2003), the Benton Visual Retention Test—Fifth Edition (Benton, 1992), the Wide Range Assessment of Visual Motor Abilities (Adams & Sheslow, 1995), the Block Design and Object Assembly subtests of the WAIS-III (Wechsler, 1997a), and the Form Board and Form Patterns subtests of the SB5 (Roid, 2003).

Memory Measures

There are a number of instruments that can be used to assess memory in adults. The most commonly used instruments include the Wechsler Memory Scale—Third Edition (Wechsler, 1997b), the Wide Range Assessment of Memory and Learning—Second Edition (Adams & Sheslow, 2003), various subtests of the California Verbal Learning Test—Second Edition (Delis, Kramer, Kaplan, & Ober, 2000), and subtests of the general neuropsychological batteries mentioned above.

Measures of Other Neuropsychological Areas

Several instruments measure other areas of concern for adults with TS. These include measures of executive functioning, such as the Stroop Color and Word Test (Golden & Freshwater, 2002) and the Delis–Kaplan Executive Function Scale (Delis, Kaplan, & Kramer, 2001). It also includes measures of verbal learning, such as the California Verbal Learning Test—Second Edition (Delis et al., 2000) and the Rey Auditory Verbal Learning Test (Schmidt, 1996). Finally, the Facial Recognition Test (Benton, des Hamesher, Varney, & Spreen, 1983) may also be helpful in assessing for problems in women with TS.

Personality Measures

Assessment of psychological adjustment is very important for women with TS. Personality measures can be divided into two general categories: self-report and projective measures.

In each of these categories, it is essential to assess for psychological symptomatology, self-esteem, and social problems that may require clinical attention.

Self-report measures can include instruments designed to assess more general psychopathology, such as the Minnesota Multiphasic Personality Inventory–2 (Butcher et al., 2001); the Millon Clinical Multiaxial Inventory–III (Millon, Davis, & Millon, 1997); the Symptom Checklist 90—Revised (Derogatis, 1994); the NEO Personality Inventory—Fourth Edition, which includes a third-party report form (Costa & McCrae, 1998); and the Personality Assessment Inventory (Morey, 1991). In addition, specific instruments for specific types of symptoms may be helpful. For example, assessment of depressive symptomatology may include instruments such as the Beck Depression Inventory–II (Beck, Steer, & Brown, 1996) and the Revised Hamilton Rating Scale for Depression (Warren, 1997). Anxiety instruments can include the Adult Manifest Anxiety Scale (Reynolds, Richmond, & Lowe, 2003), the Beck Anxiety Inventory (Beck & Steer, 1993), and the Multidimensional Anxiety Questionnaire (Reynolds, 1999).

Social problems and social anxieties can be assessed through the use of the Inventory of Interpersonal Problems (Horowitz, Alden, Wiggins, & Pincus, 2000), the Social Adjustment Scale—Self-Report (Weissman, 1999), and the Social Phobia and Anxiety Inventory (Turner, Beidel, & Dancu, 1996). Other areas—such as attention deficit symptoms (Conners Adult ADHD Rating Scale, Conners, Ehrhardt, & Sparrow, 1999); quality of life (Quality of Life Inventory, Frisch, 1994); eating disorders (Eating Disorder Inventory—Second Edition, Garner, 1991; Sterling Eating Disorder Scale, Williams & Power, 1995); and self-esteem (Tennessee Self-Concept Scale—Second Edition, Fitts & Warren, 1997)—may also be important to assess.

Finally, projective measures may aid in the assessment of some adults. Instruments that can be used include the Rorschach Psychodiagnostic (Rorschach, 1942). These instruments can provide information regarding information processing, coping styles, and personality characteristics.

INTERVENTIONS

Intervention for both children and adults with TS is critical for a positive life outcome. A girl or woman with TS is at risk for the development of a wide range of sequelae. The clinical needs of patients with TS fall across four areas: medical, social, academic, and sexual issues (Mullins, Lynch, Orten, & Youll, 1991). We focus our discussion here on interventions for medical and psychosocial (including social and sexual) issues.

Medical Interventions

Because TS is associated with a threefold increase in the overall mortality rate and with a life expectancy that is reduced by as much as 13 years (Gravholt et al., 1998), due to the wide variety of medical problems that can occur with TS, it is critical that regular medical care be obtained (Mullins et al., 1991; Orten, 1990; Orten & Orten, 1994; Rovet, 1995). It is also critical that a girl or woman with TS and her family receive accurate and sensitive medical information (Orten, 1990). Medical intervention with TS can take many different forms. The most common of these is supportive therapy. This occurs through the introduction of GH to increase adult height and estrogen replacement therapy to stimulate the development of secondary sexual characteristics and healthy bones and tissue. With early

and timely medical attention (estrogen and human GH), most girls with TS can be brought to normal height (Rosenfeld et al., 1992). This can have a critical impact on the development of self-esteem in a child. If the teasing that begins when a child with TS begins to lag behind her peers can be avoided by helping the child reach her developmental/physical milestones on time, self-esteem may be spared (Orten, 1990; Orten & Orten, 1994; Perheentupa et al., 1974).

Many other medical interventions can improve the quality of life for a patient with TS. First, speech or hearing interventions may be necessary for girls with high arched palates or hearing loss due to inner-ear defects (Rovet, 1995). Second, surgical interventions may be necessary as a result of the cardiac and renal abnormalities, ptosis, strabismus, and/or inner-ear defects. In addition, treatment of other medical disorders (e.g., diabetes mellitus, hypothyroidism, and obesity) can improve quality of life. Finally, with recent advances in fertility interventions such as *in vitro* fertilization with a donor egg, pregnancy is now a possibility for some women with TS and their partners.

The smooth transition of adults with TS from pediatric to adult medical care is also important (Rubin, 2003). Most authors suggest a multidisciplinary team approach to care for adults, much as there is for children (Elsheikh et al., 2002; Karnis & Reindollar, 2003; Ostberg & Conway, 2003; Saenger, 2004). It is generally recommended that the multidisciplinary team consist of the following specialists with specific knowledge of TS and its sequelae: endocrinologists; cardiologists; nephrologists; reproductive endocrinologists; audiological physicians; ear, nose, and throat surgeons; plastic surgeons; dentists; and psychologists.

Psychosocial Interventions

As the review above has indicated, girls and women with TS can experience a wide variety of psychosocial problems. For the purpose of this chapter, these difficulties are broken down into two categories. The first area for attention is the treatment of issues of concern associated with the diagnosis of TS. The second area is the treatment of specific psychosocial symptomatology.

Issues of Concern in TS

One of the first issues that people diagnosed with TS have to cope with is the diagnosis of a chronic syndrome with wide-ranging ramifications. Persons who are diagnosed with a chronic, lifelong illness must adapt to both the physical and psychological sequelae of the illness, as well as the fact that their lives and potentially their views of themselves have been altered. Russo (1986) and Varni and Wallander (1988) discuss the need for people with chronic illnesses to address the specific stressors that affect their lives and learn to develop positive coping strategies to deal with these stressors. Positive adjustments lead to resilience and poor adjustment leads to vulnerability to stressors (Varni & Wallander, 1988). Self-esteem issues are often involved in this adjustment. Both a person with TS and her family members may experience many emotional reactions at the time of diagnosis, and these reactions are similar to those experienced by people with the diagnosis of any major medical condition (Orten & Orten, 1994). According to Orten and Orten, these reactions can fall into four categories.

The first category of adjustment is the need to resolve "the personal meaning of TS" (Orten & Orten, 1994, p. 241). The age at diagnosis will have an impact on the initial

issues involved in obtaining personal meaning. For younger children, the main issues may revolve around medical aspects of the syndrome and potential medical intervention (treatments, hospitalizations, etc.). During the teenage years, issues may center around "being different" from others and the physical anomalies the teens may have. For late adolescents and adults, issues surrounding fertility and parenthood may arise. Coming to terms with these issues may be complicated by the severity of the medical problems that a girl or woman faces. The impact of the diagnosis can also be influenced by the parents' reactions to the diagnosis (Orten & Orten, 1994).

A second category of adjustment involves scoping with the reactions of others, especially in relation to the short stature. Teasing about short stature often begins during the elementary school years. If GH is initiated at the appropriate times, this problem may be avoided. However, girls with TS may also be teased for other physical abnormalities. For adult women, the issues of short stature and youthful appearance can cause difficulties in the workplace. Teaching ways to cope and deal with teasing and potential discrimination in a positive and helpful manner is a critical part of intervention for girls and women with TS (Orten & Orten, 1994).

Deciding whether and, if so, when to tell others about the TS diagnosis is another issue of particular concern to girls and women with TS. For children, one issue that arises is whether or not to inform the school about the diagnosis. As with any medical or psychological problem, informing the school can lead to positive outcomes, such as a greater understanding of a child's special needs and more accommodations to these needs; however, it can also result in the child's being stigmatized and treated differently in a negative way. The decision to inform or not to inform the school is one that needs to be made jointly by the treatment team, the parents, and the child if she is mature enough to participate in the decision (Orten & Orten, 1994).

Telling dating partners or potential intimate partners about TS is another issue that is often faced in adulthood. Issues surrounding fertility and parenthood again become critical issues. These issues can have an impact on a partner as well as on a woman with TS.

A final area that girls and women have to deal with in coming to terms with TS involves physical problems and their impact on lifestyle and quality of life. Often this involves grieving for lost abilities. It is important for girls and women to understand the potential cognitive implications of TS and deal with the day-to-day medical and cognitive implications.

One of the major mediating factors in coping with stress is perceived social support (Varni & Wallander, 1988; Varni, Rubinfeld, Talbot & Setoguchi, 1989). Because of this, a support group model for intervention may be very appropriate. Such groups, made up of individuals who share similar issues, can provide information and advice as well as support. Psychoeducational models often meet the needs and desires of participants in TS support groups (Mullins et al., 1991). Attention to family members and their coping with the diagnosis and sequelae of TS is also important, because families can be a major source of support for some girls and women (Mullins et al., 1991; Orten & Orten, 1994). A survey by Orten and Orten (1992) found that a large number of parents were provided with incomplete and pessimistic medical explanations at the time of diagnosis, and that the parents were very dissatisfied (and at times angry) with the explanations they were given. Thus one of the first areas of intervention with families is to ensure that they receive accurate and adequate medical, psychological, and developmental information regarding TS (Orten, 1990). In addition, good family communication is important in helping girls and women with TS cope with issues surrounding it. Finally, individual therapy may be important for some girls and women at various stages of their lives.

Other Specific Psychosocial Symptomatology

As mentioned above, there are several other areas of potential psychosocial symptomatology for girls and women with TS. The first is the area of social skills. Most interventions in this area have been cognitive-behavioral in nature. Target behaviors have included increasing the rate of social interaction, enhancing prosocial skills, and decreasing antisocial or aggressive behaviors. Interventions have included social problem-solving training, anger coping training, coaching, and behavioral rehearsal. These interventions can take place in individual therapy or groups (McFadyen-Ketchum & Dodge, 1998). The second major area of concern is the hyperactivity/inattention symptomatology present in some girls with TS. The most common treatment approaches for these problems are cognitive-behavioral and psychopharmacological or a combination of the two (Barkley, 1998). Saenger and colleagues (2001) also recommend that specific attention be given to sex education and orientation to adult sexuality. They note that because girls with TS mature much later than their same-age peers, they may not be ready for or interested in sex education when it is taught in school. Attention should likewise be paid to the development of skills necessary for independent living, and to examination of concerns regarding infertility and sexual relationships (Elsheikh et al., 2002).

SUMMARY AND CONCLUSIONS

TS, a chromosomal disorder that affects only females, can result in a myriad of lifelong physical/medical, psychosocial, and educational problems. The type and severity of the problems may vary widely across patients. However, there are some hallmark symptoms associated with the syndrome. These include short stature, failure to develop secondary sexual characteristics at puberty, infertility, visual perceptual difficulties, academic problems with mathematics, and social skills difficulties. Many of the physical/medical problems can be dealt with through supportive therapy, including hormone replacement therapy. Special attention should be given to the psychosocial sequelae of the syndrome and appropriate therapeutic interventions should be undertaken. Finally, early and appropriate intervention is critical for continued academic and occupational success. With the proper support, encouragement, and interventions, girls and women with TS can live long, productive, and happy lives.

SOURCES FOR INFORMATION

Organization

Turner Syndrome Society of the United States
14450 TC Jester, Suite 260
Houston, TX 77019
(800) 365-9944
www.turner-syndrome-us.org

This is a nonprofit organization with the following mission: to increase public awareness, to increase understanding of the people who are affected by TS, to provide a forum for those affected by TS to become acquainted with one another, and to provide an opportunity for interaction between health care professionals and those affected by TS. The society sponsors a TS conference each year and offers a number of publications on TS.

Internet Resources

www.endo-society.org/pubaffai/factshee/turner.htm (fact sheet on TS)
www.nlm.nih.gov (website with general clinical information)
www.pediatriconcall.com (website with general clinical information)
http://www.turnersyndrome.ca (website with general clinical information)
http://turners.nichd.nih.gov (website with general clinical information)

On-line Newsgroups of Interest

alt.support.turner-syndrome (TS support group)
alt.infertility (infertility support group)

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13

FRAGILE X SYNDROME

ROBIN L. HANSEN
RANDI J. HAGERMAN

Fragile X syndrome (FXS) is the most common inherited cause of mental retardation, occurring in approximately 1 in 3,200 individuals in the general population (Sherman, 2002). It is also a significant cause of autism; approximately 3–6% of individuals with autism will have the fragile X mutation (Hagerman, 2002b). FXS is caused by an expansion of a trinucleotide repeat (cytosine–guanine–guanine, or CGG), which occurs at the front end of the fragile X mental retardation 1 (*FMR1*) gene. This gene is at the bottom end of the X chromosome, at Xq27. In cytogenetic studies, when the appropriate tissue culture medium is used, a fragile site will appear at this location. Since 1991, diagnostic DNA testing has been available, which demonstrates the expansion of the CGG repeat. Unaffected individuals normally have fewer than 40 repeats. Individuals carrying a premutation, who are usually cognitively unaffected, have between 55 and 200 CGG repeats. Individuals significantly affected by FXS have a full mutation, which is considered to be more than 200 CGG repeats. When the premutation is passed from father to daughter, it remains a premutation. However, when a premutation is passed to the next generation by a female, it often expands to a full mutation. Therefore, most mothers of children with FXS have the premutation.

We now take a genomics approach to understanding the great variability that can occur in both children and adults affected by this syndrome. The *FMR1* gene normally produces a protein, FMRP, which is a regulator for the translation of many other gene messages (messenger RNAs, or mRNAs). When FMRP is absent or deficient, as in individuals with the full mutation, both over- and undertranslation of other gene messages occur. There can also be significant variability within the expression of the FMR1 gene and levels of FMRP. Mosaic patterns can occur, in which some cells have the premutation and other cells have the full mutation. Cells with the premutation are producing significant levels of FMRP, so that individuals with mosaicism are typically less affected than individuals with the full mutation who are not producing any FMRP (Loesch et al., 2003a, 2003b; Loesch, Bui, et al., 2003; Merenstein et al., 1996). Individuals carrying the premutation have recently been shown to produce elevated mRNA levels from the FMR1 gene, ranging from 2 to 10 times normal levels, and to produce varying levels of FMRP. Elevated mRNA levels are now thought to cause central nervous system (CNS) toxicity over time, particularly in older males with the premutation; this results in the development of the fragile-X-associated tremor ataxia

syndrome (FXTAS), described below (Hagerman et al., 2001; Jacquemont et al., 2003). The discovery of FXTAS has led to a new appreciation of problems associated with aging in individuals with the FMR1 mutation.

Our aim in this chapter is to describe the physical, behavioral, and cognitive phenotypes of individuals affected by the FMR1 mutation in adulthood. Although our primary focus is on those with the full mutation, we also discuss those with the premutation. Finally, we address treatment issues.

PHYSICAL PHENOTYPE

General Physical Characteristics

Few well-controlled studies exist regarding aging in individuals with FXS. The connective tissue abnormalities found in children (flat feet, hyperextensible finger joints, double-jointed thumbs) tend to be less dramatic in adults, because the ligaments tighten with age. However, occasional joint dislocations, a higher frequency of hernias, and development of mitral valve prolapse continue as manifestations of atypical connective tissue. Gastroesophageal reflux may also continue to be a problem in adolescents and adults with FXS, and may be the etiology of feeding and behavior problems (Hagerman, 2002b). Individuals should be closely monitored for both acute and serous otitis media (middle-ear infections), which again may present as irritability and behavioral changes in nonverbal individuals with FXS. Strabismus is common in children with FXS, and this problem will often persist into adulthood without treatment. Adolescents and adults with FXS need to be monitored for late-onset seizures as well. Overall, about 20% of individuals with FXS have seizures, most commonly generalized and complex partial seizures (Musumeci et al., 1999). Macroorchidism is the most remarkable physical feature in male adolescents or adults with FXS. It begins to develop at age 8 or 9 years, and the testicles reach their peak in size by age 16 or 17 years. Macroorchidism can be documented by a testicular volume of 30 ml or larger, and it occurs in 80–90% of adult males with FXS (Hagerman, 2002b).

A long face and/or prominent ears occur in the majority of adult individuals with FXS (see Figure 13.1), but approximately 30% may not have either feature. The lack of typical features should not preclude FMR1 DNA testing. This testing should be done for any individual who presents with mental retardation or autism of unknown etiology.

Neuroimaging Findings

Early neuroimaging studies of FXS found significant ventriculomegaly in approximately 40% of children and adults with the syndrome (Musumeci et al., 1991; Wisniewski, Segan, Miezejeski, Sersen, & Rudelli, 1991). Reiss, Mazzocco, Greenlaw, Freund, and Ross (1995) confirmed this finding by documenting an inverse correlation between the size of the ventricles and IQ, and a positive correlation with age. As patients aged, the size of the ventricles increased, although this was only followed into adolescence and early adulthood. Reiss and colleagues have suggested that mild frontal and parietal atrophy occurs with age, and have hypothesized an enhancement of apoptosis in FXS (Reiss, Lee, & Freund, 1994; Reiss, Mazzocco, et al., 1995).

An important finding that has been consistently observed in FXS is a smaller cerebellar vermis in both males and females than in nondisabled controls, and in the males than in age-matched developmentally disabled controls (Mostofsky et al., 1998; Reiss, Aylward,

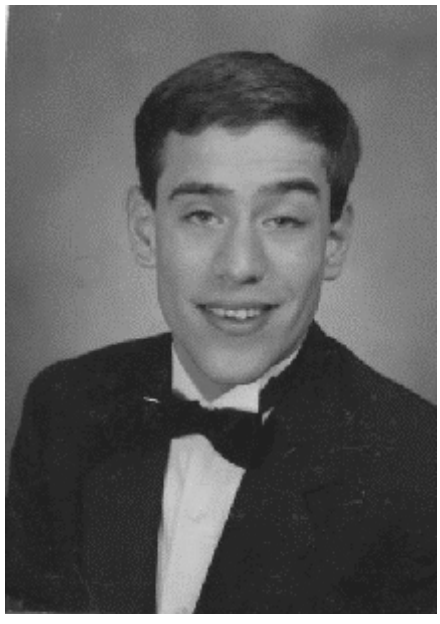

FIGURE 13.1. A 25-year-old male with FXS. Note the long face, mildly prominent ears, and ptosis of the left eye.

Freund, Joshi, & Bryan, 1991; Reiss, Freund, Tseng, & Joshi, 1991). The size in females appears to be intermediate between those of the males with FXS and controls, and the decrease correlates inversely with the activation ratio in females (Mostofsky et al., 1998; Reiss, Freund, et al., 1991). Mostofsky and colleagues (1998) found significant correlations between the size of the posterior cerebellar vermis (lobules VI–X) on the one hand and IQ, executive function, and visual–motor coordination measures on the other, demonstrating the importance of this structure for many aspects of cognition. Mazzocco and colleagues (1997) studied 28 school girls with FXS and found that the parental ratings of the frequency and severity of autistic behaviors, particularly social communication impairments and stereotypies, correlated inversely with the size of lobules VI and VII of the posterior cerebellum. These mannerisms, part of the behavioral phenotype of FXS, are uniquely correlated with the CNS structural changes and vary with the severity of these changes.

In contrast to the cerebellar findings, Reiss, Lee, and Freund (1994) reported that the right and left hippocampal volumes were increased by about 20% in both males and females with FXS (age range 6–27 years). In a follow-up study of five boys and girls with FXS, the hippocampal enlargement was less dramatic (7% left and 13% right, compared to controls) (Kates, Abrams, Kaufmann, Breiter, & Reiss, 1997). Reiss, Mazzocco, and colleagues (1995) have also reported an increase in the volume of the caudate in both males and females with FXS compared to controls, and an increase in the volume of the thalamus in females compared to sex- and age-matched controls.

Typically, individuals with FXS have large heads and brains in childhood compared to controls, both by clinical measurement and in magnetic resonance imaging (MRI) studies (Butler, Brunschwig, Miller, & Hagerman, 1992; Hagerman, 2002b; Reiss, Abrams, Greenlaw, Freund, & Denckla, 1995; Schapiro et al., 1995). Jakala and colleagues (1997) studied 10 males with fragile X (mean age 29 ± 11 years) and 10 females with fragile X (mean age 34 ± 15 years). Both individuals with the full mutation and persons with the

premutation were included in this study. The researchers found that although the males with the full mutation had larger brains than controls, the size of their hippocampus when normalized for brain size did not differ from that of males with a premutation or controls. In addition, they found that those with a full mutation had enlargement of the ventricles and perivascular spaces, atrophy relative to age, white matter changes and perivascular changes in the temporal regions, and subjectively atypical morphology of the hippocampus compared to those with the premutation. They also found that the length of the CGG repeat in males with the full mutation correlated positively with brain volume and negatively with Verbal and Performance IQ. The study by Jakala and colleagues emphasizes the importance of the MRI in detecting abnormalities in adults with fragile X.

In a study of children and adolescents with FXS, Reiss, Kazazian, and colleagues (1994) found that the size of the superior temporal gyrus decreased more significantly with age in males with FXS than in controls. Kates and colleagues (2002) also found smaller temporal lobes in boys with FXS than in nondisabled controls. In addition, the Kates and colleagues study separated boys with the fully methylated full mutation ($n = 21$) from boys with a mosaic pattern ($n = 12$), and found that those with mosaicism had significant reductions in the volume of parietal white matter, compared to boys with the full mutation. This last result is particularly germane to the RNA toxic "gain-of-function" hypothesis that is described below and thought to be responsible for FXTAS, since parietal volume loss is particularly evident in individuals with the premutation and FXTAS. Thus it is possible that the reduced parietal volumes in boys with mosaicism is a very early sign of neurological involvement as a consequence of continued production of *FMR1* mRNA.

Additional neuroimaging modalities (e.g., single-photon emission computed tomography) have shown hypofunction of the frontal–subcortical regions in FXS. Hjalgrim and colleagues (1999) studied five males and one female with FXS and found hypoperfusion of the right frontal lobe and right thalamus compared to nondisabled controls. Guerreiro and colleagues (1998) reported frontal hypoperfusion in six patients with FXS, and parietal or cerebellar hypoperfusion in two of these patients. Functional MRI studies have shown a decrease in activation of the neural network on math tasks (Rivera, Menon, White, Glaser, & Reiss, 2002) and working memory tasks, which correlates with the deficit in FMRP (Menon, Kwon, Eliez, Taylor, & Reiss, 2000). Although the sophistication of the neuroimaging studies has advanced dramatically in the last few years, there has not been a focus on aging or longitudinal studies in FXS.

BEHAVIORAL PHENOTYPE

The behavioral phenotype of FXS in childhood includes hyperactivity and hyperarousal to sensory stimuli (Hagerman, 2002b; Miller et al., 1999). The hyperactivity typically improves with age and is usually not a problem in adulthood. However, the hyperarousal often continues into adulthood and is manifested by mood instability and outburst behavior. Approximately 30% of males have problems with physical or verbal aggression (Hagerman, 2002b). Treatment options include counseling, described in Epstein, Riley, and Sobesky (2002) and Braden (1997), and medications, described below.

Approximately 30% of individuals with FXS have autism (Bailey, Hatton, Skinner, & Mesibov, 2001; Rogers, Wehner, & Hagerman, 2001). Some of these individuals with autism are avoidant of social interactions; others are interested in people, but their significant sensory integration problems and severe anxiety interfere remarkably with social interactions. Those individuals with autism and FXS together have a lower IQ and more

severe receptive and expressive language deficits than those with FXS alone (Bailey et al., 2001; Philofsky, Hepburn, Hayes, Hagerman, & Rogers, 2004; Rogers, Wehner, & Hagerman, 2001). Additive effects from genes that interact with FMRP may lead to autism in FXS, and this is an area that is being intensively researched. Einfeld, Tonge, and Turner (1999) carried out a 7-year follow-up study of 46 individuals with FXS from adolescence into young adulthood (mean age 22.4 ± 5.47 years), and found improvements in disruptive behavior but an increase in antisocial behavior. This finding is similar to the longitudinal studies of adults with FXS by Das and Turk (2002), which found a dramatic increase in symptoms of autism as these individuals aged. Over 60% met diagnostic criteria for autism in adulthood, with a significant increase in reclusive behavior and echolalic language with age. These investigators used the Diagnostic Instrument for Social and Communicatory Disorders to evaluate behavioral problems and autism. A more detailed analysis of psychopathology is needed to clarify and expand these early findings.

In general, psychopathology in aging, intellectually disabled adults remains understudied. A few studies suggest that the intellectually disabled population of children and adults suffers from much higher rates of psychopathology than the general population (Einfeld & Tonge, 1996; Hardan & Sahl, 1997; Taylor, Hatton, Dixon, & Douglas, 2004). One study, using a structured screening instrument, estimated the prevalence of psychotic disorders at 10.2% (Taylor et al., 2004). Most researchers, however, recognize that these screening instruments overestimate the prevalence of psychopathology in disabled populations. Therefore, any attempts to characterize the prevalence of psychopathology in FXS require a reference population with similar intellectual abilities. Only limited anecdotal information is available regarding clinical experience in older individuals who have FXS.

COGNITIVE PHENOTYPE

Declines in IQ scores have been documented in the majority of males and in some females with FXS throughout childhood and into adolescence (Fisch et al., 1992; Fisch, Simensen, Arinami, Borghgraef, & Fryns, 1994; Fisch, Simensen, & Schroer, 2002; Hagerman et al., 1989; Hodapp, Dykens, Ort, Zelinsky, & Leckman, 1991; Lachiewicz, Gullion, Spiridigliozzi, & Aylesworth, 1987; Wright-Talamante et al., 1996), but no study of more than 10 patients with FXS has been conducted regarding IQ changes with aging into late adulthood. It was formerly thought that IQ remains stable throughout adulthood, but the limited work of Borghgraef and colleagues (2002) suggests that this is not the case. Borghgraef and colleagues presented a 10-year follow-up study of 10 males with FXS, whose intial ages ranged from 33 to 65 years. A significant overall IQ decline was documented on the McCarthy Scales in three subjects, a significant decline in verbal abilities in five subjects, and a significant decline in performance abilities in two subjects. A decline was also seen in adaptive skills in three of seven subjects, and an increase in one subject. Borghgraef and colleagues summarized that the declines were most remarkable in the verbal area, with the use of language decreasing over time. Detailed molecular data, including the percentage of methylation and mRNA levels, were not available. These investigators reported only that 9 of the 10 patients had a full mutation, and that the remaining patient had a premutation but also had mental retardation.

Wiegers, Curfs, Vermeer, and Fryns (1993) also found IQ declines in 39 males with FXS (initial ages 4–26 years). However, on a Dutch adaptive behaviors scale, self-help skills improved with age, although the social skills did not; the latter constituted the lowest area

of functioning. This emphasizes the problems of social relatedness in FXS and demonstrates the need for further study in aging individuals.

CHARACTERISTICS OF INDIVIDUALS CARRYING THE FRAGILE X PREMUTATION

Although early studies demonstrated the absence of intellectual deficits in individuals with the fragile X premutation (Mazzocco, Pennington, & Hagerman, 1993; Reiss et al., 1993), these studies were carried out typically on mothers who had children with FXS. More recently, some young children with the premutation have been found with cognitive deficits and autism spectrum disorders (Aziz et al., 2003; Goodlin-Jones, Tassone, Gane, & Hagerman, 2004; Tassone, Hagerman, Chamberlain, & Hagerman, 2000), suggesting that some individuals with the premutation may be at risk for developmental problems. The study of these patients led to the discovery of elevated mRNA levels in patients with the premutation (Tassone, Hagerman, Chamberlain, & Hagerman, 2000; Tassone, Hagerman, Taylor, Gane, et al., 2000). Subsequently, older men with the premutation who had grandchildren with FXS were found to have neurological problems, including intention tremor and ataxia (Hagerman et al., 2001). Further evaluation of these grandfathers demonstrated the same phenotype, which includes not only the tremor and ataxia, but a "stocking distribution" neuropathy in the lower extremities, cognitive deficits that begin as memory problems, autonomic dysfunction (including hypertension and impotence), and brain atrophy on MRI (Jacquemont et al., 2003; Jacquemont, Farzin, et al., 2004).

Jacquemont, Hagerman, and colleagues (2004) completed an epidemiological study to better understand the prevalence of FXTAS in older males and females with the premutation; this study was conducted in the state of California and involved 192 families. An increased incidence of tremor and ataxia was seen in males over age 50 carrying the premutation, compared to controls and to females carrying it. Among males with the premutation, 17% of those in their 50s were affected with tremor and ataxia, 38% of those in their 60s, 47% of those in their 70s, and 75% of those in their 80s (Jacquemont, Hagerman, et al., 2004). This study has dramatically raised awareness regarding FXTAS around the world, leading to the initiation of many other screening studies among neurological populations with movement disorders. Many children are now being diagnosed with FXS after their grandfathers are diagnosed with FXTAS. This wide recognition of FXTAS has led to the identification of rare females with FXTAS, although none have experienced dementia (Hagerman, Leavitt, et al., 2004). Perhaps the extra X chromosome and/or hormonal differences protect the females generally from FXTAS and dementia.

Older males with FXTAS show signs of dementia as well as tremors and ataxia. The neuroradiological sign most closely associated with FXTAS is a white matter change, manifested by hyperintensities on T2-weighted imaging in the middle cerebellar peduncles (Brunberg et al. 2002). In addition, there are findings characteristic of periventricular and subcortical white matter disease (Brunberg et al., 2002; Greco et al., 2002). Also, FXTAS is associated with significant brain atrophy; one study demonstrated significant differences in brain size, in addition to the white matter changes, in individuals with the premutation and FXTAS ($n = 17$), compared to age-matched controls (Brunberg et al., 2002). The presence of eosinophilic intranuclear inclusions has been documented throughout the cerebrum, with the highest density in the hippocampus, followed by frontal and temporal regions (Greco et al., 2002). A total of 10 brains of males who have died from FXTAS have been studied. All of these brains possessed numerous inclusions. Preliminary antibody studies

have demonstrated that these inclusions are tau-negative, synuclein-negative, and ubiquitin-positive (Hagerman & Hagerman, 2004a, 2004b).

Patients with the fragile X premutation and FXTAS have psychiatric problems, including irritability, anxiety, outbursts, and delusional thinking (Hagerman & Hagerman, 2004a; Jacquemont et al., 2003; Jacquemont, Farzin, et al., 2004), in addition to tremor and ataxia. Elevated mRNA levels have been documented in those carrying the premutation, with a positive correlation between the size of the premutation and the level of mRNA (Tassone, Hagerman, Chamberlain, & Hagerman, 2000; Tassone, Hagerman, Taylor, Gane, et al., 2000; Tassone, Hagerman, Taylor, Mills, et al., 2000). These findings have led to the hypothesis of an RNA toxic "gain-of-function" model, in which the elevated mRNA leads to sequestration of protein, important for neuronal function. The mRNA and the sequestered proteins form inclusions in neurons and astrocytes. This process eventually leads to enhanced cell death and brain atrophy. The toxic RNA gain-of-function model is similar to myotonic dystrophy (Hagerman & Hagerman, 2004b). It is hypothesized that the toxic gain-of-function mechanism is also leading to enhanced psychopathology in individuals with the premutation and elevated mRNA. Inclusions have not been detected in neuropathological studies of individuals with the full mutation who have FXS (Hinton, Brown, Wisniewski, & Rudelli, 1991; Rudelli et al., 1985; Sabaratnam, 2000).

INTERVENTIONS

The treatment of both children and adults with FXS involves multimodality interventions. Those who are in an educational setting require the services of special education professionals, including speech and language pathologists, occupational therapists, and special education teachers. Whenever possible, inclusion in a regular classroom is helpful for children with FXS because they imitate the behavior of the children who surround them, and nondisabled models can be very beneficial. Likewise, inclusion of adults in supervised settings that provide them with typical social and language models is important. The services of a psychologist to provide behavioral interventions and family counseling can also be extremely helpful, and descriptions of specific behavioral intervention programs have been published (Braden, 2002; Epstein, Riley, & Sobesky, 2002).

Both children and adults with FXS can be extremely sensitive to sensory stimuli, including visual, auditory, tactile, and olfactory stimuli in their environment. They can be easily overwhelmed in a crowded setting such as a shopping mall or concert, and sometimes such stimuli can precipitate a behavior outburst. Counseling in childhood and adulthood can help individuals learn calming techniques for the autonomic dysregulation that occurs in overstimulating situations. In addition, the use of medication can be quite helpful in calming behavior, decreasing aggression, decreasing anxiety, stabilizing mood, and improving attention.

The use of stimulant medication has demonstrated efficacy in children with FXS (Hagerman, Murphy, & Wittenberger, 1988). Stimulant medication is usually not needed in adulthood, because hyperactivity improves over time. Occasionally stimulants can be useful for impulsivity in adulthood. Clonidine can also be utilized to calm behavior and decrease aggression in both children and adults. Clonidine and guanfacine are alpha-2-adrenergic agonists, which also lower high blood pressure (this is often a helpful side effect in adults with FXS). Clonidine is also available as a patch preparation (Catapres-TTS-1, 2, or 3) (Hagerman, 2002a).

The most serious problem in adult behavior is intermittent aggression. This can be related to anxiety or sensory overstimulation, although there often seems to be a component of mood instability, which can exacerbate the aggression or outburst episodes. The anxiety can be treated by a selective serotonin reuptake inhibitor (SSRI), but approximately 20% of patients with FXS can have significant activation, leading to more aggression. Citalopram is the least activating of the SSRIs and can be often efficacious for decreasing anxiety (Hagerman, 2002a). Often adults with FXS who have problems with aggression will benefit from an atypical antipsychotic medication, such as risperidone or aripiprazole. This medication may be helpful in stabilizing mood in addition to decreasing psychotic thinking, which may be a problem for approximately 10% of individuals with FXS. Additional mood stabilizers include anticonvulsant medications, such as valproic acid, carbamazapine, or oxycarbazone. Older mood stabilizers (e.g., lithium) can also be helpful in patients with FXS.

Sleep disturbances are often a problem in childhood and occasionally in adulthood. The use of melatonin, a natural sleep hormone that can be purchased over the counter, is efficacious in approximately 50% of children with FXS and can also be helpful in adults. An alternative to melatonin would be clonidine at bedtime.

Recent studies regarding the genomic effects of the lack of FMRP have demonstrated that there is enhanced long-term depression (LTD) of synaptic connections, particularly in the hippocampus, related to enhanced stimulation of the group 1 metabotropic receptors (particularly the mGluR5 receptor). This receptor leads to protein synthesis that controls LTD at the synapse. This particular protein synthesis process is regulated by FMRP. When FMRP is absent, LTD is enhanced, which leads to the weak and immature synapses typically seen in fragile X neuropathology studies (Bear, Huber, & Warren, 2004). Research is in process to develop mGluR5 antagonists that will be a specific intervention for individuals with FXS. One available mGluR5 antagonist, MPEP, has been shown to reverse some symptoms of FXS (including seizures and cognitive deficits) in the knockout mouse model (Bauchwitz, personal communication, April 2004). The enhanced LTD in FXS leads to a depletion of AMPA receptors, another glutamate receptor system important for cognition. Experimental ampakine medication, which enhances AMPA receptor activity and stimulates glutamate systems in the brain, is currently being tested in adult individuals with FXS at the University of California–Davis and at Rush University Medical Center in Chicago. Results are not yet available regarding the efficacy of these new medications, but the future looks bright for specific psychopharmacological interventions that will be generally available for both children and adults with FXS.

Families identified as having a child or adult member with FXS should be referred to the National Fragile X Foundation at (800) 688-8765, so that they can receive further parent-oriented information and information to disseminate to the professionals working with the individual with FXS. They can also be linked to parent support groups throughout the United States and internationally. Information is also available and can be downloaded from the National Fragile X Foundation website at www.fragilex.org.

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14

WILLIAMS SYNDROME

RICHARD RIDER

Williams syndrome (WS) is a rare genetic disorder affecting approximately 1 in 20,000 live births (Beuren, 1972; Greenberg, 1990). It is caused by hemizygous submicroscopic deletion of several continuous genes on chromosome 7q11.23 (Ewart et al., 1993). WS often presents with mild to moderate mental retardation and an uneven cognitive profile. Many nonlinguistic functions are often impaired (Arnold, Ewell, & Martin, 1985; Bellugi, Bihlre, Neville, Jernigan, & Doherty, 1992), while language skills are often surprisingly good in comparison to the nonlinguistic functions (Bellugi, Bihlre, Jernigan, Trauner, & Doherty, 1990; Clahsen & Almazan, 1998). In young children, the diagnosis is typically suggested by the combination of developmental delay, hypercalcemia, dysmorphic facies, and/or cardiovascular disease. The presence of the cognitive profile and unique personality attributes known to be associated with WS may contribute to a WS diagnosis.

Although much is known about the cognitive functioning of children with WS, few studies of adults have been conducted. Udwin, Davies, and Howlin (1996) followed a group of 23 young adults who had been assessed in adolescence. At reassessment (with a mean age of 21 years, 9 months), these young adults had a mean Wechsler Adult Intelligence Scale—Revised (WAIS-R; Wechsler, 1981) Full Scale IQ of 61. Academic skills, on average, were about those of a 7- to 8-year-old. In a second study, Howlin, Davies, and Udwin (1998) reported on the results of cognitive, linguistic, and academic assessments of 62 adults with WS. With an average age of 26 years, their mean WAIS-R Full Scale IQ was also 61. Academic skills for reading, spelling, arithmetic, and social adaptation were in the 6- to 8-year age equivalent range. Davies, Udwin, and Howlin (1998), also in a study of 62 adults with WS ranging in age from 18 to 39 years, found a number of social, emotional, and behavioral problems. The social difficulties included isolation, disinhibition, overfriendliness, and a propensity to be too willing to trust others. This group of adults also often exhibited obsessions, high levels of anxiety, and distractibility. Not surprisingly, most adults with WS live with their parents in group homes or in sheltered environments (Davies, Howlin, & Udwin, 1997).

CLINICAL/MEDICAL MANIFESTATIONS

WS is a multisystem disorder that includes supravalvular aortic stenosis (SVAS), peripheral pulmonary arterial stenosis, elfin face, below-average stature, mental deficiency, dental

malformation, and infantile hypercalcemia (Grimm & Wesselhoeft, 1980). For a complete view of the multiple organ systems affected by WS, the interested reader is referred to Morris and Mervis (1999). As Morris and Mervis (1999) explain, two important systems are the ocular and auditory systems.

Ocular/Visual

Ocular and visual abnormalities are common in WS. A stellate lacy pattern in the iris is a common occurrence in individuals with WS (Greenberg & Lewis, 1998; Jones & Smith, 1975; Winter, Pankau, Amm, Gosch, & Wesel, 1996). Another ocular/visual condition common in WS is strabismus, which is a condition marked by misalignment of the eyes and of eye muscles and balance. Strabismus usually has its onset before age 6 and is reported in approximately half of children with WS, in contrast to an incidence of less than 1% in the general population (Atkinson et al., 2001). In strabismus, the eyes point in different directions; thus two separate images are sent to the brain. Some children without treatment learn to ignore one image and use only one eye in order to avoid double vision.

Other common ocular problems in WS are refractive errors, including farsightedness and nearsightedness. Atkinson and colleagues (2001) reported that approximately 54% of children with WS had refractive errors. Farsightedness can produce eye discomfort and strain and can interfere with near-point tasks, such as reading and writing. Nearsightedness can affect the ability of individuals with WS to engage in sports and other activities that require visual processing, depth perception, and spatial judgment.

Auditory

Hypersensitivity to sound is one of the most common auditory problems observed in WS (Bellugi, Sable, & Vaid, 1988), although many children outgrow this hypersensitivity. According to Udwin, Howlin, and Davies (1996), approximately 50% of adolescents and adults with WS experience significant problems with hypersensitivity to sound. Otitis media is a clinically significant problem for many children with WS (Klein, Armstrong, Greer, & Brown, 1990; Morris, Dempsey, Leonard, Dilts, & Blackburn, 1988), but it too tends to improve as children become older.

COGNITIVE STRENGTHS AND WEAKNESSES

In addition to the medical profile of WS, research on this disorder has concentrated on language, memory, and visual–spatial skills. A characteristic neurocognitive profile has been determined, although this is continuing to be shaped by recent research. Research has also demonstrated a wide variability of skill within these domains in individuals with WS.

Language

A number of studies have concluded that individuals with WS have relative strengths in language, in comparison to their overall neurocognitive profile (Bellugi, Lichtenberger, Jones, Lai, & St. George, 2000). Individuals with WS are often articulate and verbally flu-

ent. Speech is often intact, and vocabulary skills are also relatively strong. These individuals usually enjoy conversing with others. However, within the broad area of language skills, a wide range of abilities is apparent. Problems with comprehension of language are often seen, and some persons with WS are also relatively inarticulate. In this chapter, the language areas of semantics and syntax are discussed.

Semantics

Vocabulary has been noted as a relative strength of individuals with WS (Levine, 1993). Semel and Rosner (1991), in an analysis of their Utah study data, found that parents described 87% of children as having a well-developed vocabulary. In comparison to adolescents and adults with Down syndrome (DS) on tests of vocabulary such as the Peabody Picture Vocabulary Test—Revised (PPVT-R; Dunn & Dunn, 1981), Bellugi, Marks, Bihrle, and Sabo (1988) and Bellugi, Wang, and Jernigan (1994) found that adolescents and adults with WS had age equivalent results that were significantly higher than their mental age, but less than their chronological age. Conversely, Bellugi and colleagues (1992) found that the PPVT-R scores of adults with DS were less than their mental age and significantly lower than the age equivalent scores of adults with WS. Mervis, Morris, Bertrand, and Robinson (1999) found that although a majority of individuals with WS scored within the mental retardation range on intelligence tests, a significant minority (approximately 42%) scored in the range of normally developing individuals on the PPVT-R. In another study, individuals with WS also consistently scored higher than those with DS on the PPVT-R, and almost all the individuals with WS earned higher age equivalent scores on the PPVT-R than on the Full Scale IQ of the WISC-R (Rossen, Klima, Bellugi, Bihrle, & Jones, 1996).

Thus a number of studies have shown the proficiency of adults and adolescents with WS on formal tests of vocabulary such as the PPVT-R. The PPVT-R is a test in which a stimulus word is presented verbally, and the subject is requested to identify from a set of four pictures a picture that matches the stimulus word. Interestingly, adolescents and adults with WS often do not score well on vocabulary elements of intelligence tests, such as the Wechsler Intelligence Scale for Children—Revised (WISC-R; Wechsler, 1974) Vocabulary subtest (Bellugi et al. 1990). This relative weakness, as pointed out by Bellugi and colleagues (1992), may have to do with the requirements of the particular tests. The WISC-R Vocabulary subtest is more a measure of cognitive than of linguistic skill. The rambling style of many individuals with WS earns only partial scores or no score, whereas their recognition ability in tests such as the PPVT-R allows them to answer correctly.

Another interesting finding has been that children with WS do not differ significantly from children with DS in general verbal ability at preschool and grade school age. However, adolescents with WS routinely score higher than those with DS on vocabulary tests. This seems to reflect developmental changes in vocabulary growth during late childhood and adolescence (Mervis et al., 1995). Another unusual aspect of language development in children with WS is their use of specific words in conversation. As Pinker (1994) has noted, the normally developing child, when asked to name animals, provides a common list of pet store and barnyard animals ("dog, cat, cow, horse," etc). In contrast, a child with WS often provides "the more interesting menagerie, unicorn, pteranodon, yak, ibex, water buffalo, sea lion, saber-tooth tiger, vulture, koala and dragon" (p. 53). Still another interesting aspect of language development in adolescents with WS can be seen in their responses to homonyms. Homonyms are words with two distinct meanings that are spelled and sound alike. Normally developing individuals, when asked to interpret a homonym, usually refer to its primary meaning (e.g., "mouth" as a body part vs. a place where a stream

enters a larger body of water). However, individuals with WS are just as likely to select the less common meaning (Rossen et al., 1996).

Semel and Rosner (2003) have summarized word-finding problems in WS. These authors point out that individuals with WS often resort to substitutions, circumlocutions, word starters, and fillers. Substitutions can take the form of semantically associated words, semisynonyms, antonyms, or lexical substitutions. Circumlocutions are roundabout ways of expressing a word or a thought. Word starters are stereotypical verbal starters used to cover up difficulty in remembering a word or in stalling for time. Fillers are evasive verbalizations, including interjections. Schieber (2002) has reported that individuals with WS often have difficulty using and understanding certain simple words and concepts, such as semantic relational terms. Wiig and Semel (1984) likewise found that individuals with WS had difficulty with relational terms ("in, on, right, left, top, bottom," etc.).

Syntax

Syntax is the component of grammar consisting of the arrangement of words into phrases and sentences; it refers to the underlying structure of language and the rules that guide word order. The preponderance of researchers have generally agreed that the syntax of adolescents and adults with WS is a relative strength (Bellugi et al., 1992, 1994). Although the majority of those with WS score within the range of mild mental retardation on intelligence tests, their syntactic skills appear relatively intact. Nonetheless, individuals with WS as a group have vulnerability to many kinds of syntactic errors, and their syntax is generally less well developed than that of same-age nondisabled peers.

Some recent research has called into question the level of syntactic competence in individuals with WS. As Semel and Rosner (2003) point out, this is an important issue: It goes to the argument of whether or not language is separate from other areas of cognition, and it is also important in the identification of strengths and weaknesses of these individuals.

Although much of the research has concluded that syntactic abilities in WS are relatively strong in comparison to the rest of the neurocognitive profile, researchers do not always agree. For example, Bellugi, Marks, and colleagues (1988) found relatively good syntactic performance, although the age equivalent values on the tests did not approach the chronological age of these adult subjects. However, the subjects' syntactic abilities exceeded their mental age, as determined by the WISC-R. Although Karmiloff-Smith and colleagues (1997) obtained similar results, Bellugi and colleagues and Karmiloff-Smith and colleagues interpreted their results quite differently. Bellugi and colleagues interpreted their results more positively, stating that these subjects performed better than expected on comprehension tasks and that their expressive language was syntactically complex and correct, with occasional errors. In contrast, Karmiloff-Smith and colleagues emphasized the types of errors these subjects made, as well as the discrepancy between their chronological age and age equivalent scores on syntactic tasks; these researchers concluded that individuals with WS are not proficient at more sophisticated levels of complexity. For a more complete discussion of this topic, the interested reader is referred to Semel and Rosner (2003).

In comparison to other populations—for example, adults with DS—adults with WS demonstrate superior performance on a variety of syntactic tests (Bellugi et al., 1994). They often score significantly higher than adults with DS on a number of production and linguistic tests. The performance of adults with WS is generally equivalent to that of a nondisabled 7-year-old (Bellugi et al., 1994).

The English language is noted in part for its syntactic complexity. Mervis and colleagues (1999) administered the Test for Reception of Grammar (TROG) and found that

subjects with WS tended to perform poorly on difficult syntactic constructions. A number of studies (e.g., Karmiloff-Smith et al., 1997) found that complex grammatical structures created comprehension problems for subjects with WS, compared to nondisabled subjects with similar levels of vocabulary. Karmiloff-Smith and colleagues (1997) also noted that their subjects with WS had difficulty with spatial comparative language forms. However, again, the research is not entirely consistent; for example, Mervis and colleagues (1999) found that over 50% of subjects with WS scored in the normal range on the TROG, even though the majority of them scored in the mental retardation range on a general abilities test. Semel and Rosner (2003) discuss other morphological and syntactic errors made by individuals with WS, including difficulty with prepositions, plurals, past tense, gender rules, pronouns, and "wh-" questions.

As Semel (1988) has observed, most children with WS enjoy conversation and social interactions. Indeed, such children are noted for their talkativeness and propensity for social conversation. Semel and Rosner (2003) have commented: "Thus the overabundant speech of [children with WS] may be explained as a tendency to get 'off-track.' This may sometimes be due to problems of word finding, impulsivity, conceptual limitations, or to an overwhelming need to 'keep the conversation going.'" These authors note that subjects with WS often have difficulty with a variety of language pragmatics, including topic closure, topic relevance, tangential speech, topic preservation, turn taking, answering questions, informational exchange, and following instructions. Storytelling, however, seems to be a relative strength. Adults with WS tend to exhibit changes in pitch, volume, and stress to dramatize their storytelling (Riley, Harrison, & Klima, 1994; Riley, Klima, & Bellugi, 1990).

In the area of language, therefore, individuals with WS show a wide range of strengths and weaknesses. Nonetheless, several conjectures can be made at the group level. As Semel and Rosner (2003) point out, narrative storytelling and vocabulary appears to be the areas of greatest strength, with syntax, articulation, and prosody lagging somewhat behind. Early language development and some areas of pragmatic functioning are generally weak, and the complex aspects of syntax and higher-order conceptual semantics are most difficult.

Visual–Spatial Construction

Numerous studies of the intellectual abilities of individuals with WS have found that visual–spatial construction is an area of severe deficits. As Morris and Mervis (1999) note, two types of visual–spatial construction tasks have been the most studied: drawing and block design.

Bellugi, Sable, and Vaid (1988) using the Boston Diagnostic Aphasia Examination, found that adults and adolescents with WS often had fragmented and disjointed drawings. Spatial orientation and organization were poor. Using the Developmental Test of Visual–Motor Integration (Beery, 1989), Wang, Doherty, Rourke, and Bellugi (1995) compared 10 adolescents and young adults with WS to individuals with DS matched for chronological age and IQ. Both groups performed poorly, but the individuals with WS scored significantly lower than those with DS. Bellugi, Sable, and Vaid noted that many individuals with WS were able to correctly copy only the simplest items; anything more complex was often too difficult. This difficulty was also noted in children with WS (Morris et al., 1988), with many falling near the 1st percentile. However, when adults with WS were allowed to trace figures, many showed marked improvement (Bellugi, Sable, & Vaid, 1988).

On block design tasks, spatial cognition and visual–motor coordination can be assessed. A number of researchers have found that adolescents and adults with WS often fail block design tests, consistent with their performance on drawing tasks. Mervis and colleagues (1999) found that on the Differential Ability Scales, over 50% of subjects with WS obtained the lowest possible score on a block design task, with almost 90% being at the 1st percentile. Likewise, children with WS scored much lower than their chronological age on another block construction task (Atkinson et al., 2001).

One visual–spatial domain where subjects with WS perform relatively well is facial recognition (Bellugi, Sable, & Vaid, 1988; Karmiloff-Smith et al., 1997). Bellugi, Sable, and Vaid (1988) found that four out of five adolescents with WS fell within the normal range on a facial recognition task. Milani, Dall'Oglio, and Vicari (1994) found that while children with WS scored lower on visual–spatial construction tasks than nondisabled children matched for mental age, they scored higher than these children on the Benton Facial Recognition Test.

MULTIDISCIPLINARY ASSESSMENT AND INTERVENTION

The assessment and treatment of both children and adults with WS involve a multidisciplinary approach. Comprehensive, detailed medical, cognitive, and developmental evaluations should be conducted at the time of diagnosis. Specialists involved in these evaluations could include pediatricians, ophthalmologists, cardiologists, psychiatrists, and/or neurobehavioral psychologists. Additional professionals to involve in treatment, depending on signs and symptoms, might include speech/language therapists, physical therapists, and occupational therapists. As Morris and Mervis (1999) point out, both children and adults with WS require continued medical monitoring and support. Other types of support can include vocational training and counseling and/or medication for anxiety.

There is no cure for WS, and these individuals often experience SVAS, which is a significant health problem. One of the genetic abnormalities of WS is the lack of a gene that produces elastin, a protein that gives elasticity to blood vessels and other tissues in the body. It is likely that having only one copy of this gene results in the narrowing of blood vessels seen in SVAS. Due to this and other medical risks, most individuals with WS have a shortened life expectancy.

Again, due to the wide variability of clinical conditions, deficits, and aptitudes seen in individuals with WS, a multidisciplinary approach to intervention is required. Once an individual's idiosyncratic profile of strengths and weaknesses is understood, specific treatment approaches can be recommended. Semel and Rosner (2003) suggest several intervention strategies for WS individuals. Briefly, these include the use of effective rewards, direct instruction, and rechanneling strategies. These authors also discuss the use of verbal mediation strategies, as well as efforts to reduce external pressures and demands.

Well-thought-out use of both positive and negative reinforcement can be beneficial. Positive reinforcement may include both verbal and nonverbal components. Semel and Rosner (2003) point out that individuals with WS are often more motivated by verbal and social rewards than by material rewards (with some notable exceptions, such as those associated with an individual's special interests). Direct instruction may be used to help individuals control undesirable behaviors, such as displays of anger and extreme distractibility. These individuals can also be helped to rechannel such behaviors into more prosocial patterns. Semel and Rosner also discuss the power of verbal mediation strategies, such as verbal labeling, rehearsal, demonstration/dramatization, and self-instructional skills. In the last

case the authors point out that these individuals can be taught to use various forms of self-talk to improve their response to socioemotional stressors.

Because individuals with WS are often easily distracted, the ability to control environmental factors such as noise and clutter can prove beneficial. Removing potential sources of distraction, providing an uncluttered environment, and reducing extraneous noise can all be used to advantage. Individuals with WS often benefit from predictable routines. Finally, stress reduction can help these individuals to deal with their anxieties and fears.

An important component of treatment can be the support provided to families, professionals, and affected individuals in the United States by the Williams Syndrome Association. This organization can be found on the World Wide Web at www.williams-syndrome.org, or can be contacted by phone at (800) 806-1871.

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15

NOONAN SYNDROME

JACQUELINE ANNE NOONAN

The eponym Noonan syndrome (NS) refers to a disorder involving characteristic facies; often short stature; a high incidence of congenital heart defects (particularly pulmonary valvular stenosis), chest deformities, and learning difficulties; and sometimes webbing of the neck. Until recently, the diagnosis relied completely on physical findings, but Tartaglia and colleagues (2001) recently found mutations in the PTPN11 gene to be present in about 50% of patients with NS. There is limited published material about the natural history of NS or about adults with NS. This chapter reviews NS and presents new information regarding adults with NS.

HISTORICAL ASPECTS

Several authors have suggested that the first reported patient with what is now called NS was described by Kobylinski (1883). This was a 20-year-old male who had marked webbing of the neck; it was this feature that seemed to prompt most of the early reports. Funke (1902) reported a patient with a webbed neck, as well as short stature, micrognathia, cubitus valgus, and other minor abnormalities. This report was followed by that of Ullrich (1930), who described an 8-year-old girl with similar features. Turner (1938) reported older females who had facies similar to Ullrich's patient, but, in addition to short stature, had sexual infantilism. Before Turner syndrome was shown to be a sex chromosome abnormality, Flavell (1943) introduced the term "male Turner syndrome." This term led to considerable confusion in the literature for a number of years. Ullrich (1949) reported a series of patients whom he had noted for over two decades; in that series, there was a 4:1 predominance of females over males. Ullrich noted the similarity between his patients and mice that had been bred by Bonnevie. Bonnevie was a mouse geneticist who had bred a mutant strain of mice with webbed necks, as well as lymphedema. The term "Bonnevie–Ullrich syndrome" subsequently became popular, particularly in Europe. This term was used to describe some children who would now be recognized as having NS, and others who would now be recognized as having Turner syndrome. In 1959, Turner syndrome was found to have a 45,X0 chromosome pattern. Reports of "male Turner syndrome" or "Turner phenotype in males" continued to appear throughout the 1960s. Heller (1965) reviewed 43 cases from the literature and reported 5 additional cases of his own. These

early reports were mainly by endocrinologists who used the terms noted above for patients with a variety of testicular problems with or without short stature. A vigorous attempt to find a chromosomal abnormality in the "male Turner syndrome" was unsuccessful.

A report presented at the Midwest Society for Pediatric Research (Noonan & Ehmke, 1963) described a clinical study of associated noncardiac malformations in nine children with congenital heart disease. These nine patients shared a phenotype suggestive of Turner syndrome, and all of them had pulmonary valvular stenosis. A later report (Noonan, 1968) described a total of 19 patients as having a new syndrome that occurred in both males and females, had normal chromosomes, was associated with cardiac defects, and could be inherited. When chromosome studies became more widely available, it became clear that not all girls previously diagnosed with Turner syndrome had Turner syndrome; in reality, some of them had NS. In addition, some, but certainly not all, of the males previously referred to as having "male Turner syndrome" fit the clinical description of NS. Earlier reports of NS suggested that cardiac lesions occurred in about 50%. Later studies have demonstrated an incidence of over 80% when cardiac ultrasound is used as part of the workup (Marino, Digilio, Toscano, Giannotti, & Dallapiccola, 1999; Sharland, Burch, McKenna, & Patton, 1992).

GENETICS

It was recognized early that NS could be inherited as an autosomal dominant disorder, but the majority of cases appeared to be sporadic. The phenotype of NS changes significantly over time (Allanson, Hall, & Hughes, 1985). Clinicians learned that parents with a milder form of this syndrome could be recognized if photographs of their affected children were compared to photographs of them at the same age. As is common in other autosomal dominant disorders, there is often great variability in expression, and mild cases may go unrecognized.

By studying familial cases of NS, Jamieson and colleagues (1994) were able to map the gene for NS to the long arm of chromosome 12. It was apparent even at that time, however, that not all families with NS showed linkage to that site; this suggested more than one genetic cause for NS. Recently, using new technology and new information provided by the Human Genome Project, Tartaglia and colleagues (2001), in the group headed by Dr. Bruce Gelb, identified the NS gene on chromosome 12. This gene is called PTPN11 and regulates the product of a protein named SHP-2. This is a protein essential in several intracellular signal transduction pathways that control a number of developmental processes, including cardiac semilunar valvular genesis. Pulmonary valvular stenosis with a dysplastic pulmonary valve is the most common lesion found in NS. This suggested that the PTPN11 gene would be a likely candidate, since mice with such a mutated gene often had aortic and pulmonary stenoses. Tartaglia and colleagues (2001) showed that two moderate-sized families who had shown linkage to chromosome 12 had a mutated PTPN11 gene. Further studies have shown that about half of the patients diagnosed with NS have a variety of missense mutations in this gene. There is a higher prevalence of mutation in familial than in sporadic cases. Among those patients with NS and pulmonary valvular stenosis, mutations are found in over 70% (Tartaglia et al., 2002). Genetic studies are underway to identify other genes that may be involved in those patients with NS who do not have a mutation of the PTPN11 gene. With time, it is hoped that a genetic test will become available to make a definitive diagnosis of NS in all cases. Until then, the diagnosis will continue to rely heavily on clinical findings.

EPIDEMIOLOGY

The prevalence of NS is unknown, but it is estimated to range from 1 in 1,000 to 1 in 2,500. Males and females are equally affected. There appears to be no racial differences, and this syndrome has been found in countries all over the world. NS is one of the most common genetic disorders in children with congenital heart disease.

DIAGNOSIS

The diagnosis of NS is based on clinical findings. The characteristic facies are very helpful in diagnosis and include apparent ocular hypertelorism; antimongoloid slant of the palpebral fissures; ptosis; a deep philtrum; mild retrognathia; low-set, thick, posteriorly rotated ears; malar hypoplasia; and a short, sometimes webbed neck.

NS may be difficult to recognize in the newborn. A newborn often has redundant nuchal skin and a sloping head. Some newborns with severe NS have a stormy neonatal period, often associated with edema, respiratory distress, and sometime serious congenital heart disease. When newborns are asymptomatic, the diagnosis of NS is usually not suspected in the neonatal period. From infancy to 2 years of age, the head often appears relatively large, and the eyes become rather prominent and round. The nasal bridge is depressed, and the neck is short but is no longer webbed. By 2 years, the body becomes more stocky, and the chest deformity becomes more prominent. As childhood approaches, the facial appearance becomes coarser and more triangular as the chin lengthens. The eyes become less prominent and the ptosis more apparent. With increasing age, the neck appears longer, and the low hairline and webbing are more obvious. The teenager and young adult show triangular facial features that become much sharper. The nose has a pinched root and a thin, high bridge. The older adult has prominent labial folds, a high anterior hairline, and skin that often appears transparent and wrinkled.

PRENATAL HISTORY

Although most patients with NS have an unremarkable prenatal history, polyhydramnios is rather frequently reported. With the increasing use of fetal ultrasound, a number of fetuses who are later diagnosed with NS following delivery have been shown to develop cystic hygromas early in the second trimester, which often resolve later in pregnancy. In some fetuses, fetal hydrops (edema) develops, and this may indicate a severe form of NS. Many newborns with NS have some edema, which may not be apparent but can be recognized by excessive weight loss in the first week following delivery (Noonan, 1994). A number of previously undiagnosed mothers with NS have been recognized when fetal ultrasound revealed cystic hygromas in their fetuses.

CLINICAL COURSE AND SPECIFIC CLINICAL PROBLEMS

Feeding Problems

Many infants with NS develop feeding problems in early infancy. About 40% have mild or no feeding difficulties, while another 40% have moderate problems consisting mainly

of frequent vomiting. The remainder have severe feeding problems and often require tube feedings for a period of time (Sharland et al., 1992). Although the exact cause of this early intolerance is poorly understood, there is an increased incidence of reflux; there appears to be some delay in the normal peristalsis of the intestines; and an occasional patient is found to have a malrotation. Feeding problems can result in multiple hospitalizations. Fortunately, with time the feeding problems resolve, and by 2 to 3 years of age most children with NS are eating quite normally.

Growth

Newborns with NS are at the lower range of normal for height, but begin to fall off the curve by 3 months of age. Growth hormone studies in NS have rarely shown growth hormone deficiency, but abnormalities of growth hormone secretion have been frequently reported (Ahmed et al., 1991). Because short stature occurs in about 70% of patients with NS, growth hormone therapy is frequently recommended. The response to growth hormone has not shown any relationship to growth hormone secretion data (Noordam et al., 2001). Although hormone treatment may modulate growth, there is little evidence to implicate growth hormone deficiency as the cause of the short stature. The majority of patients have a significant delay in bone age. If growth hormone therapy is given, there is, as expected, a prompt acceleration in height. Unfortunately, this is accompanied by a similar acceleration in bone age. Although some feel that growth hormone can increase the ultimate adult height, there are no long-term serial height measurements over years comparing treated and untreated patients to show clear benefits of growth hormone therapy.

A recent study in 73 adults with NS demonstrated that 31% of males had an adult height in the normal range (Noonan, Raaijmakers, & Hall, 2003). Because of the delay in bone age, many males continued to grow until age 21 or beyond. The remaining males all fell below 66 inches in height, with 38% achieving an adult height below the 3rd percentile (i.e., less than 64 inches). In females, 32% had an adult height in the normal range (between 61 and 68 inches). The remainder were all 60 inches or less, with 54.5% achieving an adult height of 59 inches or less. It was of interest that none of the adults achieving a normal height had been treated with growth hormone. My own opinion is that the cause of the short stature in NS is still unknown. It is likely that there is a genetic cause for this growth failure. It will be important if there is a relationship between the mutated PTPN11 gene and shortstature.

Development

In general, patients with NS demonstrate a mild motor delay, which may be partly attributed to muscular hypotonia. Sitting is delayed until about 10 months; many children do not walk until nearly 2 years of age; and talking is delayed until about 2½ years of age. Hearing loss is sometimes a problem, and all children with NS should have a hearing evaluation.

Although mental retardation is uncommon in NS, learning difficulties are frequent. It is important that children with NS be evaluated for any specific learning disabilities, so that these can be addressed early when they begin school. A study by Van der Burgt and colleagues (1999) of 35 patients with NS showed an average Full Scale IQ of 86.1. The

range, however, was quite wide (48–130). These authors felt that the children with NS had relative strengths in the areas of nonverbal reasoning, verbal comprehension, social judgment, and visual–motor abilities. There were specific weaknesses in spatial knowledge and planning abilities. The latter weakness leads to limited ability in organizing academic tasks, which often have a negative effect on academic performance. A number of children with NS appear to have attention deficits, which affect organization, memorization, and ability to pay attention in school. Children may require special help in school, but the great majority are able to attend regular school and graduate from high school. Some have graduated from college, and a few have received advanced degrees.

Neuromuscular Problems

Muscular hypotonia is frequent and results in hyperextensible joints. The combination of musclular hypotonia and visual problems often leads to poor coordination. Although seizures have been reported, they are not frequent. A number of reports of Arnold–Chiari malformation have been reported, usually recognized in adolescence or adulthood. There have been reports of unexplained peripheral neuropathy. Some of the children have poor handwriting and find writing very tiresome. These children often improve in their schoolwork if they are able to use a computer for it. There is an interesting group of patients who have features of both neurofibromatosis and NS. Such patients would be at increased risk for optic glioma and medulloblastoma. Because of their lax muscles, many children with NS have relatively flat feet that are often accompanied by severe leg cramps, particularly at night.

Orthopedic Problems

Over 90% of patients with NS have a chest deformity, such as a pectus carinatum or pectus excavatum. Scoliosis and kyphosis are reported in 15–25% of patients with NS. Other orthopedic problems include cubitus valgus, genu valgum, and hand and foot anomalies.

Genitourinary Problems

About half of males with NS have one or both testes undescended. As would be expected with the delay in bone age, puberty is commonly delayed both in males and females. Eventual normal sexual development, however, is usual. Females appear to have normal fertility. Males who have their undescended testes treated are certainly able to reproduce, but among familial cases, there is a preponderance of maternal transmission. A number of kidney anomalies have been reported. Some of these are significant if they include urinary tract obstruction, but fortunately the majority are mild and generally of little clinical consequence.

Eye Findings

Eye findings are very frequent and include apparent hypertelorism, ptosis, refractive errors, strabismus, and amblyopia. An occasional patient will have a coloboma. Because of the high frequency of ocular findings, all children with NS should have a complete eye

examination. It is of interest that many patients with NS have light blue or light green irides even when unaffected family members do not.

Skin and Hair

Prominent fetal pads on the fingers and toes are common. Nevi and freckles are common, and some patients have characteristics of both neurofibromatosis and NS, as noted above. It is of interest that patients with a diagnosis of Leopard syndrome who also had other features compatible with NS have recently been shown to have a deletion of the PTPN11 gene, suggesting that Leopard syndrome may be NS with many lentigines (Tartaglia et al., 2002). Curly hair is often a feature in patients with NS. Some have rather sparse hair, and an occasional patient will have very sparse eyebrows and eyelashes.

Hematology

About 25% of patients have unexplained hepatosplenomegaly. Easy bruising is a frequent finding, and an occasional patient will have significant bleeding problems. Sharland and colleagues (1992) found a history of abnormal bleeding or easy bruising in 65% of patients with NS. They also found a poor correlation between a history of abnormal bleeding and a specific coagulation factor deficit. Factor 11 deficiency is one of the more common findings, but low levels of factor 8 and factor 12 have also been found. Platelet defects are also relatively common. Laboratory testing may be misleading. Some patients with a deficiency of factor 11 may have a normal partial thromboplastin time (PTT). Since patients with NS may require a number of surgical procedures, it is recommended that all patients with NS undergo a prothrombin time (PT)/PTT, platelet count, and bleeding time as screening tests if the history suggests a bleeding problem. Even if the PTT is normal, a factor 11 level should be obtained. Aspirin should be used with caution by patients with NS.

Recent reports have shown that patients with NS who develop juvenile myelomonocytic leukemia have mutations in the PTPN11 gene (Tartaglia et al., 2003). When this condition appears in patients with NS, spontaneous remissions are frequently reported. In patients without NS, the prognosis for this unusual leukemia is usually poor. It is unclear whether there is an increased risk for malignancies in NS. A number have already been reported, such as neuroblastoma, testicular cancers, and malignant schwannoma. There is need to obtain more information regarding the long-term risk of malignancies in patients with NS.

Lymphatics

Lymphatic abnormalities occur in about 20% of patients with NS. These have been attributed to hypoplasia or absence of superficial lymphatic channels. As mentioned earlier, fetuses are reported to have cystic hygromas that often resolve *in utero*. Puffy hands and feet are relatively common in severely affected newborns. This edema generally subsides, but in some, lymphedema may develop later in childhood or in adulthood. Although rare, intestinal lymphangiectasia leading to protein-losing enteropathy has been reported, as well as pulmonary lymphangiectasia. Spontaneous chylothorax and chylous effusions may occur,

but are more common as complications following cardiac surgery. Chylous effusions represent a serious problem and are often very difficult to manage.

Cardiac Problems

Over 80% of patients with NS have some structural cardiovascular problem (Marino et al., 1999; Sharland et al., 1992). A dysplastic, often stenotic, pulmonary valve is the lesion most characteristic of NS. In early reports, right-sided lesions such as pulmonary valvular stenosis and atrial septal defects were stressed as common in NS, in contrast to the left-sided lesions found in Turner syndrome. It is apparent, however, that left-sided obstructive lesions are also seen in NS. These include aortic valvular stenosis, subaortic stenosis, coarctation of the aorta, and patent ductus arteriosus. Indeed, almost every form of congenital heart disease has been reported, including patent ductus arteriosus, tetralogy of Fallot, ventricular septal defect, Ebstein malformation, and pulmonary atresia (Noonan & O'Connor, 1996).

DIFFERENTIAL DIAGNOSIS

It is important to take a careful history, to eliminate the possibility of alcohol abuse in the mother or the use of other teratogens; in either case, the effects might be confused with NS. Chromosome studies are indicated in a female suspected to have NS who has a left-sided cardiac lesion, such as a bicuspid aortic valve or coarctation of the aorta, to rule out Turner syndrome. Other conditions difficult to distinguish in infancy include the cardiofacial cutaneous syndrome (CFC) and Costello syndrome. CFC has characteristic skin findings, which may not be obvious in early infancy. With time, the phenotype of CFC becomes more distinctive (Kavamura, Peres, Alchome, & Brunoni, 2002; Neri & Opitz, 2000). In general, patients with CFC tend to be significantly more delayed in development and often have mental retardation. Costello syndrome resembles NS in infancy, but with time the phenotype changes (Hennekam, 2003). About 20% of those with Costello syndrome have arrhythmia in early infancy, which may be helpful in the differential diagnosis (Lin, Grossfeld, & Hamilton, 2003). Both of these conditions have cardiac lesions similar to those in NS. No specific gene has been identified in these latter two syndromes.

EVALUATION AND MANAGEMENT

All patients diagnosed with NS require extensive evaluation. A hearing evaluation and careful eye examination should be carried out at the time of diagnosis. A pediatric cardiology consult should be sought even if no murmur is heard, and a cardiac ultrasound should be obtained. If there is growth failure, an endocrine consultation should be sought. Many of these children will be seen by a geneticist for diagnosis, and certainly genetic counseling is indicated. It is important that a child be evaluated early on to uncover any potential specific learning disability, so that intervention can be started as soon as possible. Although the PTPN11 gene mutation is present in fewer than half of the patients diagnosed with NS, it is still worthwhile to obtain this test. We have much to learn about the specific mutations of the PTPN11 gene and their relationship to the phenotype. Early diagnosis will lead to earlier intervention. Long-term follow-up is essential. It will be important that

all patients diagnosed with NS be followed regularly throughout their lives by physicians knowledgeable about the syndrome.

A FOLLOW-UP STUDY OF ADULTS WITH NS

Little has been written about the natural history of NS or about NS in adults. I have follow-up data for 56 patients with NS who were at least 21 years of age. This group includes my own personal patients followed since childhood; patients who participated in the NS Support Group; and patients who responded to a questionnaire sent to a number of adults with NS with the help of the NS Support Group. Thirty-six of these adults, 17 males and 19 females, were diagnosed as children. The other 20, 8 males and 12 females, were not diagnosed with NS until they were adults. The adults in this study were relatively young, with 82% less than 40 years of age (Table 15.1). Only 2 were more than 50 years old. There were some very interesting differences between the group diagnosed as children and those diagnosed as adults.

Adults Diagnosed in Childhood

Of the 36 adults who were diagnosed in childhood, marital status was known for 30; only 7 of these were married, 3 males and 4 females (Table 15.2). Two of the males had an unaffected child each, while the other had a son with NS. Two women had one affected child each, and two other women chose not to have children, although one adopted a child. In general, the patients diagnosed in childhood tended to have more significant heart lesions, particularly pulmonary valvular stenosis. All but four were very short in stature.

Adults Diagnosed in Adulthood

Marital status was known for 15 of the 20 adults diagnosed in adulthood (Table 15.2). All but 2 of these adults were not diagnosed until an affected child was diagnosed with NS. The remaining 2, who were unmarried, were both males. One was diagnosed at age 32 when he first came to medical attention, and the other was diagnosed at age 23 after a sister was diagnosed with NS. The remaining married adults had one to three affected children with NS. As a group, these adults expressed guilt at having an affected child or children with NS.

It is interesting to speculate why a diagnosis of NS was not made during childhood. In general, these patients tended to be less severely involved. Three of the males and two of

TABLE 15.1. Ages of Patients at the Time of the Follow-Up Study

Age group	*n*
21–29 years	19
30–39 years	27
40–49 years	8
50–59 years	2

TABLE 15.2. Marital Status (Known for 45 Patients)

Status	Diagnosis in childhood	Disgnosis in adulthood
Married	7	13 (85%)
Unmarried	23 (76%)	2
Total known	30	15

the females had heights well within the normal range. Most had some learning problems, and most considered themselves different from their peers. One adult thought that she must have been adopted, because she did not resemble the rest of her family. As children, these patients were often teased because they were short or looked different from their peers. The majority did not have significant congenital heart disease, although several had pulmonary valvular stenosis requiring surgery in childhood. Most of the adults had never known or seen a patient with NS before they had an affected child and were diagnosed with the condition themselves.

Education

Of the entire group of patients, 25% claimed they had no learning problems, while the remaining 75% had some learning difficulty. Over 80% had graduated from high school; 18 had attended college; 3 had master's degrees; and 1 was a registered nurse. When the diagnosis of NS was made during childhood, it was more likely that these children received special help at school if there was a specific difficulty. Of those who were not diagnosed in childhood, problems in school were often ascribed to laziness, and special help was generally less likely to be given.

Employment

Out of the entire group, only three patients had been considered disabled from childhood. There were three adults who had previously been employed but were now disabled because of health problems. Among the female patients with NS, many worked in occupations involved with children. Five were day care workers, three were teachers, one a nurse, and another a social worker. Several were in office work, including an executive secretary, a bank worker, and an accounts-payable coordinator. A few were still attending school, and several women who had previously worked were now housewives. Among the males were warehouse managers. Other jobs included construction worker, chef, maintenance worker, counselor, electrician's helper, and truck driver. One young man, who had graduated from college, was currently working in retail but planned to go to law school.

Psychological Problems

From the information available on 51 patients, psychological problems were rather frequent. Twelve (23%) had a diagnosis of depression and were currently on antidepressant medication. Two were recovering from alcoholism; one had been diagnosed with bipolar

disorder; and another had oppositional behavior. Some of my own patients, who seemed to be quite happy and well accepted by their classmates as children, became quite unhappy and depressed as they reached adulthood. Short stature was a particular problem for males, and with their muscular hypotonia, they generally did not have much athletic ability. As mentioned earlier, the majority of patients diagnosed in childhood remained single. In the NS Support Group, several members loved children and wanted to have children, but were concerned that they might have a severely affected child with NS. As a group, these adults—particularly those not diagnosed until adulthood—considered themselves to be "fighters." They felt that they had to struggle through school and put up with taunts and teasing by their peers. They believed that this made them strong, and as adults, the great majority seemed to be very articulate, outgoing, and able to lead productive lives. Those involved in the NS Support Group appeared to derive a lot of support and satisfaction from interacting with their peers.

Other Problems

It was of interest that lymphedema, which had not been a problem in early childhood, became a problem for five patients in adolescence or adulthood. Arthritis, fibromyalgia, and back pain were frequent among the adults. One developed intestinal lymphangiectasia as an adult, and another esophageal varices. Arnold–Chiari malformation was noted in two patients; one was diagnosed with testicular cancer; and another had suspected myasthenia gravis. Hypothyroidism was diagnosed in several. It is currently unknown what health problems may develop with increasing age. We do not know what the long-term effects of a mutated PTPN11 gene are in general, and whether this gene will make patients more likely to develop future malignancies in particular.

Cardiac Status

Cardiac status was known in 45 of the patients. Forty-two, or 93% of them, had had some form of heart disease. Of these, 57% had pulmonary valvular stenosis and had undergone surgery or balloon valvuloplasty. Three patients died from cardiac complications at 39, 48, and 49 years of age. Two had been told they would need a heart transplant. One had had two surgeries, currently had a defibrillator, and was now disabled. There were two others on medications for heart failure; two had pacemakers; and three required drugs to treat arrhythmias. In summary, 31% had ongoing cardiac problems. There is clearly a need for continued long-term follow-up of the cardiac status of adults with NS.

CONCLUSION

The majority of adults with NS are leading independent, productive lives. There is, however, a wide variation in the phenotype, and some adults are significantly limited in their ability. As our knowledge has increased, patients with NS now recognize that this is a heritable disorder, and that there is a 50% risk of transmitting the condition to an offspring. The availability of a diagnostic test for about 50% of patients with NS will be useful for those seeking prenatal testing. If the diagnosis of NS is recognized earlier, it is likely that there will be fewer patients whose diagnosis is delayed until adulthood. It will be of

interest to follow patients with NS diagnosed in childhood, to see how many will choose to marry and have children as they become adults. A genetic counselor cannot predict the severity of an affected child. A mildly affected adult with NS may have a mildly affected child or a severely affected child. This is obviously a problem as patients with NS become adults, marry, and would like to have children.

Children diagnosed today with NS are often treated as "special," as many children with special needs are. Early identification and interventions to minimize their physical and educational needs are now widely available. It will be of great interest to see how they will fare as adults. Present-day adults with NS appear to have a significant risk of depression, and many have experienced much teasing as children. As a group, however, they perceive themselves as strong and as having overcome adversity. Will the present-day management of children with special health care needs lead to a happier and healthier adulthood? The answer is unknown. Children with special health care needs become adults with special health care needs, but society has not yet addressed this problem. Although many adults with NS are working, health insurance is a problem. These patients are often in occupations that do not provide good health care benefits. Physicians caring for these adults may have little knowledge of NS and related syndromes, and the long-term health care needs of these adults may be numerous. As we learn more about the role of the SHP-2 protein, we may gain a better understanding of NS. There is clearly a need for more long-term study of NS. The role of the mutated PTPN11 gene over a lifetime is clearly still unknown.

Patients, physicians, and families may receive useful information and support from The Noonan Sydrome Support Groups, Inc. (TNSSG). Wanda Robinson is founder and president. TNSSG can be reached on the Internet at wandar@bellatlantic.org or info@noonansyndrome.org. Their website: www.noonansyndrome.org. Mail: TNSSG, Inc., P.O. Box 145, Upperco, MD 21155.

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16

NEUROFIBROMATOSIS

DOROTHEE L. SERPAS

Neurofibromatosis type 1 (NF1) is a very common single-gene disorder that affects the human nervous system. NF1 is an inherited autosomal dominant disorder. The estimated prevalence rate is 2–3 cases per 10,000 individuals (Rasmussen & Friedman, 2000). By adulthood, most patients show diagnostic neurocutaneous signs of NF1, including *café au lait* spots, axillary freckling, neurofibromas (benign peripheral nerve tumors), and iris hamartomas (Lisch nodules) (Gutmann et al., 1997; Mulvihill et al., 1990; Rasmussen & Friedman, 2000).

Rosser and Packer (2002) note that some features of NF1, such as *café au lait* spots and Lisch nodules, are considered "clinically silent"; however, others, such as neurofibromas, cause a significant degree of morbidity, mortality, and cosmetic disfigurement. Childhood through early adulthood is a vulnerable period for growth of these lesions. Neurofibromas are a heterogeneous group of tumors. Symptoms arise as neurofibromas enlarge and compress other structures.

NF1 is a multisystem disorder affecting the eyes, bony skeleton, endocrine system, blood vessels, central nervous system (CNS), and peripheral nervous system (Ratner & North, 2003). Complications include short stature, plexiform neurofibromas, scoliosis, and headache. The CNS manifestations of NF1 include optic nerve pathway tumors, T2 hyperintensities on magnetic resonance imaging (MRI), increased size of white matter tracts, and macrocephaly.

Guillamo and colleagues (2003) investigated prognostic factors of CNS tumors in children and adults with NF1, in a retrospective paradigm with a median 5½-year follow-up. A total of 127 CNS tumors were observed in the 104 patients. Sixty-six percent were optic pathway tumors, and the other 34% were tumors in other locations. Twenty percent of the patients had multiple CNS tumors. Radiotherapy for optic pathway tumors was associated with vascular complications (ischemic strokes) and growth hormone deficiency in 32% and 46% of the patients, respectively.

Adults with NF1 have not been the focus of much empirical research. Not only are there potential effects on psychoeducational and vocational functioning; chronic academic failure, physical appearance of tumors, and social difficulties can all affect self-image and overall psychosocial functioning in adulthood (Ratner & North, 2003).

ETIOLOGY AND NEUROLOGICAL FINDINGS

The NF1 gene on chromosome 17 of humans is typically classified as a tumor suppressor gene (Ratner & North, 2003). Creange and colleagues (1999) investigated neurological complications of NF1 in adulthood. They observed a wide range of neurological manifestations; the predominant neurological features of adults with NF1 were chronic pain and malignant peripheral nerve sheath tumors. Understanding how the loss of the NF1 gene product, neurofibromin, affects brain functioning and neuropsychological functioning will be important to the field.

There is much variability among individuals with NF1. Researchers are still unclear about whether the specific phenotypic expressions (learning disabilities, visual–spatial issues, etc.) might be associated with specific mutations, or whether they could be obscured by the broad array of mutations that exist throughout the gene. In addition to learning disabilities, there is wide variation in the CNS manifestations; as noted above, these include T2 hyperintensities on MRI, increased size of white matter tracts, and macrocephaly (Ratner & North, 2003).

Among the most common brain lesions noted for many younger individuals with NF are T2 hyperintensities. These are high signal intensities on MRI scans, which have been referred to as "unidentified bright objects." Duffner, Cohen, Seidel, and Shucard (1989) noted these increased T2–weighted images in approximately 60% of the children with NF1 in their sample. They occurred predominantly in the basal ganglia, thalamus, brain stem, and cerebellum. It was postulated that these areas reflect aberrant myelination, gliosis, or other brain dysplasia (Duffner et al., 1989).

The high frequency of T2 hyperintensities on MRIs led to the hypothesis that these lesions are associated with the occurrence of cognitive deficits in children with NF1, but several studies have tested this hypothesis with mixed results (Duffner et al., 1989; Dunn & Roos, 1989; Ferner, 1994; Ferner et al., 1993). These researchers have concluded that there is no association between learning difficulties or intellectual impairment and the presence of T2-weighted abnormalities on MRI. Many other studies, however, have demonstrated relationships between T2-weighted hyperintensities and lower IQ scores than for children without this MRI finding (Denckla et al., 1994, 1996; Hofman, Harris, Bryan, & Denckla, 1994; Mott, Baumgardner, Abrams, Reiss, & Denckla, 1994). In addition to this finding, North and colleagues (1994) found significantly lower scores on tests of language function, visual–motor integration, and coordination for the group with T2-weighted abnormalities.

Hyman and colleagues (2003) investigated the relationship of T2 hyperintensities and NF1. In their review of the literature, they observed that the majority of the lesions have been noted to disappear as children grow older. Cross-sectional data suggest that there are also improvements in intellect. These authors conducted a prospective longitudinal study of a cohort of 32 patients and 11 unaffected sibling controls. Neuropsychological and MRI data were collected at the beginning of the study and 8 years later. The authors concluded that the children with NF1 showed no improvement in cognitive ability as they entered adulthood, compared to controls. Consistent with previous studies, a decrease in the number, size, and intensity of the T2 hyperintensities was noted over the 8 years. The changes, however, were not associated with changes in cognitive ability. The authors speculated that T2 hyperintensities in the cortex, subcortical areas, or deep white matter are more frequent with age, and that these lesions are likely to have a different pathology from basal ganglia lesions. Hyman and colleagues concluded that the best predictor of cognitive

dysfunction in adulthood was the presence of T2 hyperintensities in childhood, rather than current lesion status.

The association between T2 hyperintensities and learning disabilities remains controversial. If data regarding increased T2 signals on MRI mount, a possible radiological marker for risk of cognitive deficits and learning disabilities could be established (Ratner & North, 2003). There has also been increasing interest in the corpus callosi of individuals with NF1. Kayl, Moore, Slopis, Jackson, and Leeds (2000) discovered that children with NF1 had significantly larger corpus callosi than controls did. They also found that more severe attention problems in children with both NF1 and attention-deficit/hyperactivity disorder (ADHD) were associated with smaller corpus callosum size.

Exciting new lines of research have evolved through advances in brain imaging technology. Studies investigating cognitive dysfunction and cortical metabolite ratios via functional MRI, positron emission tomography, and proton magnetic resonance spectroscopy (Jones, Gunawardena, & Coutinho, 2001; Wilkinson, Griffiths, & Wales, 2001) are beginning to shed new light on brain functioning and NF1.

NEUROPSYCHOLOGICAL PHENOTYPIC EXPRESSION

Intellectual Functioning

Early studies of intellect of individuals with NF1 resulted in overestimates of the incidence rates of mental retardation (for a review, see Ratner & North, 2003). These findings were confounded by the lack of standardized psychometric tools and by methodological problems. Mental retardation is not a common feature of NF1. There is an association between intracranial tumors in NF1 and lower IQ (Moore, Ater, Needle, Slopis, & Copeland, 1994). Incidences of mental retardation in more recent and better-controlled studies range between 4.8% (North et al., 1994; North, Joy, Yuille, Cocks, & Hutchins, 1995) and 11% (Wadsby, Lindenhammer, & Eeg-Olofsson, 1989).

Early studies of neuropsychological functioning in children with NF1 indicated discrepancies between Verbal IQ (VIQ) and Performance IQ (PIQ) (Eliason, 1986; Wadsby, Lindenhammer, & Eeg-Olofsson, 1989). The statistical significance of these discrepancies remains in dispute, however. Previous studies have indicated adequate functioning on certain neuropsychological tests and subtests (e.g., Picture Arrangement, Picture Completion, Rapid Automatized Naming) for children with NF1. Impairment has been noted on such measures as Judgment of Line Orientation, Vocabulary, and Block Design (Cutting et al., 2002). Cutting and colleagues (2002) looked at neuropsychological profiles of children with NF1 in order to determine whether certain cognitive functions were "spared" or "impaired" over time. They determined that over time, these children do not "catch up" to nondisabled siblings on areas of previous impairment, and they continue to perform similarly to their siblings on measures that were originally "spared."

Among the few studies of cognitive functioning in adults with NF1, Uttner, Wahllander-Danek, and Danek (2003) studied 20 adults with NF1 and 20 age- and gender-matched controls without neurological disease. Test results indicated slightly lower test scores for the group with NF1, but no specific intellectual impairment. When a computerized test of selective attention was administered, the individuals with NF1 had slower reaction times. In his review of the literature, Ferner (1994) concluded, "Intellectual problems in NF1 are not thought to be progressive" (p. 249).

Visual–Spatial Skills

As indicated above, several studies have found discrepancies between VIQ and PIQ, giving rise to the speculation that a form of neuropsychological dysfunction in the visual–spatial domain may accompany NF1. Varnhagen and colleagues (1989) compared individuals and unaffected siblings and found slightly deficient cognitive processing for individuals with NF1, specifically affecting visual–spatial integration. They also found that cognitive deficits increased as a function of the severity of the disorder. Eliason (1986) was one of the first scientists to describe this pattern of reactive weakness in visual perceptual impairments. Stine and Adams (1989) found that performance on measures of visual–motor perception and integration was approximately 2 standard deviations below population norms.

Language Functioning

During the initial phases of investigation into NF1, scientists assumed that language functioning was relatively spared (North et al., 1995), perhaps because of the focus on the VIQ-PIQ split. In more recent studies, however, the data indicate that language functioning does not fare as well as was once thought. As the model expands, more recent investigations have assessed language and reading domains and have demonstrated that language-based problems are at least as common as nonverbal deficits in children with NF1 (Cutting, Koth, & Denckla, 2000; Dilts et al., 1996; Ferner, Hughes, & Wenman, 1996; Hofman et al., 1994; Legius, Descheemaeker, Spaepen, Casaer, & Fryns, 1994; Moore et al., 1994; North et al., 1994, 1995). In addition to visual–spatial deficits, specific verbal/language deficits were noted in word definition, picture naming, and receptive grammar. Deficits were also demonstrated for verbal reasoning and recall (Mazzocco et al., 1995). Likewise, Dilts and colleagues (1996) found that in addition to the visual–spatial deficits, 58% of their sample failed a language screening test, and 26% qualified for formal diagnoses of receptive and/or expressive language disorders.

Solot and colleagues (1990) investigated language in 23 children diagnosed with NF1 and 10 nondisabled sibling controls. They found that the subjects with NF1 had delayed language development and slow acquisition of vocabulary. They also made significant syntactic, semantic, and phonological errors. Moreover, Solot and colleagues reported that problems such as motor dyspraxia resulted in mispronunciations, sound sequencing problems, and abnormal speech prosody.

Language disorders may accompany other neuropsychological problems in individuals with NF1 (Eliason, 1988). In her review of the literature, Ozonoff (1999) noted that when language dysfunctions exist, they usually accompany visual–spatial deficits, and that language disorders are rarely present "by themselves" in individuals with NF1.

Attention and Other Self-Regulatory Abilities

Executive functioning skills are associated with goal-directed and future-oriented forms of behavior and thought, and are highly associated with self-regulatory skills. They relate to attention, planning, organizational skills, and inhibition. Attention problems and hyperactivity have long been associated with NF1 (Anderson, 1992; Eliason, 1986; Legius et al., 1994; Moore et al., 1994; Stine & Adams, 1989; Wadsby et al., 1989). Eliason (1988)

investigated attention and response style in children with NF1 via a computerized continuous-response measure. He determined that although their responses were slower and less accurate than those of nondisabled controls, they were comparable to those of children with learning difficulties from other causes.

Problems with sustained attention, selective attention, and divided attention have been noted in persons with NF1 (Ferner et al., 1996; Mazzocco et al., 1995). Studies find that symptoms associated with ADHD may occur as a component of the NF1 phenotype (Koth, Cutting, & Denckla, 2000). Estimates of symptoms associated with ADHD in children with NF1 vary across studies and range from 17.8% (Bawden et al., 1996) to 42% (Koth et al., 2000).

Poor organization and planning have been evidenced in some neuropsychological evaluations of patients with NF1 and visual–spatial impairment (Bellermann, 1989; Varnhagen et al., 1988). Bellermann (1989) found that children with NF1 had troubles integrating and organizing new information. They did not manage their time efficiently, which often resulted in problems with classwork.

Deficits have been documented in the ability to copy a complex figure in an organized manner (Chapman, Wabner, Bassett, Urion, & Korf, 1996; Hofman et al., 1994), flexibility in the ability to shift cognitive set (Hofman et al., 1994; Joy, Roberts, North, & deSilva, 1995), and the ability to attend selectively to a relatively less salient dimension of one stimulus while inhibiting a competing response (Ferner et al., 1996).

Memory Functioning

Uttner and colleagues (2003) found that adult patients with NF1 scored lower on three out of four memory tests and on a measure of visual constructive abilities. Varnhagen and colleagues (1988) measured auditory serial recall in children with NF1 and compared them to controls. The patients with NF1 recalled significantly fewer words in correct order than their unaffected sibling controls. Eliason (1988) found not only that children with NF1 were more likely to present with visual–spatial problems, but that 30% of them also had memory deficits on the Rey Auditory Verbal Learning Test (Lezak, 1983).

In a study conducted with adults and children with NF1, Ferner (1994) evaluated short-term and delayed verbal memory recall. The subjects with NF1 recalled significantly fewer words, both immediately and after a delay of 20 minutes, when compared to a control group.

Motor Functioning

Gross and fine motor deficits have been documented in many studies. Eldridge and colleagues (1989) and Hofman and colleagues (1994) have found that children with NF1 have significantly more problems with balance and gait than unaffected siblings do. North and colleagues (1994) found that one-fourth of their sample had mild motor impairments, and that another half had moderate to severe lack of coordination. Ferner (1994) compared 103 patients with NF1 to 105 matched controls, using a computerized tracking measure, and found that 41 patients showed poor awareness of spatial relationships and impaired hand–eye coordination. These authors also administered the Wechsler Block Design subtests and detected poor constructional and perceptual skills in patients versus controls.

Interestingly, some studies have found these motor problems in the absence of detectable lesions. Dunn and Roos (1989) found that 8 of the 28 children with NF1 in their sample had coordination problems that were not explained by tumor or hydrocephalus. Ferner (1994) found similar results, with 43% of 103 patients. These types of findings led McKinlay (1987) to conclude that these motor problems in children with NF1 are similar to those described in children with motor learning difficulties.

LEARNING PROBLEMS

Language-Based Learning Disabilities

Weakness in any of the above-described areas of neuropsychological functioning can contribute to learning problems. Children with NF1 appear to be at risk of having learning problems. There is a broad range of learning disabilities in children with NF1, which can lead to academic struggles, reduce the capacity to benefit from higher educational options, and limit the range of vocational opportunities in adulthood (Ratner & North, 2003).

Ratner and North (2003) reviewed the literature and reported that the frequency of learning disabilities in NF1 ranges from 40% to 60%. They noted that the most frequent learning problems related to problems in visual–spatial tasks (these are discussed further below), sustained attention, coordination, memory, language, and behavior.

Ozonoff (1999) astutely points out methodological problems in the definition of learning disabilities, lack of appropriate control groups, and lower overall IQ in samples used in some research. Using the model of discrepancy between IQ and achievement, several studies have documented discrepancies in reading (Eldridge et al., 1989; Hofman et al., 1994), spelling (Eldridge et al., 1989; Stine & Adams, 1989), written language (Hofman et al., 1994), and arithmetic (Eldridge et al., 1989; Stine & Adams, 1989).

Ratner and North (2003) concluded,

> In summary, there does not appear to be a profile of LD [learning disabilities] specific to NF1. Academic LD may be associated with depressed performance in verbal tasks such as reading and spelling, and/or nonverbal tasks such as mathematics. Nevertheless, LD is not thought to be secondary to global intellectual impairment in the majority of children with NF1. (p. 103)

Costa and Silva (2002) reviewed animal models investigating how molecular and cellular mechanisms could underlie the learning problems of individuals with NF1. They note that neurofibromin has several biochemical functions, such as Ras-guanosine triphosphatase activity, adenylate cyclase modulation, and microtubule binding, all of which could be critical for brain functioning. They suggest that learning disabilities associated with NF1 are caused by Ras activity that leads to increased gamma-aminobutyric acid-A inhibition and to decreased long-term potentiation. These findings suggest the possibility of treatments for the learning disabilities associated with NF1.

Nonverbal Learning Disabilities

In addition to the traditional language-based learning problems described above, some researchers have investigated a pattern associated with nonverbal learning disabilities. A hallmark of nonverbal learning disabilities is the finding that PIQ scores are significantly lower than VIQ scores, as described earlier. Also associated with nonverbal learning

disabilities in the general population are problems in arithmetic, impaired visual–spatial skills, fine motor and handwriting problems, and social problems (Harnadek & Rourke, 1994). These characteristics are similar to those observed in children with NF1.

In discussing behavioral dyscontrol, Ferner (1994) notes that children with NF1 may misjudge nonverbal communications such as facial gestures and facial expression, which may contribute to inappropriate and intrusive behavior. It may also be that, in addition to poor self-regulation, children with NF1 share this social skill/social perception problem with children who have nonverbal learning disabilities.

Ozonoff (1999) summarized these studies well, stating, "The consensus emerging from the literature is that the cognitive profile of NF1 bears some similarities to an NLD [nonverbal learning disabilities] profile but is far from a perfect fit and diverges in a number of important ways" (p. 49). Mazzocco and colleagues (1995) reviewed commonalities and differences among the features of nonverbal learning disabilities and those associated with NF1 in the literature, and found only two similarities: visual–spatial and motor deficits.

It may also be that the syndrome of nonverbal learning disabilities as a diagnostic entity is still being defined in the general population, and that a concise diagnostic profile is still emerging. Once this syndrome is better defined in the general population, researchers may better discern whether this profile is part of the NF1 neuropsychological phenotype.

PSYCHOLOGICAL FUNCTIONING

Researchers have investigated behavioral problems among children with NF1 and the psychological effects of having NF1 on individuals with this disorder. Johnson, Saal, Lovell, and Schorry (1999) found that children with NF1 had more problems than their unaffected siblings on seven of the eight scales measured on a behavior rating scale, including Social Problems, Attention Problems, Anxiety/Depression, Withdrawal, Thought Problems, Somatic Complaints, and Aggressive Behavior. They also scored lower on other measures, such as athletic ability.

Varnhagen and colleagues (1988) reported that children with NF1 displayed aggressive tendencies compared with their unaffected siblings, and suspected that this was a result of hyperactive/impulsive behavior. Porter-Counterman, Saylor and Pai (1995) found that the children with NF1 in their sample were dissatisfied with their own behavior, and that those with the more severe manifestations of NF1 had a diminished sense of self-worth.

DIAGNOSTIC GUIDELINES

Although much of the research is focused on *children* with NF1, it is imperative to continue monitoring and evaluating individuals across the lifespan, into adulthood. Some problems may only manifest themselves when demands on performance, self-sufficiency, and so on increase as an individual reaches adulthood.

Given the wide-ranging effects of NF1 on cognition and the heterogeneity of the population with NF1, the need for comprehensive neuropsychological assessment is clear. A thorough battery for adults with NF1 would assess each domain of functioning that can be affected by the disorder. A comprehensive neuropsychological battery would assess the following:

- Intellectual functioning
- Visual–spatial skills

- Language functioning
- Attention and self-regulation
- Organizational skills
- Memory functioning
- Motor functioning
- Learning and achievement
- Psychological functioning
- Vocational interests and occupational functioning
- Adaptive behavior

In addition to psychometric tools, future technology may provide for identification of possible radiological and pathological markers of cognitive deficits. These promising techniques may help to refine the diagnostic process and better develop the parameters for a cognitive phenotype of NF1.

INTERVENTIONS AND PROGNOSIS FOR ADULTHOOD

Interventions

Ideally, improved assessment of neuropsychological functioning and individualized interventions will contribute to improved quality of life for individuals with NF1. In addition to providing the multidisciplinary team with critical information regarding functioning, arming these patients with information about their own neuropsychological strengths and weaknesses and their neuropsychological profiles can promote self-knowledge, self-sufficiency, and self-advocacy. In a multidisciplinary team approach, professionals such as physical therapists, occupational therapists, educational specialists, mental health professionals, genetic counselors, ophthalmologists, medical professionals, and speech therapists may each lend their specialized training to treating the "whole patient."

Interventions implemented by mental health professionals are broad. They may include therapy to address teasing, self-image issues, social skills deficits, and mood problems. They may also involve educational recommendations, vocational counseling, and transition planning.

Children with NF1 who display traits of ADHD have been treated with stimulants, with some good results for cognitive, academic, and social problems (Aron, Rubenstein, Wallace & Halperin, 1990; Mautner, Kluwe, Tahakker, & Leark, 2002). Although more research is needed, adults with NF1 may also benefit from such interventions.

As adults with NF1 consider parenthood, a referral to a genetic counselor may be in order. When Benjamin and colleagues (1993) assessed subjects at risk of having a child with NF1 (n = 32), 45% of the sample reported that this risk had influenced their reproductive decisions. Of the 29 subjects who were still considering procreation, 41% preferred to have a prenatal diagnosis in a future pregnancy. Only 3 subjects reported that they would terminate an affected pregnancy.

Prognosis

There are only a handful of studies investigating adults with NF1, and even fewer longitudinal studies. Ratner and North (2003) note that some manifestations of NF1 appear to worsen with age (e.g., number of cutaneous neurofibromas, size of the plexiform neurofibromas),

but less is known about neuropsychological functioning over time. Therefore, the knowledge about prognosis and prognostic indicators is very limited.

Riccardi and Eichner (1986) suggest that IQ scores improve with age. Some researchers have hypothesized, however that this may be an artifact of shifting from the IQ test for children (Wechsler Intelligence Scale for Children) to the IQ test for adults (Wechsler Adult Intelligence Scale). Other have studies found a negative correlation between age and IQ for children under the age of 16 (Legius et al., 1994; Moore, Slopis, Jackson, & De Winter, 2000; Moore, Slopis, Schomer, Jackson, & Levy, 1996).

Lorch, Ferner, Golding, and Whurl (1999) examined a group of adults with NF1. Many of the patients reported subjective improvement in reading since childhood, but enduring problems with writing. Lorch and colleagues' research bore this out: It was determined that reading difficulties were not as prevalent in these adults (13%), but that writing difficulties were present for 40% of the sample.

Ferner and colleagues (1993) collected data on 103 patients with NF1 and 105 controls between the ages of 6 and 75 years of age who were matched for age, sex, and socioeconomic status. The authors found significantly lower Full Scale IQ for the patients (mean = 88.6, *SD* = 14.6) than for the controls (mean = 101.6, *SD* = 14.2), but the impairment was considered mild. They also determined that the individuals with NF1 had significantly poorer reading and impaired short-term memory; that they had slower mean reaction times and higher error rates on a computerized performance measure; and that they were slower to develop and adapt strategies for novel and complex tasks. The presence of neurological and/or medical complications was weakly associated with lower mean Full Scale IQ in the patients with NF1. These authors noted that neither sociodemographic factors, age, nor the presence of macrocephaly contributed to neuropsychological deficits in the group with NF1.

Zoller, Rembeck, and Backman (1997) found that adults with NF1 demonstrated problems with inductive reasoning, visual construction, visual and tactile memory, logical abstraction, cognitive speed, coordination, and mental flexibility. Basic motor speed and vocabulary were not affected. The authors noted that a mood disorder (i.e., dysthymia) exacerbated the neuropsychological deficits associated with NF1 only with regard to tests assessing motor functions. That is, depressive symptoms appeared to slow down basic motor processes. The authors speculated that NF1-related cognitive deficits may partly result from white matter lesions in subcortical brain areas, due to proliferation of glial tissue, aberrant myelination, or hamartomas.

With regard to psychological adjustment, Ferner (1994) reported that 33% of adult patients experienced hostile reactions from strangers because of "unsightly" neurofibromas. Wolkenstein, Zeller, Revuz, Ecosse, and Leplege (2001) noted that NF1 can affect quality of life in numerous ways, including those associated with medical complications, cosmetic features, and uncertainty about the effects of the disorder. Wolkenstein and colleagues had adults with NF1 complete a quality-of-life survey. The results indicated that severity of cutaneous disease was associated with emotional effects. They concluded that the severity and visibility of the effects of NF1 have a significant impact on quality of life through alteration of health and appearance.

A retrospective study conducted by Benjamin and colleagues (1993) investigated 56 patients with NF1 and 25 parents of such patients. They found that the majority of the patients perceived themselves as more severely affected than their medical classification indicated. Among this group, individuals who had been diagnosed later in life, who had a child with NF1, or who were concerned about the cosmetic aspects of the disorder perceived themselves to be more severely affected. Evaluation of the psychosocial effects of NF1 at different stages of life showed that 63% of affected patients had experienced dif-

ficulties at school, and 48% reported that the disorder had caused anxiety during adolescence, especially when it was related to the cosmetic effects. The authors speculated that this constellation of factors may have contributed to later difficulties with "career attainment and confidence in relationships" (p. 569). Many patients had been teased about the skin manifestations of NF1. Not surprisingly, the authors reported that almost 50% of these patients with NF1 were distressed by the presence of neurofibromas and had changed their social behavior and style of clothing to hide them.

Samuelsson and Riccardi (1989) investigated psychiatric and social aspects of functioning in individuals with NF1. In the sample they studied, 33% had a history of mental illness; however, these authors did not discern any sort of uniform disorder or profile. The most common psychological diagnoses included depression and anxiety with vegetative dysfunction. There was a significant relationship between depressive syndromes and organic brain syndrome. Samuelsson and Riccardi noted that half of their adult patients with NF1 had "hostile feelings."

Zoller and Rembeck (1999) conducted a 12-year follow-up study of 48 adult patients with NF1. There were no matched controls. The researchers found that 33% met criteria for psychological diagnoses, with 21% of the individuals with psychological diagnoses group meeting criteria for dysthymia. The authors concluded, "The chronic stigmatizing character of NF1 may be the reason for the increased psychopathology found in this sample" (p. 63).

Although individuals with NF1 are at risk for significant morbidity, most individuals are mildly to moderately affected and can be productive (for a review, see Ratner & North, 2003). North and colleagues (1995) found, however, that simply having a family history of NF was strongly associated with lower socioeconomic status. The authors concluded that this finding was probably a secondary effect of the high incidence of learning disabilities in the NF1 population, the less frequent pursuit of higher education, and the effects of these factors on vocational options and earning potential.

CONCLUSION

NF1 is a genetic disorder of great physical and medical variability. A review of the neuropsychological research indicates that although some trends are emerging, a reliable cognitive phenotype is not yet manifest. Given the multifocal nature of brain involvement with NF1, this is perhaps not surprising.

Further psychometric and radiological research is needed. Future research, with ever more sophisticated tools and a broader foundation of research over the lifespan, will allow scientists to explore the relationship between the anatomical and neurological findings and neuropsychological profiles of individuals with this genetic disorder.

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17

SICKLE CELL DISEASE

JULIEN T. SMITH

OVERVIEW/ETIOLOGY

Sickle cell disease (SCD) is actually a group of inherited autosomal recessive diseases in which there is an abnormal type of hemoglobin, the most important molecule in red blood cells. The abnormal hemoglobin molecule (HbS) is believed to have evolved in descendents of people living in malaria-endemic geographical areas such as Africa and the Mediterranean, since individuals carrying a single abnormal hemoglobin mutation are more likely to survive malaria outbreaks. The HbS molecule is also present in descendants of other regions where malaria is prevalent, including India, South and Central America, the Caribbean, and the Middle East, but it is clearly most prevalent in those of African descent. Although the single mutation appears to serve a protective function, the inheritance of two mutations leads to a more serious illness and less resistance to malaria. Individuals who inherit this abnormal molecule from both parents (HbSS) will exhibit sickle cell anemia (SCA), while those who inherit HbS from one parent and normal hemoglobin (HbA) from the other will carry the trait (HbSA) (Schnog et al., 2004). Those with HbSA may experience no or mild symptoms, but they will not have the most serious manifestations of SCA. Other individuals may inherit the HbS molecule, along with another abnormal molecule, to develop related diseases of hemoglobin that are less severe than SCA (e.g., HbSC, beta-thalassemia). In the United States, the incidence of SCD is presumed to be 1 in 400 people of African descent, 1 in 1,000–14,000 of Hispanic descent, 1 in 58,000 of northern European descent, and 1 in 11,500 of Asian descent. The incidence of HbSA is about 1 in 12 people of African descent.

Erythrocytes (red blood cells) are negatively affected in the sickle cell disorders, and the overall life span of erythrocytes is significantly diminished in SCA, leading to the persistent anemia referred to in the name. However, the more devastating aspect of the disease comes from its first classification (Hillery & Panepinto, 2004; Rodgers, 1997). In SCD, abnormal hemoglobin molecules stick together in stiff rods after they release oxygen, and erythrocytes then become fragile, rigid, and inflexible. Fragile red blood cells collapse easily after releasing oxygen and form a crescent shape, leaving them either dead or unable to carry oxygen effectively throughout the body. Surrounding tissues are deprived of oxygen as a result of the lowered volume of red blood cells, decreased oxygen-carrying capacity, and/or blockage/narrowing of vessels. Abnormally shaped cells tend to adhere to the cells

lining arteries and lead to clots, which can cause ischemic-related pain or more devastating neurological events, depending upon the area of blockage. There are certain risk factors that promote hemoglobin dysfunction and erythrocyte collapse, such as infection, dehydration, or hypoxia. Individuals with SCA are often encouraged to avoid or minimize exposure to such risk factors, to avoid sickling crises and potential medical intervention.

Symptoms of SCA typically are present by 4–5 months of age, but can become life-threatening at any age (e.g., hemolytic, splenic sequestration, or aplastic crises). Pain crises result from damage to major organs or bones and can last hours or days. Some patients have very infrequent crises, while others experience repeated and numerous episodes. Severe pain episodes often require hospitalization for pain management and hydration. Adolescents and adults commonly experience such symptoms as acute chest syndrome, long-term damage to major organs, delayed puberty, complications during pregnancy, stroke, joint pain, anemia, leg sores, and gum disease. Acute chest syndrome and the subsequent complications are the major causes of death in older patients.

Patients with SCD are living longer, due to improved comprehension and treatment of the disease, but the research on patients with SCD during adulthood lags behind this trend (McKerrall, Cohen, & Billett, 2004). Most available research on patients with SCD and their cognitive functioning is focused on children. New research is beginning to explore the situation of adults and older adults with SCD, but typically involves purely medical interests (McKerrall et al., 2004). Newer research is finding inherent abnormalities in brain growth that may create an "abnormal developmental trajectory" extending into adulthood and compromising functioning (Steen et al., 2004). Hypotheses based on the child literature are currently being developed, but clearly the impact of early developmental compromise on the adult functioning of patients with SCD must be explored in more detail.

RISK FACTORS FOR NEUROLOGICAL COMPLICATIONS

Numerous pathological aspects of SCD can have a negative impact on neurological function; these range from passive yet insidious chronic hypoxia or "silent stroke" to the most detrimental overt stroke (Steen, Miles, et al., 2003). The corrupted ability of erythrocytes to deliver oxygen properly to tissues results in impairment or death of those tissues through catastrophic or through more insidious processes. Deoxygenization of erythrocytes as a result of the sickling process deprives body tissues of required oxygen slowly but persistently. When cells lack adequate oxygen, there is a buildup of toxins that ultimately leads to cell death. Regardless of the methods by which it occurs, neurological impairment in SCD is a serious complication.

Occlusion/Sludging

When deoxygenated erythrocytes become polymerized and deformed, they tend to adhere to each other as well as to the endothelial cells of the vessel walls. Sickled cells that bind to the vessel walls can result in the thickening of the walls and narrowing of the vessel diameter, which reduces flow volume and increases velocity. The larger arteries are more often involved in this narrowing process. Vessels can also become increasingly clogged over time with sickled cells, and blood movement around the blockage is slowed—a circumstance called "sludging." Occasionally, the blockage becomes so large that blood flow is completely obstructed. Although the smallest occlusions may not be evident, multiple or re-

current blockages within a restricted space can have as neurolgically devastating an impact as a catastrophic stroke. Sludging creates slow-moving cells that are unable to deliver oxygen at an appropriate rate, leading to chronic hypoxia in surrounding tissues, with cellular damage resulting from acidosis and ischemic necrosis. Cerebral oximetry on patients with SCD has documented low cerebral oxygen saturation levels, with obvious links to chronic hypoxia (Nahavandi, Tavakkoli, Hasan, Wyche, & Castro, 2004). Sludging and occlusion result in pain and organ damage throughout the body's periphery, and neurological damage in the brain. The small occlusions and sludging may not be immediately symptomatic, but they are probably associated with longer-term neurological and neuropsychological effects as a result of insidious neural damage. Research findings have confirmed the association of the diffuse brain injury resulting from chronic hypoxia with neurocognitive impairment (Steen, Miles, et al., 2003).

Hypoperfusion

Another risk factor for neurological complications is cerebral hypoperfusion. This occurs when pressure in arterial border regions (the so-called "watershed" regions) is reduced by blockages in preceding larger vessels; slow blood velocity causes seepage into the watershed regions. Large arteries are not as easily blocked with cells, but can be affected by a thrombus of erythrocytes, platelets, and fibrin (an insoluble protein important in clotting). Most frequently affected are the internal carotid and middle cerebral arteries; the anterior cerebral and basilar arteries are also commonly affected (Ohene-Frempong, 1991). The internal carotid artery supplies the anterior portion of the brain, with main branches serving most of the cortex. The middle cerebral artery supplies the lateral cortex; while the anterior cerebral artery supplies the medial/frontal and medial cortices; and the basilar artery supplies the brain stem and cerebellum. Consequently, it is apparent that disruptions in the flow of these main arteries have a negative impact on major areas of brain function.

Stroke

One of the most traumatic risk factors for neurological problems in SCD is the occurrence of stroke in the brain—a spontaneous and disastrous event. There are two types of stroke, infarction and hemorrhage, with infarction being far more common. Infarction results from an obstruction or occlusion of a blood vessel that leads to diminished or absent blood flow. The brain structures supplied by that artery become deprived of oxygen, leading to ischemic necrosis and resulting brain damage. Hemorrhage occurs when a blood vessel ruptures or when blood leaks out of the watershed regions, critically damaging surrounding cells. Hemorrhage, edema, and displacement or compression of tissues can be neurologically traumatic or even fatal.

Vaso-occlusive strokes in SCD are more common in children than adults, and obviously a number of adults with SCD have experienced at least one stroke in childhood. The median age for stroke in patients with SCD is 5 years (Cohen, Martin, & Silber, 1992; Ohene-Frempong et al., 1998; Wethers, 2000), and approximately 10% of patients with SCD experience stroke by age 20 (Ris & Taylor, 2000). Occlusive stroke will often compromise surrounding circulation, and weaken vessel walls secondary to increased pressure of blood flow. Weaker vessels increase the chances of aneurysm and rupture, and the risk of stroke is higher in patients who have experienced previous strokes. Of those

who experience a stroke, about 70% will have a recurrent stroke, usually within about 36 months.

About 20% of patients will evidence abnormal signals on magnetic resonance imaging (MRI) that suggest previous damage, probably attributable to "silent strokes." Silent strokes are small lesions in white matter that are typically associated with neurocognitive and neurobehavioral dysfunction rather than with gross neurological pathology. There do appear to be some differences in the incidence of silent strokes based on geography, with some populations evidencing higher occurrence in childhood, and others in adulthood (Marouf, Gupta, Haider, & Adekile, 2003). They are presumed to occur as a result of watershed seepage and ischemic damage. Because silent strokes are not obvious in a physical examination, the symptoms can only be assessed through MRI and neuropsychological evaluation. Silent strokes tend to recur, with consequent cumulative damage (Briscoe, 2001) increasing the neuropsychological dysfunction and having a strong association with reduced general intellectual functioning (Schatz, Craft, Pascual, Hsu, & DeBaun, 2002). In elderly patients, they tend to be associated with increased dementia and cognitive deterioration (Vermeer et al., 2003), while there is also evidence of cognitive decline in otherwise healthy adults (Maeshima et al., 2002). Advances in the sensitivity of newer imaging technology have revealed the prevalence of silent strokes in patients with SCD to be as high as 35–38% (Steen, Emudianughe, et al., 2003; Zafeiriou et al., 2004); these findings have led to the presumption that subtle neurological and neuropsychological issues are likely to be more common than previously understood. However, Zafeiriou and colleagues (2004) did not find concurrent intellectual dysfunction, suggesting that some patients with silent strokes may not evidence cognitive changes.

It is impossible to definitively ascertain the patients who will experience stroke. However, certain aspects of SCD seem to be associated with higher risk, such as low hemoglobin, higher white blood cell count, high blood flow velocity, cerebrovascular disease (e.g., Moyamoya syndrome), frequent acute chest syndrome, and history of transient ischemic attacks. For reasons that are not entirely clear but may relate to age-dependent changes in cerebral blood flow, adults appear to have a greater risk for hemorrhagic stroke, whereas children are at greater risk for ischemic infarction (Pavlakis, Prohovnik, Piomelli, & Devivo, 1989). Regardless of age, high blood flow velocity in particular has been repeatedly found to be associated with a higher probability of stroke (Adams et al., 1992; DeBaun, Glauser, Siegel, Borders, & Lee, 1995). Blood flow rates read by transcranial Doppler ultrasonography are more predictive of stroke risk in younger patients (under 16) than for adults. Unfortunately, the configuration of the brain and the thickness of skull bones make detection of flow rate more difficult in adults, and less predictive of those at risk.

GENERAL NEUROPSYCHOLOGICAL CONSEQUENCES

Reorganization

During the process of brain development, neurons are creating trillions of synaptic connections. Connections that are used frequently are maintained, while unused connections are eliminated. Although there are critical periods of development when specific functions are actively being innervated, fine-tuning of this system occurs throughout life. When established pathways are damaged, the brain does have the ability to recover, even after a critical period of development. Damaged neurons have the capacity to reorganize synaptic connections and develop alternative pathways for specific function and processing (Flor et al., 1995; Weiller, Chollet, Friston, Wise, & Frackowiak, 1992). So the brain continu-

ally adapts to changes in signal input. Functional cortical reorganization can often limit disability following an initial injury, as novel connections are made to continue to transmit information through a new route. As that new pathway is used more frequently, the new connections strengthen, and recovery of function is apparent. However, the greater the area of damage, the more reorganization is needed for adequate recovery of function.

Despite the functional sufficiency of reorganization, higher levels of it introduce the possibility for less adept or inappropriate pathways to develop. Although the brain recovers function by circumventing part of a previously established pathway—essentially, finding a new process for an old behavior—the new process may not be as effective or efficient (Boiler, 2004). Some recovery happens spontaneously following injury, but structural reorganization takes more time, and this explains the slower restoration of the most complex functions. Given the billions of synaptic connections to and from a single neuron, exact reproduction is impossible. Previously organized networks of connections are so complex that they cannot be completely recreated, and the new network of interconnections becomes less orderly or complete. Therefore, recovery of function (whether cognitive, behavioral, or psychological) is not an exact science, and the individual is often performing compensatory skills to adapt to a ew level of ability.

The adult brain has already established pathways for specific abilities, and injury to those pathways requires compensation for an already established behavior. However, a young brain may experience injury prior to the time a skill is developmentally acquired, which means that some skills must then be learned by a system that has been reorganized, often many times over. Consequently, the proficiency and efficacy of such skills become increasingly compromised. As the child develops, he or she attempts to apply these inadequately learned skills to increasingly complicated situations in adolescence and adulthood. If a brain that has been repeatedly reorganized as a consequence of stroke, recurrent stroke, silent stroke, or chronic hypoxia has difficulty acquiring a novel skill, it is likely to have difficulty applying that poorly developed skill in functional daily life, particularly as more advanced developmental situations demand an increased level of complexity. Adulthood then becomes compromised by the neural reorganization that affected learning and development during childhood.

Developmental Compromise/Regression

The most obvious and early neurological symptoms of large-artery occlusion are disruption of motor, sensory, or language function. Longer-term neuropsychological symptoms in cognitive functioning, learning, or neurobehavioral challenges can be more subtle and lifelong. Given the significant neuropsychological issues identified and widely researched for children with SCD, it is likely that adults will express similar difficulties at a developmentally novel level. However, the available research remains primarily focused on children. Disruption of key developmental milestones in childhood is known to have long-term impacts on adult functioning, even in the absence of other pathology. A predominant consequence of disrupted childhood learning will relate to adaptive functioning in years to come. Disturbance of developmental stages clearly has an impact on the ability to manage future cognitive and behavioral challenges successfully. So, if the findings of disrupted neuropsychological functioning in children with SCD are valid, do these impairments continue to be evident or impact the ability to function as an adult? As a result of the paucity of adult literature, generalizations from the child literature must be made at present, although the hope is that more empirical evidence will be identified in the future.

When patients are reevaluated over time, children and young adults can evidence signs of "developmental regression," meaning that they fail to maintain the same rate of developmental progress as their peers do. This is most easily identified when raw scores continue to increase while standardized scores decrease over time. Essentially, although development and learning continue, the individual falls off pace compared to his or her cohort. This is not merely slow development; the actual capacity to acquire skills may have been disrupted. The unanswered question is whether these individuals ever "catch up" (which would be anticipated in slow development), or whether developmental regression persists over time and has a negative impact on final skill acquisition or presentation. Children who have experienced stroke have a higher incidence of intellectual dysfunction, which would suggest that adults who experienced stroke as children have a greater probability of having developmental impairment.

"True regression" is obvious in the loss of skills over time, and in the deterioration of both standard and raw scores on neuropsychological examination. Because patients who have had a stroke are more likely to experience a second stroke, they are also at increased risk of true regression in function after multiple injuries. The ability of neurological tissue to recuperate is reduced when injury recurs. Repeated injury demands more and more reconstruction of disrupted pathways, leading to increasing disorganization and loss of effective or efficient function. Given the knowledge of neural reorganization and the chronic or repeated neurological injury associated with SCD (especially SCA), it is likely that adult neurocognitive functioning is compromised by interference early in development.

Although only limited research is available, some studies have indicated compromised adult neuropsychological functioning in patients with SCD. Even in the absence of overt strokes, adult patients have evidenced weaker time-based performance on attention and construction tasks (Sano, Haggerty, Kugler, & Martin, 1996); weaker performance has also been found on tests of executive functions, including planning, organization, problem solving, interference, dual tasking, and fluency (Stowe, 1996).

SPECIFIC EFFECTS ON FUNCTIONING

Neuropsychological Impacts

Given the myriad of neurological events that can impair the cognitive, behavioral, and emotional functioning of patients with SCD/SCA, it is not realistic to claim a single or even typical neuropsychological profile for such patients. The diversity and severity of symptoms are both extensive and individually unique. Because the pathology of SCD is not specific to brain structures, it is unlikely that a typical "pattern" of neuropsychological deficits will be identified. There is, however, a growing body of research suggesting that certain structures may be at greater risk of neuropsychological compromise, due to various aspects of the disease that may increase the level of risk within areas known to be sensitive to such pathology (e.g., chronic hypoxia and negative effects on temporal lobe function). There are a few data indicating no specific neuropsychological impairments compared to controls (Martin-Jackson, Gentry, & Dancer, 2000), and suggesting that identified deficits are more time-limited (Catania, 2001) and decrease with recovery. However, the vast majority of published research does indicate that aspects of SCD/SCA such as hypoxia, stroke, silent stroke, and ischemia are associated with neuropsychological compromise, even in patients without manifest complications.

The obvious impairments that result from clinical stroke are not difficult to identify on imaging or neuropsychological testing, but the more subtle symptoms apparent in patients with SCD/SCA but without overt stroke are notable. Overt stroke is much more physi-

cally devastating and specific, so consequent problems are more easily identified. Silent stroke is subtle and covert, and its results are harder to isolate. Kral, Brown, and Hynd (2001) found that lower levels of intellectual performance, language/verbal function, visual–motor and visual–spatial function, memory, academic achievement, and auditory processing were more closely associated with obvious stroke, whereas problems with attention/concentration, executive function, and visual–motor speed and coordination were more closely associated with silent stroke. Some patients with any disease in the SCD spectrum also evidence neuropsychological symptoms, even in the absence of obvious clinical or radiological findings (Sano et al., 1996; Steen, Emudianughe, et al., 2003). The available pediatric literature does suggest that a majority of patients with silent strokes have more abnormality than may be obvious or appreciated. Schatz, Craft, and colleagues (2002) found that 80% of patients with silent strokes had clinically significant cognitive deficits on neuropsychological examination, while 35% evidenced academic skill deficits. Significantly lower scores on tests of verbal abilities, attention/memory, and general functioning have been found for patients with SCD but no evidence of overt stroke (Noll et al., 2001). Bernaudin and colleagues (2000) found Performance IQ and Full Scale IQ scores to be significantly lower in patients with SCD and a history of strokes and silent strokes. The patients with silent strokes had lower specific language-based intellectual abilities. However, lower functioning was only associated with low hematocrit and hydroxyurea; this finding suggests that silent stroke alone may not necessarily be the sole factor in cognitive deficits, but when associated with low hematocrit, it is.

General Intellectual Functioning

Although the specific mechanism has not yet been identified, patients with SCD have commonly been identified as scoring lower on measures of general intellectual functioning (Bernaudin et al., 2000; Kral et al., 2001; Schatz, Finke, Kellett, & Kramer, 2002; Stith, 1997; Watkins et al., 1998). Not surprising are the findings that patients who have experienced stroke tend to have lower levels of general intellectual functioning, with more specific deficits identifiable (Ashley-Koch, Murphy, Khoury, & Boyle, 2001; Bernaudin et al., 2000; Brown et al., 2000; Catania, 2001; Davis et al., 1997; Fernando, 1997; Kral et al., 2001; Nabors & Freymuth, 2002; Sanders et al., 1997; Schatz, 1997; Schatz, Brown, Koby, & DeBaun, 2000; Schatz et al., 1999; Stith, 1997; Watkins et al., 1998). Patients with stroke have also been found to have lower functioning than sibling controls (Watkins et al., 1998), suggesting that major dysfunction may be specific to disease and not necessarily attributable to other environmental factors. However, even in the absence of neurological damage, there has been evidence of patients' evidencing lower intellectual functioning (Schatz, Finke, Kellett, & Kramer, 2002; Steen, Miles, et al., 2003). This suggests that other aspects of the disease, issues related to chronic illness in childhood, environmental factors associated with the disease, or something else may have an impact on general neurocognitive function. Whereas focal injury is easily associated with neuropsychological dysfunction, diffuse injury clearly has a relationship to overall intellectual impairment. Recurrent silent infarcts are associated with declining intellectual function, due to the fact that neurological tissue reduces its ability to recover from repeated injury.

Executive Functioning

The frontal region of the brain is an intricate network of interconnected cognitive functions that may arguably be the most "human" of our cognitive abilities. Although these functions are diverse, the frontal lobes generally support higher intellectual skills, together

with what are known as "executive" skills—the abilities to coordinate and oversee other, more specified skills. Abilities under the executive management of the frontal lobes include fine motor coordination and praxis, expressive language, divergent thought, planning and problem solving, abstracting, inductive reasoning, self-regulation, social behavior, olfaction, attentional regulation, spatial orientation, organization and working memory, affective behavior, and organization of personality. In the pediatric literature, patients with silent strokes have repeatedly been found to evidence weaker executive functioning, suggesting that the frontal region may be more sensitive to the pathophysiology of SCD (Brown et al., 2000; DeBaun et al., 1998; Kral et al., 2001; Nabors & Freymuth, 2002; Noll et al., 2001; Schatz, Finke, et al., 2002; Watkins et al., 1998). Rarely do patients with frontal lobe damage evidence a single area of impairment, and patients with silent strokes tend to have more generalized frontal deficits, suggesting compromise of central executive functions. Watkins and colleagues (1998) found executive functions weakest in those with overt strokes, slightly stronger abilities in those with silent strokes, and the most effective skills in sibling controls and other nondisabled controls. Patients with strokes tend to evidence weaker working memory functioning for verbal and nonverbal information (Salorio, 2001), which may be a result of organizational as well as attentional dysfunction. Impaired attentional skills are common neuropsychological findings in patients with silent strokes (DeBaun et al., 1998; Kral et al., 2001; Nabors & Freymuth, 2002; Schatz et al., 1999; Stith, 1997). Specific attentional impairments have been linked to contralateral parietal, midfrontal gyrus, and basal ganglia abnormalities (Schatz, Finke, et al., 2002). Even specifically within the population of children with SCD, those with overt and silent strokes tend to evidence weaker attention and concentration abilities (Brown et al., 2000). Specific contralateral parietal and midfrontal gyrus lesions have been associated with difficulty in disengaging attention, with basal ganglia injury associated with less facilitation of attention (Schatz et al., 1999). Difficulties with self-regulation and the ability to screen out interfering information are likely to be associated with attentional and speed-of-processing impairments in this population (Salorio, 2001). There has been some evidence of support for the cerebellar–executive relationship (Schmahmann & Sherman, 1998) in findings that patients with cerebellar infarction may be at increased risk for difficulties in working memory, short-term recall of complex information, and cognitive flexibility (Malm et al., 1998).

One study has indicated that adult patients with SCD demonstrated clinically significant performance deficits in executive measures, compared to matched controls (Stowe, 1996). As the most advanced area of the brain, the frontal lobes are particularly critical to successful adult functioning. Frontal lobe compromise during childhood places patients at increased risk of difficulty academically and socially, with implications of impairment in adult relationships, ability to complete advanced degrees, independent functioning, and occupational success.

Nonverbal Functioning

Right-hemisphere functions are typically associated with non-language-based abilities. A number of studies have found a variety of right-hemisphere deficits in patients with SCD/SCA, which may suggest some specific vulnerability. Research on recovery from traumatic brain injury suggests that widespread injury is associated with poorer recovery of the right-hemisphere functions, whereas less severe injury results in more restricted loss of function (Schatz, 1997). This might suggest that patients with SCD/SCA, more overt strokes, and larger areas of ischemia or hemorrhage would be at higher risk of right-hemisphere dys-

function, and some research does suggest that patients with strokes evidence more neuropsychological difficulties associated with right-hemisphere abilities. Widespread cerebral infarcts have been linked with specific spatial deficits, suggesting global right-hemisphere pathology after injury (Schatz et al. 1999). More difficulties in visual–spatial functioning were found in patients with SCA and strokes than in patients without strokes and healthy controls, whereas visual constructional and visual memory abilities evidenced no significant differences (Brinson, 1999). But other research has indicated that spatial memory skills may be at risk for impairment in patients with SCD, due to the fact that systems for verbal and nonverbal working memory fail to develop independently (Salorio, 2001). More specific impairments in visual–motor and visual–spatial function have been associated with overt strokes, while visual–motor speed and coordination deficits were associated with silent strokes (Armstrong et al., 1996; Kral et al., 2001). Schatz and colleagues (2000) found that anterior insults were associated with problems in visual orientation. Recent strokes have been more related to problems in attention/concentration, intellectual performance, and visual perceptual skills (Catania, 2001).

Verbal Skills

Once again, since research on the verbal skills of patients with SCD has been predominantly conducted on children, implications from the child literature must be applied to adults. Predictably, children who struggle with language skills will encounter more academic difficulties, and are likely to have lower levels of academic success and occupational opportunities upon graduation. In addition, difficulties in language are often associated with poor social skills, potentially further reducing abilities in academics and certain skilled or professional occupations.

Language skills are commonly affected in individuals with SCD, whether or not obvious neurological insult has occurred. The findings of lowered intellectual functioning and reduced language-based academic functioning suggests that a core language impairment may exist merely as part of the disease itself. Stroke alone has been linked with difficulties in general verbal intelligence, auditory processing, language functioning, and comprehension of instruction (Davis et al., 1997; Kral et al., 2001); silent stroke has been associated with more specific deficits in vocabulary, verbal comprehension, and verbal abstraction (Bernaudin et al., 2000). White, Salorio, Schatz, and DeBaun (2000) found more specific language impairments related to working memory, with anterior stroke location associated with weaker working memory of more complex vocabulary.

Psychosocial Functioning and Its Cumulative Impact in Adulthood

As a result of specific neuropsychological difficulties and lowered intellectual functioning in general, academic and social abilities are likely targets for dysfunction. Difficulties with social information processing, such as interpreting subtle verbal and nonverbal cues, may place patients with SCD at greater risk of difficulties with social interaction (Boni, Brown, Davis, Hsu, & Hopkins, 2001). Developmentally, the subtle social difficulties present in early childhood become greater liabilities in adolescence and adulthood, when expectations of behavior are more stringent and less forgiving. The abstruse deficits associated with SCD may have a cumulative impact on development, with behavioral challenges and internalizing symptoms prevailing in adolescence and young adulthood (Brown, Armstrong, & Eckman, 1993; Brown, Kaslow, et al., 1993).

Depression and anxiety are the most common psychological complications of chronic illnesses, but they are not fully appreciated as psychological sequelae of SCD. Depressive and anxiety symptoms in patients with SCD have been found to be as high as 63% (Udofia & Oseikhuemen, 1996). In general, psychiatric disorders in patients with SCD have been associated with treatment dropout rates, social impairments, neurocognitive dysfunction, and previous psychiatric diagnoses (Hilton, Osborn, Knight, Singhal, & Serjeant, 1997). Interestingly, the same study found a relationship between psychiatric disorders and male patients with lower body mass index, bringing up the possibility of an association between depression and social implications of the disease. In SCD, the demands for the production of erythrocytes are in direct competition with the demands of the child's growing body. Children with SCD often have delayed growth and achieve puberty later than their peers. By early adulthood, height can catch up, while weight may lag behind. The slower growth and delayed pubescence have a psychosocial impact on children with SCD; the risks include difficulties in maturity, social interaction, self-esteem, behavior, dating, and even occupational opportunities. The impact of unrecognized or underappreciated psychiatric symptoms in patients with SCD may be large, particularly in issues of compliance, pain management, transition of services, and use of health care services.

Academic Functioning and Its Cumulative Impact in Adulthood

Patients with SCD have shown an increased risk of academic problems, although research is certainly not consistent. Patients with strokes have been shown to evidence more academic difficulties in general (Fernando, 1997), with findings of lower reading (Ris & Grueneich, 2000; Sanders et al., 1997) and writing (Sanders et al., 1997) abilities; patients with silent strokes have also been shown to have lower arithmetic abilities than nonaffected patients with SCD (Armstrong et al., 2001). In addition to neurocognitive changes, various indirect effects of SCD—such as frequent absenteeism, difficulties in psychological functioning, and struggling with pain management—can have a negative impact on school performance (Bonner, Gustafson, Schumacher, & Thompson, 1999). If academic performance is affected in childhood, the result in adulthood may be fewer opportunities for advancement and lower-paying occupations due to limitations in education.

TREATMENT

Because SCD is a chronic condition, patients require consistent treatment and follow-up care, even when they are not having specific complications such as a sickling crisis or stroke. Typical medical care of SCD is generally focused on symptomatic intervention (treatment for pain episodes, priapism, acute chest syndrome, or stroke; antibiotics for infection; psychotherapy for psychosocial issues related to the disease). However, there are treatments that can prevent symptoms (e.g., chronic transfusion, hydroxyurea) or even cure the disease (bone marrow transplantation, or BMT).

Those patients who have experienced a stroke have a 50% risk of recurrence unless provided with intervention. Chronic exchange blood transfusion is often prescribed for a number of years following a stroke to dilute the volume of sickled erythrocytes in whole blood, and to maintain HbS at less than 30% (Hurlet-Jensen, Prohovnik, Pavlakis, & Piomelli, 1994; Pegelow et al., 1995), thereby reducing the risk of another stroke. Patients with higher blood flow velocity rates are often preventatively treated with chronic trans-

fusion therapy in childhood, and it is often indicated for those who have already experienced strokes. Chronic transfusion does reduce the rate of stroke recurrence and may prevent neural damage by improving perfusion and oxygenation to brain tissue. There is some evidence suggesting that the use of chronic transfusion therapy has reduced the incidence rate of first strokes in children by almost 75% (Fullerton, Adams, Zhao, & Johnston, 2004), with clear implications for improved neurological functioning in adulthood. Although the use of transfusion therapy can be life-saving, it can also have serious complications, such as iron overload and need for chelation therapy, alloimmunization, delayed transfusions reactions, and viral infections. The cost of such intervention, as well as the possibility of poor compliance with monthly transfusions, makes it less realistic for some patients. In addition, because of multiple complications regarding transition from pediatric to adult services, patients placed on chronic transfusion sometimes do not continue treatment into their adult years. Unfortunately, it has not yet been clearly determined when it is safe to discontinue chronic transfusion therapy. Wang and colleagues (1991) found that half the patients they studied experienced an ischemic event within 12 months after ending transfusion therapy. However, some research has indicated that the risk of recurrent stroke ma not increase following discontinuation (Rana, Houston, & Surana, 1997). Research is ongoing in many centers to address the questions regarding appropriate times to end therapy while minimizing risk to the patient, as well as cost–benefit analyses.

Alternatives to chronic transfusion therapy are being explored and developed. Agents that inhibit sickling, such as MX-1520 (vanillin) (Zhang et al., 2004) or beta AS3-globin (Levasseur et al., 2004), are being explored. Other agents that improve oxygen binding are also being used. Children with SCD do not typically evidence symptoms of the disease until later in infancy, due to the natural presence of fetal hemoglobin (hemoglobin F)—a protective hemoglobin predominantly present *in utero* that is highly effective in tightly binding oxygen crossing the placenta, but that ceases to be produced at about 6 months of age. A newer chemotherapeutic agent, known as hydroxyurea, is used prophylactically in patients with SCA to stimulate the production of hemoglobin F. Adults who are prescribed hydroxyurea have reported significantly fewer pain episodes, hospitalizations, and blood transfusions, and seem to have a reduced risk of mortality (Steinberg et al., 2003). Reduction of sickling crises in the brain is potentially associated with fewer negative neurological events.

BMT and stem cell transplantation (SCT) for SCD have also been attempted with some success in children (Walters et al., 1996), and the possibilities of such treatment for adults are being explored (Chakrabarti & Bareford, 2004). In BMT/SCT, a patient's own bone marrow is ablated through chemotherapeutic drugs and/or radiation, and replaced with a donor's marrow (in BMT) or stem cells (in SCT). Once the new marrow begins functioning independently, the patient is free from the disease. However, the risks associated with BMT/SCT quite often outweigh the potential benefits. The preparative regimen for these procedures is extremely toxic and dangerous, and the potential for posttransplant complications is significant (e.g., graft-vs.-host disease, organ failure, etc.). The availability of a suitable donor is often limited, particularly for minority populations. Patients themselves must be suitable candidates for transplantation, and there is a higher mortality rate (approximately 10%) as a result of the procedure, which increases with age.

As any change in life situation can be, moving from pediatric to adult care when one is living with a chronic illness can be quite challenging. Patients proceed from the role of receiving care to being required to be active participants in and directors of their own care. In addition, the natural advocates for a child, the parents, no longer play an active role in adult care and leave a patient to function independently. Patients whose

medical, psychological, or behavioral care was more complicated in childhood are more likely to continue to require intricate and complex intervention as they move into adulthood, yet are less likely to make this transition smoothly. Moreover, adolescent and adult issues in SCD add to the complexity. These issues include delayed pubescence and growth; family planning and pregnancy; and issues related to potential conflicts between independence and work on the one hand and aspects of the disease (e.g., pain crises) on the other. Some patients simply are neither cognitively able nor psychologically prepared to take on the overabundance of new responsibilities involved in adult care (e.g., appointments, medication schedules, integration of care providers, etc.). Neurocognitive impairments in self-regulation, organization, planning, and problem solving may also interfere with the ability of an adult patient to engage in appropriate self-care. Finally, there is a grieving process when a patient leaves the pediatric care providers who have been a critical part of the patient's life and development. Many patients struggle to leave the people whom they have grown up trusting and respecting for a new system of care providers and styles. When there is no appropriate support for making the transition to adult care effectively, many patients are lost to follow-up. Determining the proper time and pace for transition is essential, as some patients will be ready at differing ages and stages of their disease, and no patient wants to be rapidly shifted from one provider to another. Strong communication between the adult and pediatric services, and among the multidisciplinary care poviders, will help to ease the burden of medical complexity. Successful transition should optimally provide peer-led training and education/outreach programs that support adolescents in moving into adult services; such programs are likely to improve compliance and responsibility (Telfair, Ehiri, Loosier, & Baskin, 2004).

Patients (and family members) who are more active in using positive cognitive and behavioral coping strategies require less medical intervention, have more functional daily lives, and have stronger psychological health and adjustment (Fletcher, 2000; Gil et al., 1996; Gil, Williams, Thompson, & Kinney, 1991). In addition, patients who learn and apply coping strategies seem to continue to do so over time, and this results in fewer medical contacts (Gil et al., 2000, 2004). Patients who are capable of managing daily stressors report less pain and have fewer missed workdays; the ability to maintain a positive mood is a stronger predictor of coping than pain experience alone is (Gil et al., 2004). Although no studies have yet looked at adult coping style based on that which was learned and applied in childhood, it is tempting to predict that children who cope well with their disease, and whose family members support the children in coping, will become adults who also cope well.

Adults with SCD must face numerous issues in regard to family planning. Issues related to contraception (e.g., while on hydroxyurea), potential pregnancy complications, and parenting a child who may have SCD should be considered and discussed early. Because the risk of full-blown SCA is present only when two people carrying HbSA procreate, genetic counseling for those who are carrying the trait is often recommended to allow for informed decision making, but fears exist regarding discrimination in the workplace or by insurance carriers. Early diagnosis can allow for prompt or preventative interventions (e.g., vaccination, antibiotics) and even for anticipation of triggering situations (e.g., dehydration, hypoxia), all of which can improve the general prognosis for patients. Prenatal diagnosis is available, but it is unable to distinguish mild from severe cases and makes decision making for an expectant woman or couple difficult. Newborn screening for SCD is required in most but not all states, and lack of early detection may place a child's life at risk. Possible complications for children under age 1 who have not been screened include sepsis, bone or kidney damage, or delayed growth, and there is a 10% mortality rate for

undiagnosed infants. In addition, once a patient with SCD becomes a parent, all the issues surrounding the adult's own experience of the disease (whether positive or negative) now become part of his or her parenting experience, even if the child does not have the disease or trait. Clearly, if the child does have the trait or disease, the parent must now shift his or her role from one of patient to that of patient *and* parent of an ill child. If the parent with SCD had neurobehavioral or neurocognitive challenges as a child, these are likely to play a role in parenting and managing the child's illness. Well-educated and psychologically stable parents can be the motivating force behind children who cope well with their own chronic disease.

PROGNOSIS/CONCLUSION

Although survival into adulthood for patients with SCD used to be relatively uncommon, it is now a more predominant expectation, due to improved and more aggressive intervention. With early identification and appropriate management, more than half of patients with SCA live into their 40s and 50s. Patients who have more severe disease (e.g., frequent crises, recurrent strokes), or who have less ideal management of the illness, are more likely to have shorter lifespans. The predominant causes of death are organ failure (primarily renal), acute chest syndrome, seizure, stroke, low hemoglobin F, and infection (Platt et al., 1994). With more patients living longer, there is an increased incidence of patients requiring intervention for unrelated medical issues and challenging other groups of medical practitioners (e.g., obstetricians, anesthesiologists, or surgeons) who must consider SCD in their interventions.

The prognosis for a patient with SCD will continue to improve with better research and understanding of the disease, which will improve control and treatment. More knowledgeable and available medical care creates improved access to care for patients with the disease, as well as improved community awareness. Improved community support means better academic and occupational accommodations so that patients can lead more independent lives. Yetunde and Anyaegbu (2001) concluded that stronger levels of education, early presentation, and good access to medical treatment are strong predictors of longer lifespans. However, important additional factors included a stable and nonstressed lifestyle and family support. McKellop (2001) noted major long-term health-related outcomes for patients with SCD, such as having poorer overall health, being more frequently hospitalized, and missing more days of school and work. However, McKellop also found a surprising level of resiliency in psychological issues. So, although patients may be more medically compromised, many appear to have some strong psychological strategies for coping with this chronic illness. With documentation that patients with better coping strategies need less medical intervention and attend work more consistently (Gil et al., 2000, 2004), appropriate and available psychosocial support of adult patients is likely to contribute to better overall outcome.

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18

DOWN SYNDROME

HEATHER CODY HAZLETT

Down syndrome (DS) was named after the physician John Langdon Down, who first published a description of individuals with this syndrome in 1866. It is the most common genetic cause of mental retardation, and the characteristic physical features associated with it make it fairly easy to identify. In the United States, prevalence rates are reported to be approximately 1 per 800 live births, and an estimated 7,000 babies are born each year with DS (Nadel, 1999). Slight gender differences are evident, in that males commonly outnumber females (the sex ratio is 1.3:1); this may be due to a higher mortality rate in females during infancy (Carr, 1995). Diagnosis of DS is typically made at birth (35%) or within the first 2 years of life (46%), although in some cases a diagnosis has been made after the third year (Quine & Rutter, 1994).

GENETIC AND FAMILIAL ISSUES RELATED TO ETIOLOGY

DS has been traced to malformations in the genes and is diagnosed by clinical exam and karyotype. There are actually several different types of DS, with the most prevalent being trisomy 21 (94%), in which there is actually a third chromosome 21 rather than the normal two (Prescott, 1988). Specific genetic anomalies have also been found on chromosome 21, particularly on band q22. Specific regions of chromosome 21 have been mapped and are associated with the various features of DS. At present, approximately 25–40 genes have been mapped to chromosome 21 through techniques such as gene linkage. This is one reason for the wide range of individual variation found in the population with DS (Korenberg, Pulst, & Gerwehr, 1992). Other forms of the genetic phenotype of DS are translocation, mosaicism, and partial trisomy 21 (Coleman, 1988; Pueschel, 1992a). Translocation 21 results when one part of chromosome 21 has been transferred to a different location. Mosaicism occurs when not all of the body's cells display the chromosomal trisomy; some research suggests that mosaicism results in higher mean cognitive scores.

Relative risk for giving birth to a child with DS is approximately 1%, plus the amount of risk associated with the mother's age during pregnancy. The risk for having a child with DS increases exponentially with the maternal age. For example, a 20-year-old mother has a 1 in 1,923 chance of giving birth to an infant with DS, whereas the chance for a 49-year-

old mother is 1 in 12 (Prescott, 1988). Procedures such as amniocentesis and chorionic villi sampling can be used to screen for DS. The etiology behind the maternal age effect has not yet been determined, although it appears to be related to an increase in trisomy at conception rather than a decrease in the ability to abort a trisomic fetus naturally (Hassold, Sherman, & Hunt, 1995). Screening in pregnant women over the age of 35, who are felt to be at greater risk for giving birth to a child with DS, has led to higher rates of identification during pregnancy.

The phenotype of individuals with DS is heterogeneous, but certain characteristics are frequently associated with this syndrome. The typical physical features, medical complications, and cognitive and behavioral problems are described below, and examples are briefly provided in Table 18.1.

PHYSICAL FEATURES

In addition to mental retardation, a number of distinctive physical characteristics are observed in individuals with DS. These may include brachycephaly (broad head), a delay in the closure of the fontanels, hypoplasia of the midfacial bones, obliquely placed palpebral fissures, epicanthal folds, depressed nasal bridge, hyper- or hypotelorism, Brushfield spots (white spots on the periphery of the iris), an overlapping or folding of the helix of the ear, thickened lips, tongue protrusion and/or fissured tongue with increasing age, short and broad neck, umbilical hernias, broad and stubby hands and feet, a single palmar transverse crease, partial or complete syndactyly, and a wide space between the first and second toes (Pueschel, 1992a). In a systematic examination of craniofacial features of adolescents and adults with DS, most of the facial dimensions measured in the group with DS were smaller than those in controls (Ferrario, Dellavia, Zanotti, & Sforza, 2004). Not only did the individuals with DS have smaller features, but their faces were more narrow, less deep, and shorter. Certain physical features have been found to change over time. For example, the epicanthal folds and large neck may become less noticeable with age, while other features (e.g., a fissured tongue and dental problems) become more problematic with increasing age (Pueschel, 1992a).

Neurobiology

During fetal development of the central nervous system in DS, errors in neurodevelopment occur and result in brain abnormalities. These anomalies include a reduction in the total number of neurons throughout several cortical areas, abnormalities within the neurons themselves, and abnormalities in the ability of the neurons to communicate with each other (Florez, 1992). Although brain weight at birth is close to normal, over time brain weight estimates tend to fall in the below-average range. This condition may be related to a reduction in the neuronal density in cortical areas and decreased dendritic arborization (Florez, 1992). The most affected area of the brain, however, is the cerebral cortex, where the reduction in the number of neurons, existence of dendritic spines, and poor synaptic connections contribute to difficulties in cognitive and learning processes (e.g., attention, information processing, integration, short- and long-term memory, and language skills) (Florez, 1992).

At autopsy, neuropathology studies have found decreased brain weight, decreased cerebellum, small frontal and temporal lobes, and atypical cortical surface features, including the superior temporal gyrus (Becker, Mito, Takashima, & Onodera, 1991; Coyle, Oster-Granite, & Gearhart, 1986; Wisniewski, 1990). A few magnetic resonance imaging

TABLE 18.1. Associated Characteristics in Individuals with DS

Physical features	Medical complications	Cognitive and behavioral characteristics
Brachycephaly	Opthalmological problems	Mental retardation
Epicanthal folds	Abnormal dentition	Language problems
Depressed, wide nasal bridge	Peridontal disease	Impaired speech
Folding of the ear	Cardiac defects	Verbal memory deficits
Thickened lips	Sleep apnea	Slow processing speed
Fissured tongue	Leukemia	Depression
Short broad neck	Gastrointestinal problems	Mood disturbance
Broad hands and feet	Neuromuscular abnormalities	Oppositional behaviors
Single palmar crease	Neuropathological findings	Attention problems
Widely spaced toes (first and second)	Seizures	Impulsivity
	Hypothyroidism	Insecurity
	Hypotonia	Low self-esteem

(MRI) studies, many conducted with small sample sizes or coarse imaging parameters, have supported these autopsy findings. Decreased brain volume in children and adults, and reductions in cerebellum, brain stem structures, frontal lobe, and hippocampus, have been reported (Aylward, Habbak, et al., 1997; Aylward et al., 1999; Kesslak, Nagata, Lott, & Nalcioglu, 1994; Raz et al., 1995; Weis, Weber, Neuhold, & Rett, 1991). These have largely been adult studies, although a more recent MRI study of children with DS has also found decreased brain volume; in addition, this study found decreased cerebellar gray and white tissue volumes, decreased white matter in the superior temporal sulcus, but increased temporal lobe white matter (Pinter, Eliez, Schmitt, Capone, & Reiss, 2001). Some studies have observed normal basal ganglia (Aylward, Li, et al., 1997; Raz et al., 1995), as well as normal thalamus and lenticular nuclei (Jernigan, Bellugi, Sowell, Doherty, & Hesselink, 1993).

Growth and Weight

Various factors, such as cardiac and skeletal problems, hypotonia (deficient muscle tone), obesity, vision and hearing disturbances, and perceptual problems, may have an impact on physical growth and motor functioning in DS. Prenatally, fetuses with DS have been found to be smaller than typically developing controls. During middle childhood, growth rates become closer to normal; however, adolescents with DS experience smaller pubertal growth spurts, as well as delayed onset of menses for females (i.e., later than the typical onset of 10–14 years) (Elkins, 1992). By adulthood, individuals with DS are typically 2 standard deviations below normal in height (Cronk & Anneren, 1992). Individuals with DS are commonly found to be overweight, due to excessive weight gain during infancy and childhood (Cronk & Anneren, 1992). The etiology of this weight gain has not yet been determined, although there are some indications that it may be a factor of hypothyroidism and/or hypotonia. Although their metabolic rates do not differ from normal, individuals with DS have less body mass and slower growth and therefore require fewer calories (Pipes, 1992).

MEDICAL CONCERNS

A number of medical complications can be seen in DS, and therefore it is considered to be a heterogeneous disorder. Some of the most commonly occurring conditions are described below.

Cardiac Problems

The rate of congenital heart malformations in persons with DS has been reported to be as high as 50% (for those with trisomy 21), and cardiac anomalies continue to remain the main cause of death, especially in the first few years of life (Marino, 1992). The most common type of anomaly found involves defects in the atrioventricular canal. These anomalies produce an increased risk of congestive heart failure. Certain types of cardiac defects result in decreased pulmonary blood flow, which may contribute to pulmonary artery hypertension and pulmonary vascular obstructive disease (Howenstein, 1992).

Ophthalmological Problems

Ophthalmological problems are a major disability for individuals with DS. The most common causes of loss of vision are cataracts and acute keratoconus. Functionally, individuals may suffer from strabismus, blepharitis, and high refractive errors, which if untreated may be debilitating (Catalano, 1992; Niva, 1988). Luckily, medical intervention is available for all of these conditions; therefore, parents and health professionals should be aware of these potential difficulties and seek medical evaluation.

Oral Problems

Since the maxilla and mandible are smaller in persons with DS than in typical individuals, the tongue may appear to be larger than normal. As a result of the smaller oral cavity and relatively larger tongue, oral hygiene may be difficult. In addition, individuals with DS may have a furrowed tongue or cleft palate, which may further complicate oral health. The tongue protrusion also contributes to the split, inflamed lips that are commonly seen in these individuals. Other common problems include malocclusions, anomalies in the dentition (e.g., congenitally missing teeth, delayed eruption of teeth, delayed shedding of primary teeth), and periodontal disease (e.g., gingivitis is seen in almost all persons with DS) (Vigild, 1992). In a study by Bagic, Verzak, Cukovic-Cavka, Brkic, and Susic (2003) of 71 individuals with DS (ages 9–34 years), all possessed periodontal problems. In comparison to age- and gender-matched controls, they showed significantly less intact peridontium, and significantly more deep gum pockets and symptoms of periodontal problems (e.g., bleeding gums).

Respiratory Concerns

Respiratory problems resulting from the physical abnormalities observed in children with DS are common. For example, the small oral cavity and hypoplasia of the midfacial region create problems with airways. In addition, the lungs of individuals with DS have been found to be smaller than average (Howenstein, 1992). Pneumonia continues to be one of the major causes of death, and there is an overall predisposition for contracting infectious diseases in the lower respiratory tract. Lower respiratory tract infections have also been linked to the increased mortality rates in this population. Sinus infections and chronic rhinitis are common, and cases of bacterial pneumonia and viral infections are typically more severe in these individuals. Sleep apnea has also been reported; this is characterized by snoring, restless sleep, interrupted breathing while asleep, mouth breathing, and daytime somnolence. New technologies (e.g., cine MRI) may become useful for detecting particular problems in airway

obstruction, such as soft palate collapse or hypopharyngeal collapse, and have already been useful in a small group of children with DS (Shott & Donnelly, 2004). In addition to causing sleep apnea, respiratory conditions such as airway obstruction may cause serious problems with anesthesia (Borland, Colligan, & Brandom, 2004).

Gastrointestinal Anomalies

There are a number of gastrointestinal anomalies associated with DS, but among the most common are esophageal atresia, tracheoesophageal fistula, duodenal atresia or stenosis, and Hirschsprung disease (Levy, 1992). The etiology of these conditions can be traced to malformations during embryonic development. The esophageal atresia may cause difficulty in breathing, due to the increased production of oropharyngeal secretions. The presence of a tracheoesophageal fistula may produce a persistent cough. Both of these conditions are complicated by gastroesophageal reflux. Corrective surgery is available for these anomalies, and therefore early detection and intervention should help minimize these problems.

Dermatological Conditions

Although there is no dermatological condition specifically associated with DS, several such conditions are seen frequently in this population. These maladies include dry skin, atopic dermatitis, fungal infections of the feet and nails, and mucosal anomalies (e.g., inflammation of the lips and tongue) (Benson & Scherbenske, 1992).

Motor Difficulties

Generally, early motor development is delayed in individuals with DS; the most frequently cited causal factors are hypotonia and hyperflexia. In a cross-sectional study of 6- to 16-year-olds with DS performing a range of manual tasks, Thombs and Sugden (1991) found evidence for an increased use in precision grips among older children. In addition, the older children were found to be faster on the speeded tasks. The authors concluded that on measures of speed, strategies, and types of grip, general developmental advances are made with age. Individuals with DS may display difficulty with gross and fine motor skills, balance, posture, strength, and flexibility. An excellent review of the literature on motor development in DS has been provided by Block (1991).

Systemic Problems

Persons with DS have a higher susceptibility to bacterial infections, malignancies, and autoimmune disturbances as a result of a mild immune deficiency (Ugazio, Maccario, & Burgio, 1992). Further complications result from several hematological abnormalities that are unique to DS. These irregularities include transient myelodysplasia in infancy (which presents like congenital leukemia), red cell macrocytosis, and increased susceptibility to leukemia (Lubin, Cahn, & Scott, 1992). Individuals with DS have also been observed to be at greater risk for cancer and immune related disease. The rate of leukemia in those with DS has been reported to be nearly 19 times higher than in the general population

(Goldacre, Wotton, Seagroatt, & Yeates, 2004; Scola, 1992). Transient leukemia may occur in about 10% of newborns with DS, although the majority of these cases disappear spontaneously (Lightfoot, Hitzler, Zipursky, Albert, & Macgregor, 2004).

At one time, DS was felt to be caused by generalized endocrine failure; however, the majority of persons with DS do not suffer from endocrine dysfunction (Pueschel & Bier, 1992). Nevertheless, the prevalence rate for endocrine disturbances is greater for the population with DS than for the general population. Among the most common findings are problems related to thyroid functioning, specifically hypothyroidism (Pueschel & Bier, 1992). Of thyroid disease problems, which can be present in approximately 3% of individuals with DS, the most frequently occurring is an autoimmune subclinical hypothyroidism (Tonacchera et al., 2003). Any hypothyroid condition, however, may predispose individuals with DS to become overweight.

Other Medical Complications

The genitourinary system may also be affected in persons with DS. Research has identified smaller-than-normal kidneys, obstructive lesions of the urinary tract, and difficulty with uric acid and creatinine clearance (Ariel & Shvil, 1992). Additional characteristics involve the genitalia. One commonly observed characteristic has been hypogenitalism, particularly with males. At one time it was hypothesized that hypospadias and cryptorchidism were also linked to DS, but these reports were not supported (Ariel & Shvil, 1992). In females, hypermenorrhea or menorrhagia may occur with the onset of puberty (Elkins, 1992). This problem may be due to a number of factors commonly associated with DS, such as hypothyroidism and/or obesity.

Neuromuscular abnormalities are commonly reported in cases of DS, and these often contribute to the increased morbidity rates within this population. Among the problems reported, subluxation and dislocation of the cervical spine, hip, and patella are the most life-threatening (Pueschel & Solga, 1992). Each of these conditions may impede physical activity by causing severe discomfort, which in turn contributes to decreased mobility and physical activity. Other orthopedic difficulties may arise from cervical spine instability at the atlanto-occipital and atlantoaxial region. Persons with DS may suffer from severe scoliosis and typically have problems with collapsing flat feet and bunion deformity (Pueschel & Solga, 1992). Additional difficulties result from hypotonia, which is considered to be a major universal characteristic and is related to delays found in gross motor development.

Disorders of the liver, such as hepatitis, have been linked to DS. Individuals with DS who are institutionalized are at particular risk for contracting hepatitis B. Proper hygiene, immunization, and education may provide protection against hepatitis B.

Neurological problems that some individuals with DS often face are seizure disorders. Increased rates of seizure disorders have been associated with DS, with prevalence rates reported as high as 33% in some cases (Pueschel, 1992b). Most seizures will begin before age 1 (40%) or after individuals reach their 30s (40%).

PSYCHOLOGICAL FEATURES

Cognitive Deficits

The mental retardation evident with DS may range from mild to profound (in terms of the American Association on Mental Retardation's classification system)—a fact that adds to

the heterogeneity of this population. Individuals with mosaic forms of DS have been found to score 10–30 points higher on IQ measures than those with trisomy 21, and have demonstrated normal visual perceptual skills (Fishler & Koch, 1991). Perhaps the most consistent finding regarding cognitive development in children with DS is that there is a decline in the rate of cognitive development as the children get older (Carr, 1995). However, Wishart (1995) cautions that, generally speaking, there is no fixed "ceiling" of cognitive development for individuals with DS, and research findings show that learning continues well beyond adolescence for this population.

Interestingly, females with DS have been found to have higher average scores than males in both childhood and adulthood (Carr, 1995). Many possible reasons for this finding have been suggested, but to date there are no established conclusions about any gender differences. When compared to groups of children with other disabilities, those with DS may not perform that differently. One study comparing the cognitive skills of adolescents with DS to those of adolescents with cerebral palsy or nonspecific mental retardation found no significant differences among the groups (Smith & Phillips, 1992). The group with DS failed to show progress in language acquisition on a second assessment, but they did display some gains in cognition and copying skills compared to the group with nonspecific mental retardation.

Associated Neuropsychological Deficits

Other neuropsychological cognitive deficits noted in children with DS include limited memory functioning (particularly for spatial stimuli and verbal material); reduced task persistence and increased distractibility; slowed reaction time and information-processing speed; and difficulty with reasoning and judgment (Gibson, 1991). Other reports indicate that when adults with DS are matched with typically developing children on expressive language and verbal ability, they perform equally well on a nonverbal analogical reasoning task (Natsopoulo, Christou, Koutselini, Raftopoulos, & Karefillidou, 2002). Individuals with DS have also been reported to have reduced short-term memory, and to have greater difficulty recalling auditory than visual information (Florez, 1992). Seung and Chapman (2004) found that individuals with DS had shorter sentence memory (representative of a short-term memory deficit) than controls matched for mental age. Dichotic listening studies have found that individuals with DS have reversed hemispheric dominance (right- rather than left-hemisphere dominance) for processing speech (Dahle & Baldwin, 1992).

Language Delay and Deficits

Compared to children without mental retardation, children with DS develop language skills more slowly than they do other motor or cognitive skills. Although the rate of vocabulary learning is typically consistent with their developmental age, children with DS do not progress at a rate that is consistent with their other cognitive skills (Miller, 1995). Difficulties in language development involve (1) an asynchrony in language production, relative to language understanding and other cognitive skills; (2) an onset of productive deficits that coincides with vocabulary growth; (3) a slowness in the development of syntactic skills; and (4) heterogeneous language development for the population (Florez, 1992). Longitudinal examinations of language abilities in adolescents and adults find that although gains in nonverbal ability, receptive language, and grammar comprehension occur across this developmental

period, problems with phonological memory remain (Laws & Gunn, 2004). This same research group reported previously that expressive language (vs. comprehension) and grammar (vs. vocabulary) were the most problematic areas in adolescents (Laws & Bishop, 2003).

Some factors involved in these delays in language skills may be directly related to the physical characteristics associated with DS. Problems with otitis media and vision may impede a child's ability to gather auditory and visual cues concerning language. In addition, difficulties with articulation may be exacerbated by hypotonia of facial muscles and related congenital abnormalities.

Language production appears to suffer from greater deficits than language comprehension. Within expressive language, the grammatical/syntactic components of language rather than the lexical or nonverbal aspects seem to show the greatest impairments (Fowler, 1988; Miller, 1995). When adaptive behaviors were assessed with the Vineland Adaptive Behavior Scales in a group of children with DS (ages 1–11½ years), a relative weakness in communication skills compared with daily living and socialization skills was found, primarily driven by low expressive language (Dykens, Hodapp, & Evans, 1994).

Social Characteristics

Because of the motor, perceptual, cognitive, and language deficits that individuals with DS exhibit, their ability to gain social competence may also be diminished. For this reason, children with DS may seek out developmentally matched, rather than age-matched, children for peer interactions. Play development has been reported to follow developmental trajectories as well (Beeghly, Perry, & Cicchetti, 1989). Earlier hypotheses that children with DS are more sociable than other retarded children and that this is a defining quality of the whole group have not been definitively supported by research, although some sex differences in sociability have been described. Ruskin, Kasari, Mundy, and Sigman (1994) found that young children with DS paid more attention to people during a social interaction paradigm than did mental-age-matched controls, demonstrating a greater focus of attention to the social cues provided. However, when presented with ambiguous stimuli paired with either positive or negative facial expressions from their parents, toddlers with DS were found to display significantly less appropriate responses (e.g., they responded with positive affect to negative expression) than did mental-age-matched controls (Knieps, Walden, & Baxter, 1994). Therefore, although children with DS may be as socially responsive as other children, they fail to learn social reference cues.

Behavioral Presentation

An examination of children and young adults with DS found that overall, individuals with DS were less at risk for externalizing and internalizing behavioral problems than were controls matched for intellectual disability (Nicham et al., 2003). However, the individuals with DS still had more problems than their typically developing peers. These authors also found age-related differences in the types of problems reported. Children with DS (5–10 years old) had significant externalizing behaviors (opposing/refusing, impulsivity, inattention), while adolescents and adults (10–30 years old) had more internalizing behaviors (e.g., insecurity, low self-esteem, shyness).

Myers (1992) reviewed the literature on psychiatric conditions comorbid with DS. She found that under the age of 20, disruptive behavior disorders such as attention-deficit/

hyperactivity disorder, conduct disorder, oppositional defiant disorder, and aggressive behavior accounted for most of the disturbances. In persons over age 20, aggressive behavior, major depressive disorder, and stereotypic behavior were reported most frequently. Myers also stated that whereas children and adolescents with DS showed lower risk for developing a psychiatric disorder than other individuals with mental retardation, they were still at greater risk than the general population. Autism has been identified as another psychiatric disorder that may be comorbid with DS (Rasmussen, Borjesson, Wentz, & Gillberg, 2001). Because individuals with DS are at increased risk for depression, as Myers (1992) noted, symptoms of depression should be investigated seriously. Particularly in adulthood, as challenges related to independence and vocation emerge, problems with depression may require intervention.

DEVELOPMENTAL COURSE

Although the majority of children with DS display delayed motor function, cognitive development, and language acquisition, there are individual variations in rate and level of achievement. Because of their special needs, however, these children may require some environmental supports in order to achieve their developmental milestones. Developmental stages generally mimic those of typically developing children in the Piagetian domains of sensorimotor functioning, conservation, and mastery of space, time, and moral judgment, although these skills are acquired at a slower rate (Hodapp & Zigler, 1990).

The developmental delay and language impairments associated with mental retardation may contribute to the finding that individuals with DS are at slightly greater risk for autism than the general population (Myers, 1992). Children with DS may display impairment in school, occupational, or social functioning. These lags may be manifested in mood disturbances (anxiety or depression), physical complaints, social withdrawal, or work inhibition (Myers, 1992). Although depression in children with DS has not been well documented in the literature, adults have been found to exhibit depression. The prevalence of major mood disorders in adults with mental retardation has been estimated to be 1–3.5% (Myers, 1992).

Neurological Decline

One of the most commonly reported neurological characteristics of individuals with DS is the fact that later in life they tend to present with an Alzheimer-like dementia. It is still unclear what the pathophysiology of this dementia may be, but individuals over age 40 tend to show the characteristic features of Alzheimer disease in their central nervous systems. These consist of cortical atrophy, neurofibrillary tangles, and neuritic plaques (Lai, 1992; Mufson, Benzing, & Kordower, 1995). Efforts to find a genetic link between DS and Alzheimer disease have had mixed results. It has been proposed that a gene for Alzheimer disease may be located on the long arm of chromosome 21, although other genes have also been examined (DelBo et al., 2003; Lucarelli et al., 2003). Recent reports have found that certain neuronal features, such as enlarged neuronal endosomes, may serve as early markers for Alzheimer disease (Cataldo et al., 2004). When the pathophysiologies of Alzheimer disease and DS have been compared, a similarity has been noted in the presence of certain cortical neurons associated with diffuse and neuritic plaques (Bernstein et al., 2003).

Hirayama, Horikoshi, Maeda, Ito, and Takashima (2003) found that certain antibodies appeared in diffuse plaques after age 32 in a sample of individuals with DS compared to controls. Specifically, these antibodies were observed in the axons around senile plaques. Neuroimaging studies have also found similarity in neuropathological features between DS and Alzheimer disease (Emerson, Kesslak, Chen, & Lott, 1995). Normal age-related changes in the brain, such as dilation of ventricles or peripheral atrophy, are seen earlier in DS. The clinical presentation associated with Alzheimer disease does become evident in persons with DS who live to be 50. The symptomatic presentation is essentially the same as that for groups without DS, but it may appear to be somewhat exaggerated due to the physical and cognitive features already associated with DS (Lai, 1992).

Mortality

When he originally characterized DS, Down commented on the shorter life expectancy for these individuals. This phenomenon held true until the 1940s, when life expectancy figures rose from approximately 9 to 12 years of age. Current trends indicate that nearly half (44%) of the children with DS born between 1952 and 1981 will live to be at least 60 years old (Carr, 1995; Sadovnick & Baird, 1992). Although the shorter life expectancy was at one time attributed to the congenital heart defects that often accompany DS, this hypothesis has not been substantiated (Sadovnick & Baird, 1992). In a large-scale examination of mortality causes in DS in Sweden and Denmark, Hill and colleagues (2003) found increased risk of mortality from acute lymphocytic and nonlymphatic leukemias, cancers (testicular, liver, stomach), dementia (Alzheimer disease), epilepsy, heart disease or anomalies, and infectious disease. Among individuals with DS, males have been found to have a longer life expectancy than females; this is the opposite of what is typically found in the general population (Glasson et al., 2003).

KEY ISSUES REGARDING ASSESSMENT

Cognitive Assessment

Assessment of individuals with DS may be difficult for a variety of reasons, one being the instability of test performance and mental retardation. Great variability has been found within a population of young children with DS (Wishart & Duffy, 1990). Failure to engage in the task and differences in responding were factors that added to the instability of their evaluations. Comparisons of cognitive and neuropsychological performance in research studies are often most appropriately made between adults with DS and typically developing children, after the two groups are matched for verbal ability.

The dementia resulting from Alzheimer disease is difficult to identify in persons with mental retardation (especially in those with profound mental retardation), and therefore clinical studies intended to investigate dementia in populations with DS are difficult to do. One group of investigators had success using the Rivermead Behavioural Memory Test (children's version) with 19- to 44-year-old adults with DS (Wilson & Ivani-Chalian, 1995), and found an adequate range in performance for these individuals. Other difficulties with assessing dementia in adults may be caused by hypothyroidism, poor nutrition, and depression, since all of these may masquerade as dementia and are also common problems for adults with DS.

Behavioral Assessment

There are no characteristic behavioral problems associated specifically with DS; rather, the full range of behaviors seen in behavioral or psychiatric disorders may be exhibited by individuals with DS. Typical rating forms and assessment tools can be used to elicit evaluations from parents, teachers, or caretakers, although interpretation demands that an individual's developmental age be considered in any assessment of problem behaviors. Obstinacy, aggression, withdrawal, and self-injurious behaviors are among the most frequently seen problem behaviors in childhood, and they are also ones that elicit the most frustration from parents and educators. Some of these behaviors continue into adulthood, but also may diminish. Internalizing behaviors are often the chief complaints of adults with DS.

TREATMENT OPTIONS AND PROGNOSIS

During the preschool and school years, early efforts should focus on remediating common orthopedic problems (e.g., bunions, severe flat feet, dislocated hips), treating dental problems, and providing additional vaccinations (e.g., against influenza, pneumococcal infections, and hepatitis B) for at-risk children. Special behavioral programs may be beneficial to improve self-help skills, communication, and nutrition, and to ameliorate problems related to aggression, self-injurious behavior, and poor school adjustment. For example, some children with DS display food behavior problems, such as throwing or hoarding food (Pipes, 1992). Skills that preschool programs should concentrate on in order to increase independence include separation from parents, eating and drinking, handwashing, toileting, gross and fine motor skills, social skills, and language acquisition (see Love, 1988, and Oelwein, 1988, for model instructional plans). Principles of applied behavior analysis are often successful when care providers are attempting to teach such tasks as feeding, toileting, cessation of habitual tongue protrusion, and gross and fine motor skills. Since the developmental age of a child with DS often lags behind his or her chronological age, it is necessary to maintain an awareness of which activities the child is ready to perform successfully.

In 1991, the National Down Syndrome Society (NDSS) sponsored a conference on DS health care, where suggestions were made for important medical interventions (Lott & McCoy, 1992). It was recommended that during the neonatal period and early infancy there should be attempts to establish chromosomal karyotype, communicate the diagnosis to parents, and refer parents to available support groups. In addition, several types of screenings were recommended, based on the known health concerns of children with DS. These should include screening for cataracts, blockage in the gastrointestinal tract, congenital heart disease, thyroid dysfunction, and hearing problems. These exams should continue annually into early adulthood.

During school age, placement in a regular classroom may improve academic attainment in children with DS. One study of academic attainment in children with DS (ages 6–14 years) found that although cognitive ability level had the greatest impact on achievement, type of school attended was the next largest contributing factor (Sloper, Cunningham, Turner, & Knussen, 1990). Additional factors influencing academic attainment were gender (female), fathers' locus of control ratings, and chronological age.

The numerous medical conditions that can complicate the health of individuals with DS require practitioners to be well informed about the specialized health needs of these patients. Failure to address problems, or misdiagnosis of problems, may lead to further com-

plications. Bosch (2003) has recently reviewed health needs that should be addressed in adult patients with DS. Psychoeducational evaluation and remediation should also take place as early as possible, with follow-up provided throughout individuals' academic careers.

Over the years, various alternative treatments have been proposed to address dysfunctions seen in DS. Some of these treatments have sought to improve intellectual functioning, and others have attempted to alleviate physical conditions, but they are considered unconventional. Practitioners may wish to familiarize themselves with these therapies, in order to discuss them competently with parents who show an interest in them. Some of the more common of these treatments are (1) pituitary extract, given to improve intellectual and social development; (2) glutamic acid; (3) thyroid hormone, given to improve intellectual functioning; (4) 5-hydroxytryptophan, administered to improve behavioral and motoric functioning; (5) dimethyl sulfoxide, given to improve behavior and learning; (6) sicca cell (fetal cell) therapy, intended to increase intellectual functioning and growth; (7) vitamins, mineral, enzymes, and hormones, administered to ameliorate mental retardation; and (8) facial plastic surgery, intended to improve characteristic features (for a detailed review, see Pueschel, 1992a). Parents may be willing to try these alternative therapies, despite evidence that demonstrates their lack of efficacy, and they may be reluctant to bring up their use with a physician (Prussing, Sobo, Walker, Dennis, & Kurtin, 2004).

Beginning in adolescence, an individual's emotional health should be carefully monitored for symptoms of depression. As noted earlier, individuals with DS are at increased risk for developing major depression, and they have also been noted to develop learned helplessness (Harris, 1988). Activities to build self-esteem and self-concept, as well as to provide training in vocational matters, should be initiated during middle or high school. However, attempts to predict adult outcomes based on childhood psychopathology have shown that there is not a direct relationship. In other words, child problem behaviors and family variables (with the exception of socioeconomic status) have not been good predictors of adult outcomes for psychiatric disorder (McCarthy & Boyd, 2001).

As the individual with DS enters young adulthood, concerns regarding vocation and independent living emerge. Prior to the implementation of P.L. 94-142, vocational training was not considered an integral part of service for adolescents with disabilities. Currently, individuals can prepare for functional independence by receiving training in vocational skills and independent living skills. A range of opportunities currently exists for individuals with DS, through sheltered workshops and other less supportive job sites. On-the-job training may be provided through vocational schools, job coaches, community colleges, or sheltered workshops (Renzaglia & Hutchins, 1988). The use of computers to teach language skills has been advocated as another supportive tool (Meyers, 1988). Specifically, the computer provides structure and scaffolding for the acquisition of spoken and written language skills, such as vocabulary, spelling, comprehension, and sentence construction. Providing auditory instruction during tasks may also be beneficial.

Additional counseling should focus on further development of social skills, sexuality, and separation from parents. Reproductive counseling for females is especially important, given the risk of producing a child with DS or congenital anomalies (Elkins, 1992). Most importantly, individuals with DS should be viewed as people first, with the same desires for developing relationships and becoming productive adults as individuals without disabilities have. Assistance should focus on the development of well-rounded persons who can live in the least restrictive environment possible—whether that means independently in the community, in supervised semi-independent settings, or within group home environments.

SUMMARY

DS is a genetic disorder with a distinct physical phenotype but a heterogeneous presentation of learning, behavioral, and medical conditions. It is the most common genetic cause of mental retardation, and some degree of mental retardation is present in all individuals with DS. Despite a plethora of medical comorbidities, ranging from cardiac defects to dermatological conditions, improvements in management and intervention has extended the average lifespan of these individuals until the fourth decade of life. Whereas learning disabilities and language deficits are commonly seen in childhood, older individuals with DS are at risk for an Alzheimer-like dementia. Depending on adaptive behavior functioning and cognitive ability, a degree of independence is possible if proper supports are in place. Sheltered workshops and supportive semi-independent living arrangements ensure that adults with DS will continue to develop skills as they mature.

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19

KLINEFELTER SYNDROME

HEATHER CODY HAZLETT

OVERVIEW

Klinefelter syndrome (KS) is a disorder occurring in males that results from a specific chromosomal abnormality. It was first described in 1942 by Klinefelter, Reifenstein, and Albright, who used the term to describe a small group of infertile men. More than a decade later, the discovery of an extra *X* chromosome in these individuals was used to identify the syndrome. Consequently, KS is considered a sex chromosome disorder. Normal males are born with 46 chromosomes; their gender is defined by a pairing of one X and one Y sex chromosome. Males born with KS, however, typically show an XXY pattern. There are some variations, such as XXXY or XXXXY, and also cases considered to reflect mosaicism, when a combination of normal and abnormal cells exists. The incidence of KS has been estimated to range from 1 per 400 to 1 per 900 live-born males (Drugan, Isada, Johnson, & Evans, 1996b; Geschwind, Boone, Miller, & Swerdloff, 2000; Rovet, Netley, Keenan, Bailey, & Stewart, 1996).

Decades ago, studies of males with KS reported an increased risk for psychiatric disorders, criminality, and mental retardation in this population (Forssman, 1970; Schroder, Chapelle, Hokola, & Virkkunen, 1981). These studies, however, had serious methodological problems, because they were generally conducted with populations of men who were already institutionalized or imprisoned (Cohen & Durham, 1985). More recent research indicates that although individuals with KS may display some specific cognitive, psychiatric, or behavioral problems, these earlier descriptions are no longer acceptable characterizations. No current research supports the older contention that these individuals have higher rates of criminality or mental health problems.

Several longitudinal studies have contributed to our understanding of developmental outcomes in sex chromosome disorders. Large prospective studies conducted during the late 1960s and early 1970s compiled outcome data for children born with a variety of sex chromosome abnormalities. Bender and Berch (1990) outlined the most important findings from this research. First, children with sex chromosome disorders appear to have an increased risk for developmental, language, learning, and behavioral problems, compared to typically developing children. However, their profiles indicate much less disability than earlier stereotypes suggested; this supports the notion that the earlier studies examined

biased samples. Second, there is a great deal of variability in the phenotype of children within the same syndrome, and therefore significant variability is present in KS.

GENETIC AND FAMILIAL ISSUES RELATED TO ETIOLOGY

KS is one of the most frequently occurring sex chromosome abnormalities seen in males. The abnormality is a specific phenomenon referred to as "nondisjunction." This occurs when a chromosome pair fails to separate during either the first or second division of meiosis. When nondisjunction occurs, it results in "aneuploidy" (the addition or absence of a single chromosome). Aneuploidy is the most common type of chromosome anomaly found in live births or spontaneous abortions, occurring in approximately 3% of all confirmed pregnancies (Evans, Drugan, Pryde, & Johnson, 1996; Thomas & Hassold, 2003). In KS, at least one extra X chromosome is present. Rather than the normal XY genotype that signifies the male gender, these boys typically display a trisomy or XXY pattern of sex chromosomes, although some of them may have several additional X chromosomes (e.g., XXXY). Approximately 10% of individuals with KS exhibit mosaicism, meaning that only a portion of their cells display trisomy of the sex chromosomes; others retain a normal XY pattern (Pierce, 1990). Roughly 50% of KS cases are caused by maternal meiotic errors, although some researchers have reported paternal nondisjunction in slightly over half (57%) of the cases (Evans et al., 1996; Thomas & Hassold, 2003). Up to three-fourths of cases show significant effects of maternal age (Bojensen, Juul, & Gravholt, 2003; Drugan et al., 1996b; Gardner & Sutherland, 1996). There are no familial indicators that would suggest a higher risk for producing a child with KS, although females with trisomy XXX have been reported to be at greater risk for producing offspring with KS or XXX, and in fewer cases, trisomy 21 and monosomy X0 (Drugan et al., 1996b).

A diagnosis of KS is made by karyotype. This may be done either prenatally through amniocentesis or chorionic villus sampling (Pierce, 1990) or postnatally. Since maternal age is a known risk factor, in some cases a prenatal diagnosis of KS may be possible. In a large prevalence study conducted in Denmark over a 30-year period, prevalence of KS by prenatal diagnosis was reported to be 153 per 100,000, while postnatal diagnosis was observed to be 40 per 100,000 (Bojensen et al., 2003). Characteristic physical features may or may not be present at birth, and therefore the existence of an extra X chromosome may not be discovered until puberty or during testing for infertility (Drugan, Isada, Johnson, & Evans, 1996a). Physical characteristics (e.g., small testes, abnormal leg length) are not visible at birth, and so there is no obvious reason for genetic testing to be conducted. Bojensen and colleagues (2003) found that fewer than 10% of their postnatally diagnosed cases of KS were detected before puberty. In an overview of genetic disorders and their onset, Weatherall (1991) noted the average age for early detection of KS to be 5 years, after identification of elongated leg length. However, most individuals are either diagnosed in adolescence when examined for hypogonadism or in adulthood after testing for infertility (Geschwind et al., 2000).

PHYSICAL FEATURES AND MEDICAL CONCERNS

Genital Anomalies

In a review of the literature on the physical characteristics of KS, Theilgaard (1984) found several classic attributes common among these individuals. The chief physical features of this syndrome are abnormal genital and sexual development. According to Schwartz and

Root (1991), KS is the most common cause of hypogonadism in males. This becomes problematic during puberty, when secondary sex characteristics may fail to emerge because of decreased levels of testosterone. At puberty, hyalinization and atrophy of the seminiferous tubules are also common. Normally, the seminiferous tuberules comprise 85% of the volume in the testes, but in males with KS the testes are often noted to be abnormally small by mid-childhood (Bender & Berch, 1990; Schwartz & Root, 1991). Typically, individuals with KS possess smaller-than-average testes size (3–5 ml volume), but normal penis size (Ratcliffe, Bancroft, Axworthy, & McLaren, 1982). Infertility is caused by azoospermia (absence of sperm) and is one of the primary disabling features of KS. Azoospermia associated with KS has been found to be distinguishable from idiopathic azoospermia based on chromosomal differences, indicating that a different mechanism resulting in azoospermia may occur in KS (Lee, Kim, Kim, Kim, & Kim, 2000). Older case descriptions associate cryptorchidism and hypospadias with KS, but these are not common problems.

Hormonal Disturbances

Endocrinological differences are also among the common features of KS. Increased levels of gonadotropin produced by the pituitary have been reported in these males, as well as decreased androgen production in the testes. In addition, individuals display lower levels of testosterone and higher concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) upon entering adolescence (Robinson et al., 1986). These hormones are critical for normal male development. LH stimulates testosterone secretion, while FSH stimulates the development of sperm during puberty. Therefore, although males with KS will enter puberty at a normal age, inadequate testosterone secretion prevents normal pubertal development (Styne, 1991). Serum inhibin B is an indicator of Sertoli cell number and function; the Sertoli cells are responsible for secreting gonadal peptide hormones at the onset of puberty, and in adult males reflect spermatogenesis. Christiansen, Andersson, and Skakkabaek (2003) found levels of serum inhibin B in a small sample of prepubertal boys with KS that were similar to levels in controls. However, they found that inhibin B levels decreased by late puberty in the boys with KS to low or even unmeasurable levels, while levels remained unchanged in the controls. A recent report shows significantly lower testosterone levels in 18 prenatally diagnosed males with KS than in controls, but no differences in FSH, LH, or inhibin B (Lahlou, Fennoy, Carel, & Roger, 2004). This indicates that testosterone levels are abnormal prior to birth, but other hormonal levels may not show significant differences from normal until puberty. Lastly, there have also been mixed accounts of thyroid conditions (particularly hypothyroidism) in these individuals, with some studies indicating an increased incidence for congenital hypothyroidism and others showing no significant findings (Schwartz & Root, 1991).

Neurological Findings

Some literature indicates that abnormal electroencephalograms and seizure activity are seen more frequently in the population with KS than in nondisabled individuals. Whether or not there is an increased incidence of epilepsy in these males has not been determined conclusively. Neuromuscular findings show that when compared to controls, boys with KS had lower scores on tasks involving fine and gross motor skills, coordination, speed and dexterity, and strength (Robinson et al., 1986).

There are some hypotheses linking neuronal development and sex chromosome anomalies. Bender and Berch (1990) hypothesized that a sex chromosome anomaly may alter normal patterns of brain growth either by causing abnormal rates of brain tissue growth and maturation, or by resulting in abnormal hormonal levels (such as testosterone in KS) that would affect brain growth and functioning. Netley and Rovet (1982) found evidence for diminished dermal ridge counts in a group of children with KS, indicating that prenatal brain growth may be slower.

Hemispheric specialization in KS has been studied by observing differences in performance on verbal and nonverbal tasks. Netley and Rovet (1984) found that a group of boys with KS performed more poorly than controls on a number of tasks involving lateral presentation of material. For example, the boys with KS did more poorly on dichotic stop consonants, whereas their performance was better than that of controls on dichotic melodies and half-field dots. The authors interpreted these findings to mean that boys with KS have difficulty in dealing efficiently with information normally preferentially processed by the left hemisphere, and that their right-hemispheric functions appear to play a larger role in both nonverbal and verbal processing. Overall, when compared to age-matched controls, children with KS were found to display diminished left-hemisphere specialization for language and enhanced right-hemisphere specialization for nonverbal processing (Netley, 1990). This finding is supported by the fact that language deficits are also seen in females with XXX, particularly in expressive language and auditory processing (Walzer et al., 1986). A study examining dichotic listening performance found that left-hemispheric processing of dichotic syllables was impaired for the group with KS, compared to a control group (Theilgaard, 1984).

Anomalies in cerebral laterality have been reported in cerebral perfusion studies (Itti et al., 2003). In a small study of adults with KS (one of the few functional imaging studies done with this population), Itti and colleagues (2003) examined regional cerebral blood flow volumes. These investigators noted symmetrical perfusion in upper temporal and lower parietal areas in the group with KS, compared to left-sided perfusion in controls. All individuals were right-handed, and language is usually dominant in the left hemisphere in right-handed individuals, so the group with KS showed an absence of this normal profile. In addition, language scores (e.g., verbal attention, verbal memory) were inversely correlated with perfusion changes in language regions (e.g., frontal, parietal, angular temporal gyrus) for the group with KS. This finding is supported by a structural imaging study of 10 adults with KS, where significantly decreased left temporal gray tissue volume was reported (Patwardhan, Eliez, Bender, Linden, & Reiss, 2000). In this study, two cohorts of individuals with KS were examined; half had received testosterone therapy since puberty, and half were not treated. The subset who received testosterone during development had larger left temporal gray volumes than the untreated subset, although these were still smaller than those of nondisabled controls. Patwardhan and colleagues (2000) believe that testosterone replacement may help to preserve temporal lobe volume during development.

Other Medical Concerns

Boys with KS are typically taller than average due to elongated legs, and this feature can often be seen before puberty. Individuals with some variants of KS (e.g., XXXY and XXXXY) have been reported to have short stature or radioulnar synostosis (Schwartz & Root, 1991). As adults, men with KS appear to be at an increased risk for osteoporosis as a result of an androgen deficiency, which causes a decrease in their bone mineral content

(Schwartz & Root, 1991). A clinical study of 24 adult males with KS found a higher-than-average incidence of tall stature, obesity, diabetes mellitus, hyperlipemia, hypercholesterolemia, gall bladder disease, chronic pulmonary infection, and peptic ulcer (Zuppinger, Engel, Forbes, Mantooth, & Claffey, 1967). Interestingly, this investigation found that a family history of diabetes mellitus was present in a majority of these cases, leading to the hypothesis that a genetic predisposition for diabetes may exist in some individuals with KS. Another description, by Evans and colleagues (1996), included increased incidence of elbow dysplasia, elongated limbs, chronic bronchitis, and poor fine motor coordination. They found diabetes to occur in 8% of their total study population. Reports of increased cancer risk, specifically for mediastinal germ cell tumors, have also been observed (Beresford et al., 2003; Hasle, Jacobsen, Asschenfeldt, & Andersen, 1992; Hasle, Mellemgaard, Nielsen, & Hansen, 1995). It has been postulated that this cancer may be secondary to a failure of embryonal germ cells to migrate correctly to the gonads (Nichols et al., 1987).

Comorbidity for renal, cardiac, or lymphatic conditions has not been confirmed in this population (Evans et al., 1996), although case reports linking these conditions to KS exist. From the few accounts of cardiac defects associated with KS, it appears that these occur more frequently in the more rare cases of polysomy (e.g., XXXXY) than in the typical presentation (Elias & Yanangi, 1981). In addition, the number and severity of these cardiac defects may be correlated to the degree of polysomy. Single-case reports of focal nodular hyperplasia (Santarelli et al., 2003), a benign lesion of the liver usually affecting women, and cardiomyopathy (Yoshida et al., 1998), often seen with congential skeletal muscular diseases, have been published. Other nonspecific features that have been associated with KS include increased fatigue, increased incidence of venous stasis ulcers, or essential tremor (Schwartz & Root, 1991).

Course of Physical Development

Generally, physical development follows normal patterns until the individual reaches adolescence, when specific disturbances in puberty appear. Height and weight have been observed to be normal at birth in KS (Lahlou et al., 2004), but height can sometimes be an earlier physical indicator, due to abnormally long legs (Pierce, 1990). Although motor developmental milestones are not significantly different from normal, Bender and Berch (1990) noted that these males typically display reduced sensory–motor integration and motor strength. In addition, these children may appear to be slower and less coordinated than their siblings.

Normal secondary sexual development in males involves genital development and pubic hair growth. Features of puberty related to the external genitalia may begin to develop at any time from age 11 to 15 years (Wheeler, 1991). This process involves the growth of the testes, maturation of the scrotum, and growth of the penis. In males with KS, as noted earlier, the size of the penis is within normal limits, whereas the testes show diminished size and maturation. Normally, the growth of pubic, axillary, and facial hair follows on the heels of genital development. Androgens control these types of hair growth, and since males with KS have decreased androgen production, they may have diminished or absent hair growth (facial, chest, and/or pubic). During puberty, too, the voice normally deepens and the bulbourethral glands enlarge; both of these processes may be abnormal in KS. In addition, while some breast enlargement is typical in normal adolescence, in KS there may be significant gynecomastia (Wheeler, 1991) that may cause significant social–emotional difficulties. Normal pubertal development in males involves alterations in lean body mass

and fat distribution with rapid skeletal growth. In KS, fat distribution may mimic that of girls (e.g., hip and thigh) (Wheeler, 1991). Schwartz and Root (1991) estimate that 30–60% or more of all individuals with KS will exhibit gynecomastia by late puberty, and they place the incidence rate of developing carcinoma of the breast at 9 per 1,000. They are careful to note that although this rate is above that for nondisabled men and one-fifth the rate for women, the role of the extra X chromosome in this higher risk for carcinoma in KS is unknown. If severe gynecomastia is not improved with androgen therapy, mastectomy may be recommended.

PSYCHOLOGICAL FEATURES

Cognitive Deficits

Generally, research studies indicate that children with KS may display a wide range of intellectual ability, from mild mental retardation to above-average intelligence. Most studies find average or near-average intellectual ability. Bender and Berch (1990), commenting on the 23-year prospective Denver study done by Bender's group, note that Full Scale IQs are likely to be 10–15 points lower than those of controls, which helps explain the increase in the diagnosis of mental retardation with this population. In a small prospective study of the development of children with sex chromosome anomalies, Leonard and Sparrow (1986) found that boys with KS displayed variable intelligence. For example, one subject displayed average intelligence, while others fell in the below-average range. Smith (1981) estimated the average IQ for children with KS from the existing studies as a standard score of 89; however, this finding using Full Scale IQ may mask discrepancies found between Verbal and Performance IQs. Another study (Walzer et al., 1986) found that for a small group of boys with KS, their mean Full Scale IQ scores did not differ significantly from controls. However, they did exhibit significantly lower Verbal IQ scores, and deficits in verbal abilities are consistently found among individuals with KS. Verbal IQ scores on traditional intelligence tests are generally below average, while Performance IQ scores are normal (Ratcliffe et al., 1982). Some have hypothesized that the presence of an extra X chromosome is what deflates the verbal skills, since females with an extra X chromosome also display impaired verbal ability (Bender, Puck, Salbenblatt, & Robinson, 1986; Cohen & Durham, 1985; Netley & Rovet, 1982).

In a comprehensive literature review on the cognitive profile of boys with KS, Rovet and colleagues (1996) concluded that chronic cognitive deficits in verbal abilities and language processing were consistent across 27 independent research studies. General underachievement in school and a risk for dyslexia were evident in these children. Rovet and colleagues also conducted their own longitudinal study of cognitive functioning in KS and provided an excellent detailed description of the deficits seen in KS. They followed 36 boys and 33 sibling controls for 20 years. Their findings indicated that, compared to the controls, the boys with KS demonstrated significantly depressed verbal ability contrasted with normal nonverbal ability. Walzer, Bashir, and Silbert (1990) found IQ to be 10–15 points lower than that of average peers in a group of 13 boys with KS. Of these, 11 had demonstrated learning problems in reading and spelling throughout their academic histories.

Netley (1987) sought to predict intellectual obtainment in children with KS from observing the psychometric data of their siblings. He found that, compared to their siblings, the boys with KS had lower intelligence in general and lower verbal abilities in particular, although their IQ scores were highly correlated with those of their unaffected

siblings. Bender, Harmon, Linden, Bucher-Bartelson, and Robinson (1999) also reported slightly lower Full Scale IQ scores for individuals with KS, compared to their siblings.

In cases of polysomies (e.g., XXXY, XXXXY), the level of intellectual impairment appears to increase with the number of additional X chromosomes. Mental retardation is frequent in those individuals who have four or more X chromosomes (Gardner & Sutherland, 1996). Behavioral difficulties also appear more frequently in this population.

Language-Processing Deficits

Young boys with KS have also been noted to display delayed speech and language development. The presence of language-based learning disabilities may occur from 50% to 70–80% of this group (Bender, Linden, & Robinson, 1990, 1993; Graham, Bashir, Stark, Silbert, & Walzer, 1988). Specific deficits have been discovered in the areas of articulation, comprehension, verbal abstraction, sequencing, and expressing a story idea (Mandoki, Sumner, Hoffman, & Riconda, 1991). In the longitudinal study mentioned above, Rovet and colleagues (1996) determined that males with KS have greater difficulty on tasks involving auditory memory, language comprehension, and language expression. This finding supports an earlier report by Leonard and Sparrow (1986), who found language delays in a small sample of males with KS. These subjects displayed delayed language development, limited vocabulary and syntax, difficulty with concepts, and lack of fluency. In the prospective study by Walzer and colleagues (1986), speech and language delays were evident by the third year of life. Specifically, parents reported problems with articulation, word finding, sentence formation, and expressive language. Assessment of these children indicated that although their receptive language was age-appropriate, deficits existed in auditory memory and expressive language (e.g., syntax, dysnomia, and narrative production). Such language problems continue into adulthood (Geschwind et al., 1988).

Other Neuropsychological Deficits

Specific examinations of executive functioning deficits have been performed. Fales and colleagues (2003) conducted a small study of working memory and relational reasoning in a group of adult men with KS who had average intelligence. Compared to controls, the men with KS had significant deficits on a traditional verbal working memory task and a verbal deductive interference (relational reasoning) task. Both of these tasks rely on verbal encoding skills. The men with KS displayed intact nonverbal reasoning, highlighting the verbally based deficits seen in other cognitive studies.

Academic Achievement

Poor school performance is typical in children with KS, particularly in reading and spelling. Academic difficulties have been reported in the areas of reading, spelling, and arithmetic (Schwartz & Root, 1991). Difficulties with speech production, language processing, verbal processing speed, verbal and nonverbal executive functioning abilities, and sentence structuring are thought to interfere with academic performance (Boone et al., 2001; Mandoki et al., 1991). Researchers examining the development of reading and spelling in KS

have proposed that the course follows normal developmental patterns at first, but becomes arrested at some point (Seymour & Evans, 1988). Both prospective and longitudinal studies (Robinson et al., 1986; Walzer et al., 1986) reveal that children with KS are more likely to be referred for special education evaluations by their classroom teachers, and also more likely to be enrolled in a learning disability classroom.

In the longitudinal study by Rovet and colleagues (1996), boys with KS were found to perform significantly worse on measures of word decoding, reading comprehension, spelling, written language skills, arithmetic, math problem solving, and the acquisition of conceptual knowledge in such areas as science and the humanities. In addition, the boys with KS were found to perform lower on standardized achievement tests and tended to fall further behind grade and age levels as they grew older. By ages 18–20, they were several grades behind age-matched peers in language, arithmetic, problem solving, and knowledge integration (Rovet et al., 1996). However, these authors characterized the learning disability seen in KS as primarily language-based. The specific deficits demonstrated throughout all their findings appeared to be auditory processing deficits. This hypothesis is supported by earlier research that demonstrated significant impairments in reading and auditory short-term memory in a group of boys with KS (Bender et al., 1986). Their sample was characterized by average intelligence, language dysfunction associated with slow processing and poor short-term memory, and a history of reading difficulty in school. In addition, impaired reading (i.e., on the Passage Comprehension subtest of the Woodcock–Johnson Psycho-Educational Battery—Revised) and poor short-term recall were noted. A more recent study of adolescent boys and young adults with KS found them to have significantly lower language skills than controls on neuropsychological testing (Boone et al., 2001). This would suggest that difficulties with reading persist into adulthood.

Behavioral Characteristics

As mentioned above, research studies conducted in the 1960s and even early 1970s on adult populations with KS tended to report increased incidence of aggressiveness, alcohol and other substance abuse, arson, criminal behavior, depression, personality disorders, bipolar disorder, and schizophrenia (Schwartz & Root, 1991). However, these studies possessed methodological flaws (as noted earlier), and these perceptions are no longer appropriate. More commonly, individuals with KS are described as introverted, passive, and socially withdrawn (Geschwind et al., 1998, 2000). In fact, some of the behavioral characteristics associated with KS (e.g., low activity, high pliancy) have led some researchers to describe individuals with KS as warm, likeable, anxious to please, and helpful. A tendency to withdraw in novel situations and to be less assertive than peers has also been observed (Walzer et al., 1986). Data taken from the various prospective studies done with this population describe individuals with KS as less active, less assertive, and more susceptible to stress than controls (Bender & Berch, 1990).

Temperamentally, as boys these individuals are depicted as quiet and less sociable. They have been described as pliant, withdrawn, and low in energy intensity (Netley, 1990). Specific temperamental characteristics were observed in a study of XXY males from birth to age 7 (Walzer et al., 1986). Interview and observational data were obtained on such variables as activity level, intensity of responding, pliancy (e.g., manageability, assertiveness), approach–withdrawal, adaptability, and capacity to relate. Compared to a control group of peers, children with KS were consistently rated as lower in activity, lower in intensity, more pliant, and more withdrawing in new situations. On the Personality Inven-

tory for Children (Lachar & Gruber, 1994), boys with KS were found to differ significantly from controls on ratings of achievement, intelligence, and development, in addition to ratings of lower-than-average activity (Stewart, Bailey, Netley, Rovet, & Park, 1986).

A study of the psychological characteristics of adults with KS found them to be less teasing and sarcastic, and more submissive, than controls and another comparison group of men with XYY (Schiavi, Theilgaard, Owen, & White, 1984). Geschwind and colleagues (1998) hypothesized that the psychosocial problems typically seen in this population are rooted in abnormalities in frontal systems (e.g., executive functioning, impulse control), rather than language problems.

Psychosocial Issues

In a review of several studies regarding psychosocial adjustment in boys with KS (Robinson, Bender, Linden, & Salbenblatt, 1990), common features included shyness, immaturity, restrained or reserved interpersonal relations, and poor peer relationships. The presence of a supportive and stable family environment was noted to have positive effects on psychosocial adjustment for these children. Other studies have described this population as cautious in new situations, low in motor activity, and possessing easy dispositions (Walzer et al., 1990). The authors commented that these characteristics predisposed children with KS to present as "low-key" children who were well liked by their teachers and who had few behavioral management problems. However, one problem with this study that plagues much research with the sex chromosome disorders is that the study included polysomal (e.g., XXY, XYY) cases, and such individuals may display more severe problems.

Bender and colleagues (1990) described a "risk" profile for children with sex chromosome disorders, based on the results of a prospective study. High-risk children tended to be those who had problems communicating with peers, academic problems marked by low achievement, few hobbies or little participation in extracurricular activities, behavioral immaturity, and social isolation. This profile was viewed as a risk for poorer psychosocial functioning as well as adult psychopathology. The authors also recognized the importance of environmental factors for determining outcome.

The abnormal sexual characteristics as well as the academic difficulties often result in low self-esteem and poor self-concept. A follow-up study indicated that adult males with KS are often lonely, immature, passive, and with few friends (Nielsen, Johnsen, & Sorensen, 1980; Nielsen & Wohlert, 1991). Testosterone treatment as therapy for the problems with sexual development has also been found to improve problems stemming from low self-esteem (Schwartz & Root, 1991). Mazur and Clopper (1991) reviewed clinic cases they had seen with gynecomastia and determined that one of the greatest related concerns was the impact of gynecomastia on psychosocial functioning. They reported that their patients had a history of being teased by peers regarding their breast development, which resulted in social isolation and withdrawal in approximately 70% of these individuals. Cases of anorexia nervosa have been described in conjunction with KS, and the poor body image and problems with puberty have been implicated in the etiology (El-Badri & Lewis, 1991; Hindler & Norris, 1986). There are also accounts of schizophrenia in KS, with the hypothesis that the presence of an extra X chromosome and/or the abnormal hormonal levels during prenatal development may cause this association (Pomeroy, 1980; Roy, 1981). Other types of psychopathology, such as bipolar disorder, have been linked to KS, but there is less consensus regarding this relationship (Everman & Stoudemire, 1994). However, most accounts base the etiology of the bipolar disorder on the presence of the extra X chromosome.

In an older study examining the sexual development of individuals with KS, these males were found to date and become sexually involved at a later age then their peers (Raboch, Mellan, & Starka, 1979). Considering the tendency toward withdrawal and negative peer interactions for those with KS, this relative delay is understandable. In a survey of men who were seen at an infertility clinic and found to have KS, these men reported more problems with below-average school performance, little energy, poor relations with parents or siblings, and mental illness than a control group did (Kessler & Moos, 1973). However, it should be noted that many individuals with KS do marry and have successful relationships as adults. New developments in assisted reproductive therapies have also made it possible for individuals with KS to father children.

DIAGNOSIS

Clinical Presentations and Diagnostic Methods

Schwartz and Root (1991) provide an excellent outline of common clinical presentations of individuals with KS across developmental stages. During infancy, KS may be discovered during routine evaluations of hypospadias, microphallus, or cryptorchidism. School-age children may present with learning or behavioral problems. During adolescence, clinical presentations may result from gynecomastia, delayed onset of puberty, abnormally tall stature, small testes, or eunuchoid habitus. Adults may be discovered during evaluations for malignancies, other tumors, or (most frequently) infertility.

When genetic testing was performed in a large population referred for fragile X testing to investigate mental retardation of unknown etiology, 8 out of 670 prepubertal males (<13 years old) tested were found to have KS (1.2%), and none had been previously identified (Khalifa & Struthers, 2002). Clinical features and Barr body analysis were used in another large sample of males suspected of having KS, and this approach was reported to have 95% specificity and 82% sensitivity for KS diagnosis (Kamishchke, Baumgardt, Horst, & Nieschlag, 2003). Of the 309 cases suspected of having KS, 85 were eventually diagnosed with KS by karyotyping. This group were significantly taller, had smaller testes, had higher FSH and LH levels, and exhibited less secondary hair distribution than the group of 224 males who were referred but negative for KS. The majority of those positive for KS (93%) were found to have azoospermia. Interestingly, serum levels of testosterone, estradiol, sex hormone-binding globulin, and prostate-specific antigen were not significantly different between these two groups. This would indicate that azoospermia, low testicular volume, and elevated gonadotropins are strongly indicative of KS when seen together clinically. Early identification may be an important tool to improve outcomes, as some investigators have reported better academic and developmental success when KS is diagnosed prenatally versus postnatally (e.g., Samango-Sprouse, 2001).

Key Diagnostic Issues

Several issues are relevant to KS within the context of diagnosis and assessment. First, the diagnosis of KS may be made at birth or shortly thereafter. If this is the case, both physiological development and learning problems can be assessed early and monitored over the course of the child's schooling. However, a child may not receive an early diagnosis, since many of the features most typical of KS (e.g., delayed puberty, diminished testes, absent secondary sex characteristics) do not appear until the child begins to enter adolescence.

Therefore, parents, teachers, and other child care professionals should be familiar with the characteristic learning, behavioral, and physical presentation of KS, in order to refer these children for genetic evaluation. Lastly, should an assessment be performed, it should include an evaluation of verbal abilities with an emphasis on expressive versus receptive language functioning, verbal memory, and auditory processing. Since these children are at special risk for reading and spelling disabilities, evaluators need to be aware of potentially important Verbal–Performance IQ discrepancies, and should be prepared to compare functioning with the most reliable estimate of cognitive performance.

TREATMENT OPTIONS AND PROGNOSIS

The onset of adolescence is typically not delayed in KS, but it is during this period that the major implications of this disorder become manifest. As discussed above, among the chief physical features are small testes. In a study using testicular sonography technology, adult men with KS were found to have significantly smaller testicular volume, irregular testicular readings (echogenicity), and less intratesticular blood flow than nondisabled peers (Ekerhovd & Westlander, 2002). Androgen deficiency can be determined by testing blood levels, and can typically be treated with testosterone replacement. Although some literature recommends that this treatment begin at age 12 for all children with KS, this policy remains debated (Gardner & Sutherland, 1996). Beneficial results of this treatment include development of masculine sex characteristics, reduced breast size, improved self-esteem, and increased sexual interest (Pierce, 1990). A small study examining both physiological and psychological changes as a result of testosterone treatments found that males with KS began to develop a more masculine physique and secondary sex characteristics, and also had improved perceptions of body image, increased assertiveness and goal-directed behavior, and heightened sexual drive (Johnson, Myhre, Ruvalcaba, Thuline, & Kelley, 1970). Psychological therapy may be useful in helping individuals with KS cope with physiological or psychological concerns associated with KS that are not successfully treated medically.

Complications can be associated with some of the medical treatment options. One report of prostate cancer following long-term (approximately 35 years) testosterone replacement therapy has been reported (Hwang, Dharmawardana, Uchio, Wynberg, & Phillips, 2003). A common side effect of testosterone replacement in adults is prostate enlargement, but the effects of long-term testosterone treatment remain unknown. Routine screening for prostate-specific antigen is therefore recommended to monitor cancer risk.

Infertility is one of the primary concerns for individuals with KS. Although infertility has been found to be the general rule in KS, some exceptions have been reported in the literature, as reviewed by Gardner and Sutherland (1996). These authors hypothesized that these reports were most likely attributed to cases of mosaicism. Big advances in infertility treatments have been made within the last several years, although success rates are still low and complications exist. Okada and colleagues (2004) reported on two conventional methods for testicular sperm extraction (TESE)—multiple testicular biopsy technique and microdissection TESE—and found that both caused decreased testosterone levels that did not return to baseline levels following the procedure. They have recommended testosterone replacement therapy to address this problem. Tournaye and colleagues (1996) reported on the first successful surgical sperm recovery, which can be used to allow men with KS to produce children by intracytoplasmic sperm injection (ICSI). Fertility success rates as high as 50% in KS have been reported, with better outcomes with ICSI than with round spermatid injection (Ulug, Bener, Akman, & Bahceci, 2003). However, actual rates of pregnancy

resulting from successful sperm extraction and implantation are lower (27.2%), and not all of these have resulted in successful births (Ulug et al., 2003). Due to the low pregnancy success rate reported with ICSI and issues related to possible genetic transfer of sex chromosomal abnormalities, genetic counseling is recommended (Simpson et al., 2003). Although the probability of having children with KS is believed to be rare, the risk of passing on this genetic disorder is virtually unknown. There is also little known about the recurrence rate of producing a child with a chromosomal disorder. Genetic counseling for the individual with KS should therefore play an important role in family planning. Since infertility is often the primary referral problem, marriage counseling may also be beneficial to deal with issues related to sterility. Alternatives such as adoption, insemination by donor, and other assisted reproductive therapies should be discussed with men who wish to have children.

SUMMARY

KS is a sex-linked chromosome disorder that has distinct learning, behavioral, and physiological features. Language-based learning disabilities are perhaps the most challenging academic problems, and language processing deficits persist into adulthood. The physical anomalies and hormonal disturbances present in this disorder can create both social and emotional challenges, particularly with the onset of puberty and into adulthood. Advances in testosterone replacement therapies have provided treatment for many of the hormone-related problems, and there is evidence that early treatment may also serve as a protective mechanism against some of the cognitive and neurological impairments. New techniques in reproductive medicine have also made it possible for men with KS to consider having children. Early genetic identification, perhaps even prenatally, can help lead to earlier intervention for both the learning and physiological features. As further advances are made in the years to come, it is likely that there will be additional gains in the treatment outcomes for individuals with KS.

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20

RETT SYNDROME

ROBERT T. BROWN
KATHLEEN K. McMILLAN
ALEXIS HERSCHTHAL

Rett syndrome (RS or RTT) is a genetically based disorder that presents in infancy or early childhood as a striking deterioration after apparently normal initial development. (The common acronym for Rett syndrome is RS, which will be used in this chapter, but *Online Mendelian Inheritance in Man* (2004) and numerous papers use RTT.) Although occasionally still misdescribed as a degenerative or progressive disorder, RS is neurodevelopmental, "an essentially early developmental problem which manifests itself in a predictable sequence and is accompanied by changing risks throughout life" (Kerr & Witt Engerström, 2001, p. 1). The American Psychiatric Association (2000) classifies it as a pervasive developmental disorder (Rett's disorder, code number 299.810). It is indeed pervasive, affecting virtually all domains of functioning. Although RS has no overall effective treatment, available techniques may alleviate a variety of its symptoms. Of particular interest here is that only about 80% of females found to have RS are diagnosed in childhood, suggesting that many adolescent and adult cases remain undetected. Indeed, in one study, 7 of 30 older subjects had not been diagnosed until adulthood (Smeets et al., 2003); in another, an institutionalized woman was not diagnosed until age 52 (Jacobsen, Viken, & von Tetzchner, 2001). The probable existence of undiagnosed RS in older individuals indicates that clinicians working with adolescent and adult populations should have knowledge of RS's characteristics, diagnosis, developmental trends, and treatments.

Major additions to, and some changes in, knowledge about RS have occurred since the publication of the chapter on this syndrome (Brown & Hoadley, 1999) in the *Handbook of Neurodevelopmental and Genetic Disorders in Children*. These include discovery of a genetic basis and cases in males. Areas where relatively little has changed will be summarized from the Brown and Hoadley chapter.

RS involves a slowdown in normal development, deceleration of head growth, lack of interest in the environment, deterioration of motor functioning, loss of hand use and subsequently of locomotion, hand stereotypies (typically hand wringing or clapping), loss of expressive language, sleep and breathing abnormalities, frequent seizure disorders, autistic and self-abusive behavior, and eventual severe or profound mental retardation. Although it is a rare disorder, with prevalence of approximately 1 in 15,000 females, it may be the

second most common form (after Down syndrome) of severe mental retardation (Hagberg, 1995b), and the most common cause of profound mental retardation (Percy, 2002), in females. The several thousand known cases occur apparently equally in all parts of the world and in all ethnic groups. About 3,000 cases have been found in the United States (e.g., Naidu, 1997).

RS is unique in several ways:

1. The apparently normal initial development is only apparent, being frequently marked by growth retardation from birth and passivity in early infancy.
2. The rapid mental and physical deterioration is often followed by stabilization or reduction of some symptoms (e.g., Budden, 1997; Hagberg, 1995b).
3. Although RS was initially thought to affect only females, cases of RS and RS-like disorders have been reported in males.
4. As Moser and Naidu (1996, p. 379) note, "The pattern of evolution and symptomatology in patients [with RS] has been remarkably consistent," but RS was not described until 1966 and not brought to wide attention until 1983.
5. A mutation in the gene MECP2, which encodes the protein MeCP2, appears to cause RS in about 85% of female cases. However, no one-to-one relationship between genotype and phenotype is known, and MECP2 mutations are involved in other conditions.
6. Although RS has been the subject of numerous articles in the popular press, hundreds of professional articles, several books, and sophisticated websites, it is still relatively unknown in comparison to many other developmental disorders of comparable prevalence but less severity.
7. RS occurs in both the classic form and a number of variant forms.
8. Although the typical symptomatology in affected individuals is severe, physical appearance is normal in childhood, and life expectancy is often near normal.

HISTORY AND BACKGROUND

Apparently owing to the structure of health services in Austria, Andreas Rett, a pediatrician at the University of Vienna, saw many Austrians who had severe or profound mental retardation in the early 1960s. One day in his clinic, he observed two unrelated thin girls sitting next to each other who were wringing their hands in an unusual manner and rocking back and forth in autistic-like movements. The observation of two simultaneous cases may have been important in evoking Rett's interest, as at least one isolated case of possible RS was described as early as 1847 (Brown, 2004). In 1966, Rett published his observations on several girls who had similar symptoms and developmental history: After apparently normal development up to 6–18 months, the girls showed general deceleration of psychomotor development, cognitive and linguistic regression, and development of repetitive and stereotypic hand wringing or washing (see Hagberg, 1995b, for a summary of Rett's work).

Although followed by several other publications in German and at least one in an obscure source in English, Rett's initial findings were largely overlooked until Hagberg, Aicardi, Dias, and Ramos (1983) published a major report on 35 cases in a journal in English. Owing to that article, RS became known throughout the world. Hagberg's subsequent work has contributed much to our knowledge about RS.

DIAGNOSIS OF RS AND RS VARIANTS

An expert panel sponsored by the International Rett Syndrome Association (IRSA) (Hagberg, Hanefeld, Percy, & Skjeldal, 2002) has established revised necessary, supportive, and exclusionary diagnostic criteria for RS, as well as necessary and supportive criteria for RS variants. (Much of the first two paragraphs of this section is closely based on Hagberg et al., 2002.) One intent of the IRSA was to provide common criteria for diagnosing cases for the IRSA RS Clinical Database, which relates various genotypes (gene mutations) to various phenotypes (observable physical symptoms) and is linked to the IRSA MECP2 Variations Database (Fyfe, Cream, de Klerk, Christodoulou, & Leonard, 2003). Of importance, as Hagberg and colleagues (2002) emphasize, is that diagnosis of RS should be based on clinical signs, not genetic analysis. The relationship between RS and MECP2 gene mutations is not perfect, as described above. RS and MECP2 mutations do co-occur, but each also occurs without the other. Some 20% of individuals with RS do not have the mutation, and some with the mutation do not show RS. Also of importance is the variability among those with RS in terms of the severity of symptomatology (e.g., Naidu et al., 2003).

Several phenotypes are associated with MECP2 mutations in both males and females. In addition to RS itself, female phenotypes include the preserved-speech RS variant, the delayed-onset RS variant, mild learning disability, Angelman syndrome, and the carrying of a mutation without evident disability. Male phenotypes include fatal encephalopathy (most cases), Rett–Klinefelter syndrome (47,XXY genotype), Angelman syndrome, X-linked mental retardation/progressive spasticity, and somatic mosaicism/neurodevelopmental delay (Hagberg et al., 2002; OMIM, 2004).

The revised criteria for RS and RS variants are presented in Tables 20.1 and 20.2, respectively, and should be used in place of those originally established by the Rett Syndrome Diagnostic Criteria Work Group (e.g., 1988) and revised since (e.g., Hagberg, 1995a, 1995b). As Table 20.1 indicates, necessary for diagnosis is apparently normal pre- and perinatal development, followed by sudden deceleration of head growth and loss of acquired skills such as hand use and communication (including language), beginning in infancy or early childhood. Also required are evidence of mental retardation and the appearance of intense and persistent hand stereotypies. Those who had developed walking must show gait abnormalities; some never develop walking. Electroencephalographic (EEG) abnormalities, seizure disorder, spasticity, marked scoliosis, and overall growth retardation are also typical.

In diagnosis, "a battery of clustered remarkable RS behavioral and other clinical oddities can be of considerable help" (Hagberg, 1996, p. 144). As described in Hagberg (1995b), this battery consists of the following:

1. *Stereotypic hand movements*. "The almost continuous repetitive wringing, twisting or clapping hand automatisms during wakefulness constitute the hallmark of the condition" (Hagberg, 1995b, p. 973). Adult females with mental retardation who show RS-type hand stereotypies should be considered to have potential RS and referred for diagnosis.
2. *Episodic hyperventilation and breath holding*. Characteristic are irregular episodes of hyperventilation, interrupted by breath holding for 30–40 seconds.
3. *Bloating*. Moderate air swallowing leading to some abdominal bloating is common, and severe bloating occurs in a small percentage of cases.
4. *Bruxism*. A creaking sound made with the teeth, "similar to that when slowly uncorking a bottle" (Hagberg, 1995b, p. 973), is characteristic although not specifically diagnostic.

TABLE 20.1. RS: Revised Necessary, Supportive, and Exclusionary Diagnostic Criteria

Necessary criteria

1. Apparently normal prenatal/perinatal history.
2. Psychomotor development delayed from birth or apparently normal to about age 6 months.
3. Normal head circumference at birth.
4. Postnatal retardation of head growth (most cases).
5. Loss of purposeful hand skills between 6 and 30 months of age.
6. Development of persistent stereotypic hand wringing/squeezing, clapping/tapping, mouthing, and/or washing/rubbing.
7. Progressive social withdrawal, loss of verbal/nonverbal communication, and cognitive impairment.
8. Progressive partial to complete loss of locomotor ability.

Supportive criteria

1. Disturbed breathing (hyperventilation, breath holding, forced expulsion of air/saliva, air gulping) while awake.
2. Bruxism.
3. Impaired sleep patterns, perhaps from early infancy.
4. Abnormal muscle tone, resulting in muscle wasting and dystonia.
5. Peripheral vasomotor disturbances.
6. Progressive scoliosis/kyphosis.
7. Growth retardation.
8. Hypotrophic, cold feet; small, thin hands.

Exclusionary criteria

1. Organomegaly or other signs of storage disease.
2. Retinopathy, optic atrophy, or cataract.
3. Specific perinatal or postnatal brain damage.
4. Metabolic or other progressive neurological disorder.
5. Neurological disorder owing to severe infections or head trauma.

Note. From Hagberg, Hanefeld, Percy, and Skjeldal (2002). Copyright 2002 by the European Paediatric Neurology Society. Reprinted by permission.

5. *Night laughing*. Among the more common sleep disturbances, shown in 80–90% of preschool girls with RS, are bouts of sometimes long and disturbing night laughing. These tend to be episodic over age, but may persist into adulthood.

6. *Hypoplastic, cold, red–blue feet*. Small, cold, red–blue feet are commonly, but not always, seen in RS.

7. *Scoliosis*. Neurogenic scoliosis is characteristic. Degree is variable, but tends to progress relatively rapidly.

8. *Changed sensitivity to pain*. Pain perception is never absent, but may be delayed or reduced.

9. *Intensive eye communication*. Eye communication, including eye pointing, appears to occur in most girls with RS after the regression stage described below. However, the validity of claims of eye pointing must be interpreted with caution: Using a blind procedure, Meyer, Kennedy, Shulka, and Cushing (1999) found that caretakers did not accurately interpret the eye pointing of an adolescent with RS, but were making inferences based on their familiarity with her.

The RS variant model in Table 20.2 was developed owing to the realization that females with RS are much more heterogeneous than originally thought (Hagberg, 1995a, 1995b). Diagnosis of an RS variant should be made only in girls age 10 years or older when at least three necessary and at least five supportive criteria are present. These behaviors

TABLE 20.2. RS Variants: Revised Main and Supportive Diagnostic Criteria

Patient must meet at least three main and at least five supportive criteria.

Main criteria

1. Absence or reduction of hand skills.
2. Reduction or loss of babble speech.
3. Monotonous pattern of hand stereotypies.
4. Reduction or loss of communication skills.
5. Deceleraton of head growth from first years of life.
6. RS disease profile: A regression stage followed by a recovery of interaction contrasting with slow neuromotor regression.

Supportive criteria

1. Breathing irregularities.
2. Bloating/air swallowing.
3. Harsh-sounding grinding of teeth.
4. Abnormal locomotion.
5. Scoliosis/kyphosis.
6. Lower-limb muscle atrophy.
7. Cold, purplish feet, usually with growth impaired.
8. Sleep disturbances, including night screaming outbursts.
9. Laughing/screaming spells.
10. Diminished response to pain.
11. Intense eye contact/eye pointing.

Note. From Hagberg, Hanefeld, Percy, and Skjeldal (2002). Copyright 2002 by the European Paediatric Neurology Society. Reprinted by permission.

may appear throughout childhood. Typically, girls who meet the criteria for an RS variant show less severe symptoms than those associated with classic RS. Both gross and fine motor control may be more spared, and mental retardation is less severe. These girls may retain some language, although it tends to be abnormal and telegraphic. Those with language tend to have had a later and milder regression period.

Of importance, particularly for parents and therapists, is accurate diagnosis as early as possible. Although some physicians may be reluctant to diagnose RS early, owing to its eventual severity, many parents (as shown in our case description below) are frustrated by the lack of a diagnosis that fits their children's behaviors or has implications for treatment and care. A symptom checklist is now available to help determine whether a girl should be referred for testing for presence of an MECP2 mutation (Huppke, Köhler, Laccone, & Hanefeld, 2002).

DEVELOPMENTAL TRENDS

Classic RS develops through a predictable four-stage sequence of behavioral and physical changes, first described by Hagberg and Witt Engerström (1986) and since elaborated by many others. Kerr and Witt Engerström (2001) provide a useful descriptive table of changes across the stages. Age of onset, duration of transition from one stage to another, and duration of the stages are highly variable, however, and not all affected individuals show all features of each stage. This section describes the major characteristics of early development and of each stage, along with disorders from which RS should be differentiated. Except as specifically referenced, the information in this section comes from the Brown and Hoadley

(1999) chapter, which in turn was based on Budden (1997), Hagberg (1995b), Hagberg and Witt Engerström (1986), Kerr (1995), and Naidu (1997).

Pre-Stage 1: Early Development

Much development before stage 1 appears normal, and the necessary criteria for diagnosis include apparently normal development until at least 5–6 months of age. Early motor skills, including reaching for objects, usually appear. Infants commonly develop self-feeding and can be weaned onto solid foods. Many develop babbling and (often with unusual gait) walking. However, normality is in most cases only apparent; subtle signs of RS appear much earlier. Newborn females who later develop RS generally have lower-than-normal occipital frontal circumference (OFC), length, and weight, suggesting that MECP2 gene mutations have prenatal effects (Huppke, Held, Laccone, & Hanefeld, 2003). Many infant developmental milestones are delayed or absent. Feeding difficulties, floppiness, jerkiness, delays in motor development, poor mobility, repetitive limb movement, and limited play may appear in early infancy. In one study (Charman et al., 2002), some 70% of cases showed pre-stage 1 abnormalities, most commonly hypotonicity and delayed motor development, but also failure to recognize familiar adults and delays in babbling and play skills. Kerr (1995) noted repeated opening and closing of a hand with which an infant is attempting to grasp an object. Repeated facial and mouth twitching in some infants at 2 or 3 months of age suggests possible cortical abnormality (Kerr, 1995).

Many girls develop single-word communication and a few use short phrases, but most parents report that their daughters with RS only showed indiscriminate use of "mama" and "dada" before stage 1 (Tams-Little & Holdgrafer, 1996). Of interest from a potential early diagnostic standpoint, Tams-Little and Holdgrafer (1996) also found that parents of only 1 of 17 girls with RS reported use of three gestures (giving, pointing, and showing) that normally appear at about 9–10 months of age and reflect development of intentional nonverbal communication.

Stage 1: Early-Onset Stagnation

The first stage begins at 6–18 months of age and generally has a duration of months. Although some advances may occur, particularly in gross motor control, in many ways the infant appears to hit a developmental wall. Many aspects of cognitive development cease. Deceleration of head growth occurs, and head circumference is generally below normal by the end of the second year of life (Kerr, 1995). Hypotonia, lack of interest in play and the environment, loss of acquired hand functions, and random hand movements are typical. No obvious pattern of abnormalities is apparent, however. Differential diagnoses include benign congenital hypotonia, cerebral palsy, Prader–Willi syndrome, and metabolic disorders.

Stage 2: Rapid Developmental Regression

At an average age of about 18 months (range of 1–4 years), affected children's functioning begins to deteriorate so generally and rapidly that the onset may be taken for a toxic or encephalitic state (Hagberg & Witt Engerström, 1986). Indeed, Budden (1997, p. 2) re-

ports that the onset "may be so acute that parents can sometimes give a specific date after which their child was no longer 'normal.'" General cognitive functioning, purposeful hand use, and expressive language deteriorate. Hand stereotypies, including hand wringing, washing, and mouthing, typically appear and may be continuous during waking hours. Walking may deteriorate or not develop. Girls who can walk generally show gait abnormalities, particularly a spread-legged stance. Hyperventilation, bruxism, and breath holding are common, as are behaviors characteristic of autism. Seizures and vacant spells resembling seizures may occur, and virtually all girls with RS have abnormal EEGs by the end of stage 2. Sleep patterns may become erratic and accompanied by bouts of screaming and inappropriate laughter (Kerr & Witt Engerström, 2001). Differential diagnoses include autism, encephalitis, metabolic disorders (including inborn errors of metabolism), and neurodegenerative disorders.

Stage 3: Plateau

Stage 3 has a highly variable age of onset and lasts several years, generally until about 10 years of age. Hand stereotypies continue, and mobility may further deteriorate. Mental retardation in the severe–profound range is characteristic. However, autistic symptoms may diminish, and social interactions, hand use, communication, alertness, and self-initiated behavior may increase. Tremulousness, ataxia, teeth grinding (bruxism), hyperventilation or breath holding, and seizures may all occur. Overall rigidity (hypertonia) often increases, and scoliosis appears. Nonverbal communication through eye pointing appears to improve. Differential diagnoses include cerebral palsy and other motor disorders, Angelman and Lennox–Gastaut syndromes, and spinocerebellar degeneration.

Stage 4: Late Motor Deterioration

The final stage generally begins whenever stage 3 ends. Motor function decreases further, with increased rigidity and muscle wasting. Scoliosis occurs in most cases where it did not earlier appear and becomes progressively severe. Mobility continues to decrease; many girls will be wheelchair-bound, although others will maintain walking with altered gait throughout life. Hands may be held in the mouth for long periods. Puberty is often somewhat delayed, but otherwise normal. Owing to limited verbal and nonverbal communication, affected girls may be unable to convey that they suffer from menstrual discomfort or vaginal infection. Expressive language, if previously present, generally disappears, and receptive language decreases. Eye pointing as communication may continue. Chewing and swallowing may be lost, necessitating artificial feeding. Differential diagnosis is for unknown neurodegenerative disease.

RS IN ADOLESCENCE AND ADULTHOOD

The final phenotypic characteristics of classic RS vary widely:

> With increasing age and advanced state of the disease, the final differences in severity of motor disability, pattern of neurology and degree of impairment are striking. Thus, in adulthood, there are ambulant RS females, certainly dyspraxic, but nonetheless not dissimilar to other

> uncomplicated severely retarded patients. Other RS females have never learned to walk, some being completely helpless, with severe extrapyramidal syndromes, combined with neurogenic atrophies and secondary grotesque body deformities. (Hagberg, 1995b, p. 972)

Relatively little change in behavior or medical problems occurs in many areas during or after adolescence (stages 3 and 4), particularly by comparison with the dramatic changes in the first two stages. For example, Leonard, Fyfe, Leonard, and Msall (2001) found that parents reported little overall change after their daughters with RS were 5 years of age on the Functional Independence Measure for Children. The range in scores was very high, such that some girls showed considerable functioning in some areas, whereas others were almost totally dependent. Girls with RS were most dependent in self-care, sphincter control, mobility (particularly transfer from one setting to another such as getting into/out of chair or wheelchair, shower, and toilet), daily movement, communication, and social cognition. Most communication was by apparent eye pointing or flash cards (Leonard et al., 2001).

Similarly, using both direct assessment and parent reports on 87 females with RS, Cass and colleagues (2003) found only modest changes in most behaviors from below 5 to beyond 20 years of age. Repetitive hand stereotypies were virtually universal at all ages, being absent in only two cases. With little variation in age, approximately 80% of the females had some problem with feeding, and for some 72% the problems were at least moderate in severity. The prevalence of skeletal deformities and seizures increased with age. Specifically, the presence of scoliosis increased from about 30% for under 5 years of age to 84% for those over age 20; the occurrence of fixed-joint problems (hips, knees, ankles, etc.) increased from fewer than 10% for those under 5 to over 90% for those over 20; the prevalence of seizure disorders virtually doubled from under 5 to 5–9 years of age and thereafter showed little change. Virtually all individuals drooled, with severity erratically related to age. Particular breathing abnormalities (breath holding, hyperventilation, air swallowing, and abdominal distension) also varied erratically with age, but for the group as a whole increased dramatically from below age 5 years to 5–9 years, and then decreased after 20 years. Overall motor ability showed little age-related change, but, as in the Leonard and colleagues (2001) study, about half of these girls were severely impaired in mobility. Most of them could sit independently and stand with assistance, but inability to stand at all increased with age.

A variety of sleep disturbances appear in about 80% of cases, beginning at a young age and persisting into adulthood (e.g., Kerr & Witt Engerström, 2001). Adults with RS show different types and levels of behavioral abnormalities from those in a normative sample of adults with severe mental retardation. Ratings by caretakers of 50 adult females with RS on the Aberrant Behavior Checklist showed lower levels of irritability, hyperactivity, and inappropriate speech (probably owing to overall language deficits), but higher levels of stereotyped behaviors and lethargy, than those found in a normative sample (Mount, Hastings, Reilly, Cass, & Charman, 2002).

The most dramatic changes with age appear to be in physical growth. Of Cass and colleagues' (2003) subjects, the percentages falling below the 3rd percentile in weight, height, and head circumference increased, respectively, from 20%, 17%, and 30% of those age 5 to 80%, 50%, and 100% of those over 20. Growth deficits are related to feeding difficulties, but other factors that are not well understood also contribute (e.g., Reilly & Cass, 2001). As would be expected from the small head circumference, brain size of those with RS is also reduced: Average brain weight at autopsy of 51 females with RS was about 990 grams, compared with an average normal weight of about 1,280 grams (Armstrong &

Kinney, 2001). Brain weight apparently does not decline with age, but the sample size of older subjects was small.

Although females with RS are often reported as having normal vision and hearing, some studies (e.g., Pillion, Rawool, Bibat, & Naidu, 2003) suggest that many with RS have hearing loss that increases with age and use of phenytoin, but not other anticonvulsant agents. RS individuals with hearing loss may benefit from hearing aids, but caretakers will need to attend carefully to their use. At the least, parents, therapists, and teachers need to adjust oral communication and even music therapy to the auditory functioning of those with RS.

Mobility and feeding generally require the most day-to-day intervention by caregivers. Individuals with RS, as described above, have limited hand use and locomotion. In addition, many have difficulty chewing and swallowing, as well as keeping their mouths closed while doing so. In extreme cases, tube feeding may be necessary. Owing to feeding and other difficulties, many with RS will be underweight. Those who can self-feed, on the other hand, may become overweight. Constipation is a common problem, which may be difficult to correct through diet or additional fluids (e.g., Kerr & Witt Engerström, 2001). Keeping a detailed food intake record may help identify foods that are consistently accepted or refused. "Chewy" foods appear to be rejected by many individuals with RS (Isaacs, Murdock, Lane, & Percy, 2003).

Life expectancy is difficult to estimate, in part because most individuals diagnosed with RS are under 18 years of age. Death rate is higher than normal across the age range, owing to illness, wasting, or "sudden death" during sleep. About 95% live to ages 20–25 years and about 70% to 25–40, compared to 98% and 97%, respectively, of the general female population in the United States. Many with RS live into their 50s or beyond. Average life expectancy may well be above 45 years, far higher than the 27% overall for those with profound mental retardation (IRSA, 2004; Naidu, 1997). The woman mentioned in the introduction, who was diagnosed only at age 52, lived to 60 (Jacobsen et al., 2001).

GENETICS

As indicated in the previous chapter (Brown & Hoadley, 1999) and numerous other sources, RS has been assumed to be a single-gene X-linked dominant disorder for many reasons, including these : (1) Concordance is virtually 100% in monozygotic twins and 0% in dizygotic twins; (2) about 1% of RS cases are familial; and (3) early findings indicated that RS fully appears only in females, with a few cases of males with Rett-like symptoms (but see the following section, "RS in Males").

This assumption was confirmed when Amir and colleagues (1999) reported mutations in the X chromosome gene MECP2 (methyl CpG binding protein 2) in several cases of spontaneous and familial RS. Subsequent research has indicated that the correlation between RS and MECP2 mutations is high, but not perfect: About 80% of females with RS and 50% of those with RS variants have mutations on exons 3 and 4 of MECP2, but some with RS show no mutations, and some with mutations do not show RS. Although the severity of symptoms in those with RS generally appears not to be related to the type of mutation, studies have linked both the timing of symptoms' appearance and their severity to particular mutation locations (Colvin et al., 2004; Naidu et al., 2003). However, Naidu and colleagues (2003) find considerable variability in severity in girls with the same mutation, leading them to suggest that additional factors, such as X chromosome inactivation, influence severity. MECP2, pronounced "meck-pea-two" (National Institute of Neurological Disorders and

Stroke [NINDS], 2004), is located at the tip of the long arm of the X chromosome and encodes a protein, MeCP2, a transcriptional repressor that controls the expression of other genes (Johnston, 2004). Most mutations appear to reduce or eliminate function of MeCP2. Impaired function of MeCP2 in turn may disrupt the normal developmental pathway by leading other genes to turn and/or stay on at inappropriate times, resulting in uncontrolled gene expression (Johnston, 2004).

Over 100 mutations have been identified on exons 3 and 4, but none on exon 2 of MECP2, which has four exons. Recently, Mnatzakanian and colleagues (2004) have located mutations on exon 1 (previously thought to be noncoding) of MECP2 in several girls with RS who showed no other MECP2 mutations. These mutations may underlie RS in girls who do not have mutations on exons 2 and 3.

A mouse model, in which MECP2 mutations in heterozygous females result in RS-like conditions, is providing interesting leads about RS in humans. These mice show apparently normal development for about 6 weeks, but then develop common RS characteristics, including tremors, motor impairments, low general activity, apparent anxiety, seizures, curvature of the spine, and stereotypic forelimb movements (Shahbazian et al., 2002). Selective deletion of MeCP2 from mouse brains produces the same impairments, supporting the position that it may be necessary for normal brain development and function. Providing hope for eventual prevention of the effects of MECP2 mutations, Luikenhuis, Giacometti, Beard, and Jaenisch (2004) have described a procedure that "rescues" mice from the adverse consequences of MECP2 mutations. In mice, MeCP2 regulates brain-derived neurotrophic factor (BDNF), which encodes a secreted protein essential for adult neuronal plasticity, which in turn is essential for learning and memory. MECP2 mutations deregulate this protein in mouse models of RS, and this deregulation, through its action on BDNF, may be responsible for RS (e.g., Chen et al., 2003; Gabellini, Green, & Tupler, 2004). Neul and Zoghbi (2004) summarize the details and complexity of genetic influences.

RS IN MALES

Case Reports

Independent reports by Coleman (1990) and Philippart (1990) of two possible cases of RS in males appeared over a decade ago. Subsequent case reports indicate that RS, RS variants, and RS-like conditions do occur in males, although at an extremely low rate.

As might be expected, classic RS has been reported in a few cases of boys with the classic 47,XXY karyotype of Klinefelter syndrome or with the 47,XXY/46,XY mosaic karyotype. In one (Schwartzman et al., 1999), the boy initially developed normal sitting, grasping, playing, and feeding, and had begun to say a few individual words appropriately. By a year of age, he was losing hand, language, and social skills and was developing stereotyped hand movements, bruxism, and constipation. By age 3 years, he was severely retarded, had lost purposeful hand movements, and had general hypotonia—all behaviors characteristic of RS, but not Klinefelter syndrome. Genetic tests indicated that the second X chromosome came from the father through nondisjunction. In a highly unusual case (Maiwald et al., 2002), a boy who was determined to be male by prenatal sonogram and postnatal phenotype, but who had a female 46,XX genotype, showed at age 24 months several characteristics of RS, including delayed motor development, lack of language, hypotonia, microcephaly, and loss of purposeful hand movements.

RS-like symptoms—including growth retardation, mental retardation, hypotonia, absent or lost language, microcephaly, seizures, scoliosis, abnormal EEG patterns, and

respiratory irregularities—have been reported in boys in families with recurrent RS in their daughters (Schanen et al., 1998), as well as in boys with somatic mutations in MECP2 (Clayton-Smith, Watson, Ramsden, & Black, 2000; Topçu et al., 2002). One of Schanen and colleagues' (1998) cases died at age 18 months, apparently from respiratory failure, and the other showed motor and other delays and a head circumference below the 5th percentile at 9 months of age. The boy reported by Clayton-Smith and colleagues (2000) developed hand stereotypies, whereas the one reported by Topçu and colleagues (2002) did not. Furthermore, cases summarized by Moog and colleagues (2003) indicate that nonmosaic MECP2 mutations in 46,XY males are manifested in disorders ranging from mild to severe: classic RS, RS variants, congenital encephalopathy leading to early death, severe mental retardation in association with a variety of neurological disorders (e.g., ataxia, seizures, and hypotonia), PPM-X syndrome (pyramidal signs, psychosis, mental retardation, and macro-orchidism), and mental retardation alone (ranging from mild to severe).

Why Is RS Rare in Males?

Two explanations have been offered for the unusually high female–male ratio in RS. Although they may be seen as competing, both explanations could operate in particular cases. Both assume that RS is an X chromosome disorder, and both were developed prior to the discovery of the relationship between RS and MECP2 mutations. The more frequently cited explanation is that the responsible gene is prenatally fatal to males, as males' shorter Y chromosome lacks a normal gene to moderate the effects of the mutated one on the X chromosome. Thus males with the mutated gene may be nonviable, dying either prenatally or early postnatally (NINDS, 2004). The second explanation, proposed by Thomas (1996), is based on evidence that (1) RS is a dominant X chromosome disorder; (2) RS is largely nonfamilial and thus is probably largely attributable to spontaneous mutation; and (3) mutations generally occur more frequently in sperm than in eggs, at least partly owing to the fact that sperm go through two meiotic divisions during gametogenesis, whereas eggs go through only one. Since chromosomally normal women (46,XX) get one of their X chromosomes from their fathers, and chromosomally normal males (46,XY) always get their X chromosome from their mothers, more affected females than males may be expected on the basis of normal inheritance patterns. If most RS is based in spontaneous mutation of eggs or sperm, then familial cases may be expected to be rare (as they are), supporting Thomas's explanation.

Until recently, more evidence supported the explanation that the gene causing RS is lethal to males prenatally. For example, Akesson, Hagberg, and Wahlström (1997) reported significantly fewer male siblings among girls with RS than would be expected. Since males' X chromosome is received from their mothers, maternal transmission was indicated in these cases. Furthermore, after establishment of the link between RS and the MECP2 mutation, several cases of early postnatal deaths in males with MECP2 mutations were reported, suggesting that most such deaths were prenatal. Finally, a knockout MECP2 mouse model produced no surviving male offspring (see Trappe et al., 2001, for details and references). However, Trappe and colleagues' (2001) own research provides strong support for Thomas's explanation. In an analysis of 27 females with RS owing to spontaneous MECP2 mutations, they found that 26 had inherited the mutation on the X chromosome from their fathers. Given that most cases of familial RS and RS-like conditions in both males and females arise from a maternal MECP2 mutation, most cases of RS (some 99% of which are nonfamilial) can probably be attributed to a spontaneous paternal MECP2 mutation. In Trappe

and colleagues' words (2001, p. 1097), "males are, therefore, naturally protected from the sporadic form of [RS], which is caused by de novo mutations, and . . . [RS] should no longer be considered lethal in males." However, the two explanations are not mutually exclusive; therefore, both may be involved in the low prevalence in males.

NEUROPATHOLOGY

RS is associated with dramatic neurological, neurochemical, and neurophysiological effects. As might be expected from its widespread effects, some abnormalities are global, but as might be expected from its particular effects, some areas are more severely affected than others. The impact on areas involved in motor control is profound. As would be expected from common seizure and sleep disorders, EEG patterns tend to be abnormal (e.g., Jellinger, 2003).

Perhaps the most striking overall effect of RS is the small brain size relative to age and height: The size is about that of a normal 12-month infant and appears to remain unchanged virtually throughout life. On initial inspection, many parts of brains affected by RS appear to resemble those of normal mature brains (Armstrong & Kinney, 2001), and affected brains show no abnormal neuronal migration or obvious cell loss or atrophy (Neul & Zoghbi, 2004). However, numerous abnormalities have been documented. The cerebral hemispheres show progressive atrophy, with overall reduction of gray and white matter, particularly in the frontal and temporal lobes (e.g., Kaufmann, 2001). The corpus callosum may be 30% below normal size. Brains affected by RS have small dendritic trees in pyramidal neurons of layers III and V in the frontal, motor, and temporal lobes; small neurons with increased neuronal packing density in the cerebral cortex, thalamus, basal ganglia, amygdala, and hippocampus; and reduced numbers of synapses in many areas (e.g., Armstrong, 2002; Jellinger, 2003; Neul & Zoghbi, 2004). Blood flow is reduced throughout the cortex (e.g., Armstrong & Kinney, 2001), particularly in prefrontal and temporoparietal areas (e.g., Jellinger, 2003). The midbrain, cerebellum, and basal ganglia, particularly the caudate nucleus and thalami, are smaller (e. g., Dunn et al., 2002; Jellinger, 2003). The cerebellum additionally shows abnormalities suggestive of prenatally arrested development (Jellinger, 2003). Positron emission tomography scans show reduced uptake of fluorodopa, but increased dopamine D2 receptor binding, in the caudate and putamen of girls with RS relative to nondisabled controls (Dunn et al., 2002). Dunn and colleagues (2002) suggest that RS involves a presynaptic deficit of nigrostriatal activity.

Substance P, a neuromodulator, is substantially reduced in girls with RS. Its reduction in spinal cord areas involved in transmission of pain stimuli could be involved in these girls' often reported reduced pain perception. It is also involved in the control of many other functions that are affected in RS, including respiration, transmission of visual and olfactory information, heart rate and rhythm, growth, and sleep (e.g., Armstrong & Kinney, 2001).

Levels of many neurotransmitters are reduced in those with RS (e.g., Armstrong, 2002; Neul & Zoghbi, 2004). Dysfunction of the cholinergic forebrain system, which causes reduced choline acetyltransferase activity, is often found (e.g., Jellinger, 2003). Brains affected by RS generally have low levels of dopamine, norepinephrine, serotonin, and their metabolites. On the other hand, postmortem studies of elderly women with RS revealed no overall low levels of dopamine, but low levels of dopamine and serotonin and their metabolites in the substantia nigra. Consistently found is reduced pigmentation in the substantia nigra (Jellinger, 2003). Some of these abnormalities may owe to the reduced

concentrations of nerve growth factor found in the cerebrospinal fluid of girls with RS (Riikonen, 2001).

The variety of respiratory and cardiovascular conditions associated with RS led Julu (2001, p. 132) to suggest that RS is a "congenital dysautonomia" and that "early brainstem dysfunction underlies the respiratory disturbance and may contribute to sudden deaths in the RS disorder." Levels of cardiac sensitivity to baroflex and cardiac vagal tone in girls with RS are almost 50% lower than normal, indicating that RS involves a lack of integration in the brain stem, particularly in the nucleus tractus solitarius (Julu, 2001).

Of interest, brain stem neural systems that develop between 36 weeks gestational age and 2–3 months postnatally appear to be abnormal, whereas those developing earlier appear normal. Thus the onset of RS may occur in late fetal or early postnatal development and may be caused by early lesions of monoamine neurons (Nomura & Segawa, 2001). According to Nomura and Segawa (2001), low functioning of noradrenergic and serotonergic neurons that develop during that period could be responsible for sleep disorders associated with RS, and deficiencies in dopaminergic neurons would follow. They propose that "the symptoms and signs of RS are explained by . . . early lesion[s] of the [monoamine] neurons in the brainstem and midbrain. . . . These lesions may cause maturational arrest or insufficient synaptogenesis at each level of the brain [including the cortex] . . . , which do not show progression except for the appearance of receptor supersensitivity. The maturational arrest is manifested in a caudal to rostral sequence, leading to the age dependent clinical features." This "monoamine hypothesis" seems in keeping with Naidu and colleagues' (2003) proposal that MECP2 mutations lead to failure of appropriate timing of MeCP2 in developing cerebellar neurons and increased glutamate and *N*-methyl-D-aspartate (NMDA) receptors. High levels of glutamate and NMDA receptors in turn lead to hyperexcitability of neurons in the brain, contributing to many of the symptoms associated with RS. At this writing, Naidu, Bibat, and their team at Kennedy Krieger Institute (G. Bibat, personal communication, 2004) are undertaking a study to determine whether dextromethorphan, which blocks NMDA receptors, reduces RS symptoms in children and adolescents who have MECP2 mutations.

TREATMENT AND MANAGEMENT

Although no completely and generally effective treatment regimen for RS is available, active intervention may delay the appearance of some symptoms and alleviate others: "A vigorous approach to caring for RS girls is advocated" (Glaze, 1995, p. 79). Some treatment approaches show considerable promise in modifying specific behavioral patterns, but as expected from the low prevalence of the disorder, most involve only a few subjects. Of importance, several treatment programs have been successful for older individuals with RS.

Several factors need to be considered in planning interventions:

1. Those with RS typically have very long latencies (as long as a minute) to respond to directions. Therapists must allow time for response.
2. Accurate diagnosis is important to ensure effective, and avoid ineffective, treatment. For example, three girls with RS, initially diagnosed with autism, were inadvertent participants in Lovaas's intensive behavior modification program (Smith, Klevstrand, & Lovaas, 1995). Although this program is demonstrably effective with autistic children, it had few positive effects on the girls. Their intellectual performance declined during treatment, and except for a reduction in tantrums, gains tended to be offset by losses.

3. Individual differences in degree and type of impairments and responsiveness to, as well as tolerance of, various interventions necessitate individualized treatment programs (e.g., Van Acker, 1991).

4. Owing to the multiplicity and diversity of problems associated with RS, a team approach is indicated.

5. Most behavioral interventions involve extensive training. Much effort, persistence, and tolerance for frustration are required, since the changes reported in some studies have been slow and even difficult to see. Indeed, Piazza, Anderson, and Fisher (1993) suggest that parents be warned about the effort involved and the need to keep careful response records in order to see progress.

6. Generally, those with RS appear to respond strongly to music (e.g., Kerr, Belichenkob, Woodcock, & Woodcock, 2001). It facilitates learning and development of skills to such an extent that "music therapy should now be regarded as an essential part of communication assessment and therapy" (Kerr, 2002, p. 283). Although no systematic evaluation of response to music is apparently available, music preferred by individual children with RS may be useful as a reinforcer (e.g., Merker & Wallin, 2001).

Specialized behaviorally based programs have successfully modified a variety of behaviors in girls with RS of different ages, generally in institutional settings. Some of these behaviors had been considered inherent to the disorder and not subject to modification. Age has not always been relevant to success. Using verbal and physical prompts and reinforcement (praise), Piazza and colleagues (1993) attempted to teach five girls with RS who initially had very limited self-feeding skills to scoop food onto a spoon, bring the spoon to their mouths, and put the spoon in their mouths. The girls' self-feeding improved to varying degrees both during the 8-week program and in later follow-up. One girl was almost completely feeding herself 18 months after the end of the program. Through use of shaping, graduated guidance, and hand regulation, Bat-Haee (1994) increased self-feeding, ambulation, and use of an adaptive switch in a 24-year-old woman with RS who had been completely dependent on staff.

Of interest is a program (Roane, Piazza, Sgro, Volkert, & Anderson, 2001) that successfully reduced stereotyped hand movements in two females with RS, one adult and one adolescent, who engaged in chronic and stereotyped hand wringing and hand mouthing, respectively. Such behaviors are among those thought to be inherent to RS. Initial observations indicated that the stereotyped behaviors occurred almost continuously across situations and regardless of external contingencies, suggesting that they were under "automatic reinforcement" (Roane et al., 2001, p. 142) that produced or alleviated stimulation. The most successful treatment involved response interruption: Whenever one of the patients engaged in a stereotyped hand movement, a therapist said, "Hands down, [patient's name]," while moving the patient's hands away from her face and holding them for 20 seconds. During treatment sessions, both patients' stereotyped hand movements declined to near zero levels. However, treatment involved some 65–100 sessions lasting 10 minutes each and given 8–10 times daily, 5 days a week; also, the effects showed little generalization to other settings. Using physical restraints that prevent hand-to-mouth movements, simply holding a girl's hand, or allowing the girl to hold a favored toy may also be effective in reducing stereotyped hand clasping and other movements. In one case, hand wringing was reduced by giving the girl a set of baby keys, which she would manipulate for long periods of time (Hanks, 1990).

Mechanical and computer-based devices have been used to modify the behavior of girls with RS. Using a computer fitted with a touch-sensitive screen and voice synthesizer,

Van Acker and Grant (1995) presented combined visual–auditory representations of favored foods (and, in a subsequent phase, new favored foods not initially presented and nonfavored foods) to three girls with RS. In training, a picture of a favored food item appeared on the computer screen as the voice synthesizer asked, "Would you like some _____?" To varying extents, the girls learned, with initial guidance, to touch the screen to receive a small amount of one or more of the pictured foods. Initial acquisition took some weeks at two sessions a day. In the later phase, two of the girls clearly discriminated between the new favored and nonfavored foods, learning relatively quickly to respond at a high rate for the favored foods while maintaining a low rate of response to the nonpreferred foods. In subsequent generalization testing, the same two girls responded appropriately in lunchroom and home settings.

Working with a nonambulatory, nonverbal, and hypoactive 3-year-old girl with RS, Sullivan, Laverick, and Lewis (1995) tried to increase contingent responding for music and musical toys. They fitted the girl's orthopedic chair with two pad switches, one behind her head and one between her hands. Pressing on either pad led to presentation of a toy for as long as the switch was depressed. The child rapidly acquired the head-pressing response, keeping the switch closed for minutes at a time. Hand-pressing responses also occurred, although at a lower frequency. Subsequent introduction of novel toys led to increased responding. After 6 months of training, the girl began to show positive anticipatory emotions at the outset of sessions, as well as smiling, laughter, and vocalizations during sessions; after 9 months, she began to show positive emotions in anticipation of a session as her chair was being presented.

Adaptive technology may help to overcome some of the motor and language impairments of those with RS. For example, a combination of restraining the nondominant hand with splints in order to increase use of the dominant hand by girls with RS, and providing them with augmentative and alternative communication (AAC) devices related to their storybooks, increased communication between the girls and their mothers while the mothers read the stories to them. The mothers began asking their daughters more questions, which the daughters could answer with the AAC device. Communication between the mothers and daughters became more synchronized into actual dialogue. Mothers also increased their responses to their daughters' communications (Skotko, Koppenhaver, & Erickson, 2004).

The Halliwick method of hydrotherapy has shown promising results in reducing stereotyped behaviors and increasing motor skills (Bumin, Uyanik, Yilmaz, Kayihan, & Topçu, 2003). In the Halliwick method, a therapist guides an individual client through a structured four-phase sequence: (1) mental and physical adjustment to water; (2) rotation control, designed to increase control over balance; (3) controlled movement in water, teaching the client to float and lie flat in both still and turbulent water; and (4) movement in water, teaching the client elementary swimming (e.g., Starfish Club, 2004). Bumin and colleagues (2003) describe an 11-year-old girl with RS who was given weekly treatment sessions of unspecified length. Her stereotypical hand movements declined after the first session and continued to decline. After 8 weeks, she showed improved hand use in feeding, holding objects, and transferring them from hand to hand; improved balance; increased interaction with the environment; and reduced hyperactivity and anxiety. This technique obviously warrants evaluation with more subjects over a longer period of time.

Because apraxia and other distortions of motor movements are virtually universal in RS, physical therapy is critical (e.g., Hanks, 1990). It helps girls with RS to maintain or reacquire ambulation, "one of the critical skills to develop and maintain in persons with Rett syndrome" (Van Acker, 1991, p. 395), and to develop or maintain the transitional behaviors needed to stand up from sitting or lying positions. Such therapy may involve use

of a therapy ball and activities to stimulate balance, weight shifting and bearing, and gait. Gait is further impaired by rigidity in the heels of the feet, leading to toe walking. Ankle–foot orthoses and physical therapy help to maintain more normal walking (Budden, 1997). Whirlpool baths may be helpful. Most girls with RS begin to develop scoliosis before age 8, and many also show kyphosis (hunchback) (Huang, Lubicky, & Hammerberg, 1994). These disorders are basically neurogenic, but are exacerbated by factors such as loss of transitional motor skills and spatial perceptual orientation, postural misalignment, and rigidity (Budden, 1997). Physical therapy and careful positioning in seated positions may slow development of scoliosis, but corrective surgery is often required.

Girls with RS often show abnormal sleep patterns, including delayed onset of sleep and irregular sleep. Two quite different approaches have successfully helped to reduce abnormal and increase normal sleep. Using a behavioral approach with three cases, Piazza, Fisher, and Moser (1991) woke the girls from daytime sleep that occurred outside of normal naptimes, removed them from bed for 1 hour if they showed delayed sleep (response cost), and gradually advanced bedtimes (fading). Treatment increased regular sleep patterns and nighttime sleep, and decreased daytime sleep and waking during the night. Using a 4-week treatment of melatonin with nine girls with RS, whose mean age was 9 years, McArthur and Budden (1998) reported that subjects had long sleep onset and short, interrupted total sleep time during baseline. Melatonin decreased sleep onset generally, and increased total sleep time and efficiency in girls whose baseline sleep was most impaired. However, the girls' response to melatonin was highly variable.

Although showing strong appetites, most girls with RS exhibit serious growth retardation, to the point of often meeting criteria for moderate to severe malnutrition. Chewing and swallowing problems, as well as gastroesophageal reflux and digestive problems, contribute to this retardation. Speech therapy may be helpful not so much for retaining language as for facilitating chewing and swallowing. Supplementary tube feedings may be necessary to help increase growth (Glaze & Schultz, 1997), and some older girls may need to be fitted with gastric tubes, as in the case of Maggie (see below). Further complicating feeding issues is frequent constipation; although this is generally controllable through diet, laxatives or enemas may be necessary.

Seizures occur in most girls with RS, particularly in stage 3 (Glaze & Schultz, 1997). Unfortunately, parents may overestimate daytime seizure activity, some of which may be behaviorally based, but miss actual seizures, many of which occur during sleep (e.g., Budden, 1997; Glaze & Schultz, 1997). Most seizures can be controlled with antiseizure medication, most frequently carbamazepine and/or valproic acid. Occasionally, in otherwise intractable cases, a ketogenic diet may be used (Budden, 1997; Liebhaber, Riemann, & Baumeister, 2003), although it presents management problems.

Agitation, screaming, and tantrums are frequently reported. The rapid neurological and physical changes associated with the onset of the disease may understandably provoke emotional outbursts. Girls with RS frequently respond negatively to stimulus or routine change, so transitions from one setting or pattern to another should be gradual and accompanied by a parent if possible. Agitation or screaming may also reflect physical pain or irritation for which those with RS may have no other signal. Since the girls go through puberty, caretakers need to be sensitive to their menstrual cycles; agitation in older individuals may reflect premenstrual discomfort or a gynecological disorder that may be easily treatable (Budden, 1997). Behavior modification may be helpful; one of us (KKM) successfully used behavior modification to reduce her daughter's tantrums, as described below. Other suggested treatments include medication (particularly at night), music, quiet settings, massage, and hydrotherapy (particularly warm baths) (see, e.g., Van Acker, 1991).

Because RS has a lifelong impact on parents and other family members, ranging from home care issues to decisions about educational and other placement, counseling for them will be particularly important (Lieb-Lundell, 1988). Training the parents in behavior modification may help them in managing some aspects of their daughter's behavior, including tantrums. Of importance, given the degree of care that adults with RS may require and their relative longevity, parents will eventually need to face the issue of lifelong care and make financial arrangements for their daughter after they can no longer care for her.

MAGGIE: FROM INFANCY TO ADULTHOOD

As the second author of this chapter and mother of Maggie, an adult female with RS, I (KKM) have experience with much of what is described in this chapter. My husband and I have gone from having a daughter with a severe but undiagnosed condition for 10 years, to having one of the first 250 or so daughters diagnosed with RS worldwide, to the current situation where RS public service announcements appear on TV.

Maggie was our first child, born in 1974 (years before RS was known in the professional community), when my husband was in the U.S. military. Maggie was born spontaneously 3 weeks past term after an uncomplicated pregnancy. She weighed 7 pounds and 9 ounces. Her Apgar score of 7 was affected by skin conditions and the need for oxygen at birth. She sat at 4 months, could wind up toys by 7 months, said her first word at about 12 months, and had a vocabulary of about 16 words and showed interest in books at 16 months. But at about 12 months, she started having tantrums. By 16 months, she was losing instead of gaining words, throwing toys or using them as weapons, and putting everything she picked up (including dirt) into her mouth. At 20 months of age, when a younger sister was born, Maggie was saying only "mama" and "papa." Her pediatrician told me not to worry; he said that Maggie was showing "normal regression."

Maggie appeared to be extremely jealous of her sister, and pushed, hit, and scratched her severely enough to scar her face. She not only lost the ability to wind up toys, but by 24 months could not even pick one up. Growth retardation became prominent and persistent. Maggie entered an apparently autistic phase and began smearing feces on herself and her surroundings. At 28 months, she began to defecate in her hands and throw the feces at me. If I left her bed at night, she screamed and vomited. One of her grandmothers, insensitive to the possibility of a serious problem, urged me to spank her. But when I did, Maggie laughed, suggesting insensitivity to pain. Some of her behaviors were bizarre: She chewed ice; she bit glasses and chewed the broken glass as though it were ice; and once she started to eat a dead animal she found in the yard. At one point, I became so frantic that I was afraid of becoming abusive. A military base physician recommended that I take a course in behavior modification. Use of behavioral principles led to cessation of vomiting and reduction in many other attention-getting behaviors. The program gave me a handle on Maggie's behavior for the first time since infancy.

Physicians proposed various diagnoses, including schizophrenia, autism, mental retardation, childhood aphasia, and hyperactivity. Because Maggie was small and did not gain weight, malnutrition was suggested, even though she ate a lot. At age 7, she was placed in a class for autistic children. A year later, she began to have frequent tonic–clonic seizures. Even on medication, she had some 20 seizures daily. Tests indicated multiple allergies. Given the interest at the time in diets for disorders such as hyperactivity, one should not be surprised at the hypothesis that the problems were caused by allergies, but dietary

manipulation had few effects. At about age 9, she began again showing aggressive behaviors to herself and others. Once she slapped her face so hard that she deformed her jaw and began to cry hysterically. When I tried to soothe her, Maggie bit me so hard that I had to pry her off. My husband and I considered residential treatment because of the seizures and aggressive behavior. But Maggie was admitted to a hospital for observation after having a severe seizure and falling down a flight of stairs. I had been reading about RS and described it to some physicians. Fortunately, her neurologist had recently attended a conference on RS and diagnosed her correctly. When Maggie was put on divalproex (Depakote), which had been found effective for girls with RS, both her seizures and her aggressive behavior diminished; she became once again a "happy-go-lucky child." We dropped plans for residential treatment, although she still showed severe mood swings. Speech and physical therapy were provided. The speech therapy was ineffective, but Maggie's continued walking may be attributable to the physical therapy.

Maggie showed virtually all diagnostic criteria for RS and went through the four developmental stages described earlier in this chapter. Her cognitive development became largely arrested. She developed classic RS hand stereotypies, mainly hand mouthing, to such an extent that she developed infections on her hands. Although she maintained walking, her body movements became jerky, and she showed gait apraxia. She had surgery for scoliosis at age 15 years. Bruxism, air swallowing, and breath holding were common. Growth retardation continued. Compared to her earlier "Jekyll and Hyde" behavior, however, Maggie's temperament became calmer; by her late teens, she was easy-going most of the time, had fewer seizures, and regained some lost skills, but was still totally dependent on others for her basic needs.

As Maggie approached the end of her last year in public school, we began to worry about her long-term future in light of her need for care and our own ages. Again considering residential care, we listed its advantages and disadvantages. We could provide Maggie with love and support, but the residential home provided many services that we could not: around-the-clock care; frequent bed checks at night; full-time nursing; physical, speech, occupational, and aquatic therapy; and a degree of both independence and inclusion in the home's community. At age 19, Maggie moved into her own room in the residential home. The timing of the move was very important: She was used to a regular schedule and to being away from her family, and if she had become accustomed to living at home full time after completing public school, adjustment to the residential home would have been more difficult. The home provides large number of activities, including fishing, dances, movies, parades, and even overnight trips. These made Maggie's transition much easier, because each day was an adventure. Her favorite activity was going out to eat, as indicated by a 17-pound weight gain her first year! Unfortunately, she later developed a serious problem with swallowing food, as if she could not remember what to do once it reached her mouth. Her weight began to plummet, and a gastric tube was implanted in 1998.

Maggie graduated from the on-site school and now attends the home's adult day program. Each client is assessed, and jobs are created to meet his or her individual needs and abilities. Maggie helps make dog and cat biscuits that are sold to local pet stores. She cannot roll out dough, but sprinkles flour on the bread board and crushes cans in a specially designed crusher. The program also offers pet therapy, computer learning, horticulture, and aquatics.

In 2002, Maggie was given an aloe-vera-based herbal supplement, which appeared to improve her quality of life: She started climbing steps with little assistance in alternating feet; looking where she was walking; communicating more through smiling, clapping, and eye gazing; and even petting her dog. The center described the effects as Maggie's "awak-

ening period." Unfortunately, a change in the formula to eliminate a potentially harmful ingredient in 2003 adversely affected her progress. Her walking skills have regressed, but she retains communication through eye pointing and gestures. Of course, we as well as many scientists and professionals would like to know whether the gains and losses are attributable to the original formula and its change or the recurring gain–loss cycle of RS.

At this time, Maggie can see and hear but not talk, and, unlike many adults with RS, she can walk. However, she has gait problems and is somewhat unsteady on her feet. When stricken with a seizure, she falls like dead weight, regardless of the staff's best efforts to support her. As a result, she has lost several teeth (replaced with a partial bridge and crown), fractured her clavicle, and received many minor injuries. Her mental age is about 12 months. Her hands are often clasped at her mouth, leading to balance problems. She drools, leaving her hands wet and subject to fungal infections; she gulps air and has H-pyloris, both leading to gastric distress; and she has occasional tonic–clonic seizures, only partially controlled by medication. She appears to communicate through eye pointing, but with a long latency of response. Generally loving and appreciative, she occasionally lashes out, apparently to communicate pain caused by the gastric distress.

The photographs (Figures 20.1–20.4) show Maggie from late infancy to adulthood. Note the hand clasping in all these photographs, and particularly the decreasing relative height and head size in the later photos. At age 15, Maggie was taller than her 10-year-old sister (our third child), but at age 26 she was far shorter than this sister (who is the bride in Figure 20.3) and her mother.

FIGURE 20.1. Photograph of Maggie at age 22 months. Note the stereotyped clasping of an object with the hands, even at this age.

FIGURE 20.2. Photograph of Maggie at age 15 years, with her 10-year-old sister. Note that she is still taller at this age than her sister, and that stereotyped hand clasping is again evident.

FIGURE 20.3. Photograph of Maggie at age 26 years, with the same sister as in Figure 20.2 (the bride) and her mother. Note that she is now far shorter than either her sister or her mother.

FIGURE 20.4. Photograph of Maggie at age 29 years; note that her hands are once again stereotypically clasped. (Many other pictures of Maggie show her hands at her mouth, as they are much of the time.)

SOME GENERAL OBSERVATIONS ON ADULT CASES

The IRSA maintains on its website a set of parents' descriptions of their adult daughters (www.rettsyndrome.org/main/I-am-woman.htm). Those cases and Maggie's indicate both commonalities and differences among affected individuals and their families.

Many cases of RS were not accurately diagnosed until adulthood, and the daughters described on the IRSA website had been earlier diagnosed with a variety of disorders, as Maggie had. One had been institutionalized at age 9 as having a severe case of cerebral palsy. Only years later was she diagnosed with RS, at which time she was moved to an appropriate group home. Generally, parents describe years of frustration before accurate diagnosis. Parents of children with apparent disabilities are frequently portrayed as "shopping" for a favorable diagnosis. But the parents in the IRSA descriptions and those known to the three of us knew that something was wrong with their daughters and that initial

diagnoses did not fit their daughters' characteristics. They were not looking for a favorable diagnosis, but an accurate one. Initially, Maggie's mother had little success convincing physicians that anything serious was wrong, and she was instrumental in the final diagnosis of RS. Her pediatrician's claim that Maggie was just showing normal regression after the birth of her sibling seems almost bizarre, even given the advantage of hindsight. One wonders on what normative data he based his observation. The evidence that parents seek the "best" diagnosis for their children, at least for serious disorders, has never been strong and clearly does not apply to these cases. Although little effective treatment of RS is available, knowledge of their children's condition was critical for both Maggie's parents and those on the IRSA website in understanding what was happening to their daughters, in arranging care, and in knowing what to expect.

The cases have some characteristics in common, including, of course, hand stereotypies, lack of language, and scoliosis. Most adults are described as having pleasant or at least even temperaments, in contrast to their behavior during difficult periods in their childhood. They have likes and dislikes, preferred and nonpreferred activities, and can indicate what they enjoy through behaviors such as facial expressions and laughter. One way or another, they express a variety of emotions. They are aware of their surroundings and may react strongly to unexpected stimulus change. Unfortunately, all also are wholly dependent on others to meet the needs of their day-to-day lives.

The cases also reflect the high variability often referred to in this chapter, most of which does not appear to be correlated strongly with age. Some of the adults are living with their families at home; some are in group homes. Some are ambulatory; some are not. Some are in good health; some have serious health problems. Some are toilet-trained; some are not. Some can swallow; some have gastric tubes. Some have seizures; some do not. Some appear to enjoy going out; some do not. In sum, the notion initially applied to RS that all affected individuals are essentially alike and should be treated alike applies no more to RS than to most other severe disorders.

CONCLUDING REMARKS

Much progress has been made in understanding the genetic basis of RS, its phenotypic variability, and its neurological correlates. Unfortunately, similar progress has not occurred in treatment. Indeed, those involved with treatment may feel as did Ignaz Semmelweis (1861/1981) when he was searching for the cause of childbed fever—that their attempts are "like a drowning man, who grasps at a straw . . ." (p. 390). Several promising treatments are now available, but all have been used on only small numbers of cases, and most require many sessions. Greatly needed are evaluations of these programs, particularly those that can be relatively easily implemented, with larger numbers of cases and with long-term follow-up. Furthermore, the fact that most known cases of RS have been diagnosed in children suggests that a significant number of older affected individuals, including males, may not have been properly diagnosed. Undiagnosed individuals with RS may receive treatment that is not only nonoptimal, but actually counterproductive. Of particular concern with adults with RS is the fact that their virtually complete dependency on others and often near-normal longevity present serious and continuing problems for caretakers. As parents (or other caretakers) themselves age, they will be confronted with difficult decisions concerning the optimal placement for their offspring with RS. Those making the decision should not be made to feel guilty if they decide that the optimal placement is a residential institution.

Perhaps what we can state with most confidence is that some material in this chapter, given the rapid accumulation of new findings, will be discarded as outdated. It is quite likely that some is not true now; unfortunately, we do not know which material that is. We hope, of course, that the first material to be discarded will be the current frustrations over the lack of effective treatments.

For current information on RS, go to the International Rett Syndrome Association website at www.rettsyndrome.org/index.htm. Routine updates of research information are posted at Online Mendelian Inheritance in Man at www.ncbi.nlm.nih. gov/entrez/dispomim.cig?id=312750.

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21

LESCH–NYHAN DISEASE

JASPER E. VISSER
DAVID J. SCHRETLEN
JAMES C. HARRIS
H. A. JINNAH

Lesch and Nyhan (1964) first described a specific clinical phenotype in two brothers who were originally diagnosed as having cerebral palsy. The clinical findings included neurological abnormalities and self-destructive behavior, combined with hyperuricemia. Subsequent genealogical data on additional families suggested an X-linked disease (Nyhan, Pesek, Sweetman, Carpenter, & Carter, 1967). In 1967, the biochemical basis for the condition was elucidated: a deficiency of the purine salvage enzyme hypoxanthine–guanine phosphoribosyltransferase (HPRT) (Seegmiller, Rosenbloom, & Kelley, 1967). In 1983, the human HPRT gene was cloned and sequenced (Jolly et al., 1983).

HPRT deficiency is frequently referred to as "Lesch–Nyhan *syndrome*," because of the characteristic collection of clinical features patients exhibit. However, based on current genetic and biochemical knowledge, "Lesch–Nyhan *disease*" (LND) is the more appropriate designation.

CLINICAL FEATURES

The clinical phenotype of LND described in published reviews and case reports has recently been summarized (Jinnah & Friedmann, 2001). The clinical features can be broadly categorized into five main areas: (1) overproduction of uric acid and the consequences thereof; (2) movement disorder; (3) cognitive disability; (4) behavioral manifestations, including self-injurious behavior; and (5) a miscellaneous category, including growth retardation and anemia.

Though LND is often regarded as a single disease, there is a marked phenotypic variability among patients with HPRT deficiency. Shortly after the identification of HPRT deficiency as the underlying metabolic cause of LND, it was noted that a subgroup of patients with HPRT deficiency displayed a much milder syndrome (Kelley, Greene, Rosenbloom, Henderson, & Seegmiller, 1969). This condition, characterized by hyperurice-

mia with few or no neurobehavioral features, has been labeled "Kelley–Seegmiller syndrome" in the past. Subsequently, intermediate cases with hyperuricemia and varying degrees of neurological impairment were identified, suggesting a more continuous spectrum of disease severity rather than two distinct populations (Jinnah, De Gregorio, Harris, Nyhan, & O'Neill, 2000; Page, Bakay, Nissinen, & Nyhan, 1981; Puig et al., 2001). Today the term "Kelley–Seegmiller syndrome" is no longer used. Instead, the partial syndromes without self-injurious behaviors are described as "Lesch–Nyhan variants" (LNVs). This group is often broken down into hyperuricemia without neurological features (HPRT-related hyperuricemia, or HRH) and both hyperuricemia and neurological features (HPRT-related neurological dysfunction, or HRND). Although patients with HPRT deficiency can be grouped into these three categories based on their clinical phenotypes for heuristic purposes, it is important to recognize the existence of a continuum of abnormalities, rather than clearly distinct subgroups. A schematic representation of this concept is shown in Figure 21.1A.

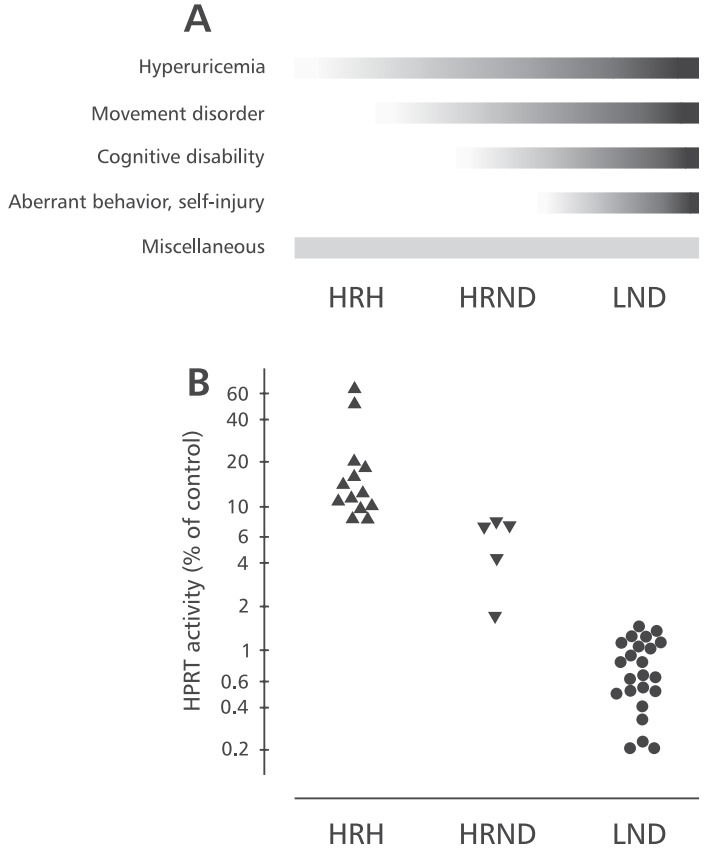

FIGURE 21.1. Clinical phenotypes associated with HPRT deficiency. (A) Schematic representation of the spectrum of clinical features of HPRT-related hyperuricemia (HRH), HPRT-related neurological dysfunction (HRND), and classic Lesch–Nyhan disease (LND). (B) Correlation of clinical phenotype with residual HPRT activity, as percentage of normal values. Each symbol represents a single case. From Jinnah and Friedmann (2001), based on data from Page, Bakay, Nissinen, and Nyhan (1981) and Page and Nyhan (1989).

After biochemical assays for accurate quantitative measurement of HPRT activity became available, it was demonstrated that the clinical phenotype seems to be largely dependent on residual enzyme activity (Hersh et al., 1986; Page & Nyhan, 1989; Page et al., 1981). This relationship is illustrated in Figure 21.1B. All patients with less than 50% residual HPRT exhibit overproduction of uric acid and its consequences. Those with less than 8–10% residual HPRT also demonstrate some neurological abnormalities, and patients with less than about 1.5% residual HPRT have the added element of abnormal behaviors, including self-injury.

Hyperuricemia and Its Consequences

In nearly all cases, HPRT deficiency is associated with hyperuricemia due to a marked overproduction of uric acid (Jinnah & Friedmann, 2001). Average values for serum and urine uric acid measures are shown in Table 21.1. The average total renal uric acid excretion in classic LND is about fourfold that of controls. Despite this overproduction, efficient renal clearance limits average serum uric acid levels, which may be only mildly elevated above normal ranges.

Chronic hyperuricemia may result in the deposition of urate crystals in joints, kidneys, and subcutaneous tissues. If untreated, this may cause gouty arthritis, nephrolithiasis, and subcutaneous tophi. Normal uric acid levels in serum in healthy controls are close to the limits of urate solubility, and serum urate values in excess of 7.0 mg/dl are associated with an increased risk for gouty arthritis and urolithiasis (Becker, 2001).

Before effective drug treatment of hyperuricemia became available in the 1960s, many patients with LND died from complications due to nephrolithiasis, including renal insufficiency and sepsis caused by urinary tract infections. Even with adequate control of uric acid production with medication, subclinical renal dysfunction is often evident from calculated creatinine clearance values (Emmerson & Thompson, 1973; Watts et al., 1982), and kidney stones developing among patients already receiving adequate medication have been described (Brock, Golden, & Kaplan, 1983; Kranen, Keough, Gordon, & Emmerson, 1985; Ogawa, Watanabe, & Minejima, 1985).

Although serum uric acid levels in HRND and HRH may fall in the same range as in classic LND, the total uric acid production is usually less severe (Table 21.1). However, because the neurological and behavioral abnormalities are usually less severe than those in classic LND, complications from hyperuricemia are frequently the main focus of clinical attention in these conditions.

TABLE 21.1. Uric Acid Measures in HPRT Deficiency

Measure	Controls	HRH	HRND	LND
Serum uric acid (mg/dl)	4.5 ± 1.3	13.4 ± 6.2 (22)	13.1 ± 3.5 (15)	11.7 ± 4.4 (70)
Uric acid–creatinine ratio	0.3 ± 0.1	1.0 ± 0.4 (10)	1.3 ± 0.7 (7)	3.0 ± 1.1 (17)
Uric acid excretion (mg/kg/day)	9.7 ± 3.7	25.4 ± 16.4 (10)	25.5 ± 13.5 (9)	39.6 ± 13.9 (24)

Note. Average ± *SD* serum uric acid, uric acid–creatinine ratio, and uric acid excretion in controls and in patients with HPRT-related hyperuricemia (HRH), HPRT-related neurological dysfunction (HRND), and classic Lesch–Nyhan disease (LND). Data from Jinnah and Friedmann (2001), based on cases reported in prior literature. Numbers in parentheses denote the number of individual cases for which data was available.

Movement Disorder

A severe movement disorder, which is typically recognized between 3 and 12 months of age, is a characteristic feature of classic LND. Patients are hypotonic, and are frequently unable to hold up their heads or sit unsupported (Christie et al., 1982; Watts et al., 1982). Further development is delayed, and even previously achieved motor milestones may be lost. By 1–2 years of age, the neurological examination is usually more clearly abnormal. The motor dysfunction in classic LND is usually sufficiently severe that it prevents ambulation.

Reports on the nature of the motor abnormality in LND have been inconsistent. In the original description of classic LND, choreoathetosis and hypertonia were noted as the major neurological features (Lesch & Nyhan, 1964). The two largest case series published to date (including 19 and 10 patients, respectively) described spasticity or hypertonia in all but one subject, as well as other corticospinal signs, such as scissoring of the legs or extensor plantar reflexes (Christie et al., 1982; Mizuno, 1986). Only a minority displayed dystonia. In contrast, another series of 8 cases described dystonia rather than choreoathetosis as the major motor abnormality, and all cases were described as having hypotonia rather than hypertonia (Watts et al., 1982). Multiple additional smaller series of cases and individual case reports have described various combinations of choreoathetosis, dystonia, ballismus, spasticity, hypertonia, hypotonia, and/or ataxia (Jinnah & Friedmann, 2001). Although the differences in motor symptoms reported in these studies might represent phenotypic heterogeneity among the patients reported by different groups or temporal variability due to disease progression, it is more likely that they represent variations in the use of descriptive terminology of movement disorders.

To clarify this issue, the motor disorder of LND was recently reconsidered in a prospective study of 20 affected individuals, using currently accepted criteria for diagnosis of motor syndromes (Visser et al., 2005). The patients with LND demonstrated a characteristic motor syndrome, with only minor phenotypic variability (Figure 21.2A). Muscle tone was most frequently decreased, but sometimes hypertonia was noted in the same patient as well. All patients displayed signs characteristic of dystonia, including excessive co-contraction of agonist and antagonist muscles during voluntary movement, twisting and sometimes sustained postures, overflow of contractions to extraneous muscle groups, and hypertrophy of chronically active muscles. Dystonia affected both axial and appendicular muscles, and was frequently precipitated by stress, excitement, or attempted actions. Other extrapyramidal signs such as chorea and ballismus were noted as well, but these were both less frequent and less severe than dystonia. True spasticity was uncommon, and ataxia was not seen. In our view, the motor syndrome of LND is best described as dystonia superimposed upon hypotonia.

Other abnormal movements in LND involve ocular motility (Jinnah et al., 2001). Patients have difficulty suppressing reflexive saccades toward minor distractions. Conversely, voluntary saccades are often delayed or sometimes even absent when head movement is restrained. Once saccades are initiated, their speed and accuracy appear relatively normal. Other ocular motor functions, including smooth pursuit, ocular range, and other reflexive eye movements, appear normal in most patients with LND. In addition, speech in classic LND is severely affected, and several studies concur that dysarthria is a universal feature of LND (Christie et al., 1982; Jinnah et al., 1998; Lesch & Nyhan, 1964; Mizuno, 1986; Watts et al., 1982).

The movement disorder in HRND is similar in quality to the one in classic LND, but there is a much broader range of severity. Patients with HRND that is neurologically

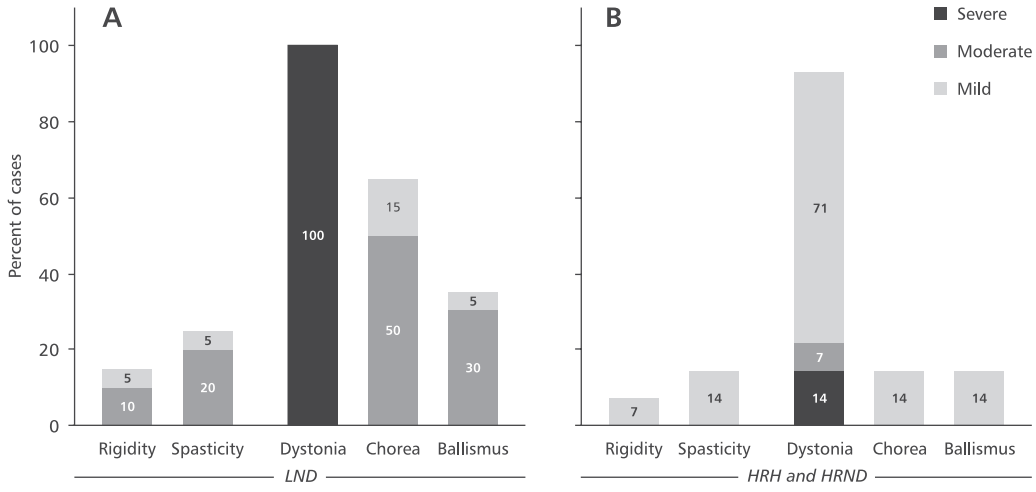

FIGURE 21.2. Motor dysfunction due to HPRT deficiency. The prevalence and severity of motor abnormalities in 20 patients with classic LND (A) and 14 patients with HRH or HRND due to partial HPRT deficiency (B). Numbers refer to the percentage of cases in which the particular motor abnormality was present; bar shades denote severity levels. Data from Visser et al. (2005) and Jinnah et al. (2004).

indistinguishable from classic LND, with severe extrapyramidal and pyramidal features, have been described (Adler & Wrabetz, 1996; Bakay, Nissinen, Sweetman, Francke, & Nyhan, 1979)—as have subjects with a grossly normal appearance (Dancis, Yip, Cox, Piomelli, & Balis, 1973; Emmerson & Thompson, 1973; Geerdink, de Vries, Willemse, Oei, & de Bruyn, 1973; Hersh et al., 1986). Patients with HRH are usually thought to have no obvious neurological deficits. However, they may have slight clumsiness (Emmerson & Thompson, 1973) or indistinct speech (Geerdink et al., 1973; Hersh et al., 1986), which may only become evident with careful testing.

In a recent series of 14 patients with partial HPRT deficiency (either HRND or HRH), only 1 patient was completely free of any motor defects (Jinnah et al., 2004). Dystonia was again recognized as the most frequent and most severe movement disorder (Figure 21.2B), but the severity ranged from mild clumsiness to severe dystonia similar to that in classic LND. All patients also had dysarthria, while choreoathetosis and spasticity were noted only sporadically. In the study on ocular motor dysfunction in LND, partial HPRT deficiency resulted in similar findings as in classic LND (Jinnah et al., 2001). However, ocular motility was relatively normal in those with higher residual enzyme activity levels. The patients with HRH and only minor clumsiness, and the patients with HRND and motor defects indistinguishable from those of LND, emphasize the existence of a continuum of motor impairments associated with HPRT deficiency.

Cognitive Disability

Classic LND has traditionally been associated with intellectual disability. The two brothers described in the original publication by Lesch and Nyhan (1964) were thought to be mentally impaired, but the severity of their motor defects made cognitive testing difficult. Most subsequent case reports have confirmed the original impressions that individuals with

LND have significant mental retardation, with IQ scores generally reported in the 60–80 range (Ball, Datta, Rios, & Constantine, 1985; Barry, Buckley, & Tully, 1978; Benke & Herrick, 1972; Benke et al., 1973; Bunn et al., 1975; Emmerson & Thompson, 1973; Hoefnagel, Andrew, Mireault, & Berndt, 1965; Michener, 1967; Partington & Hennen, 1967; Reed & Fish, 1966; Sass, Itabashi, & Dexter, 1965; Wood, Fox, Vincent, Reye, & O'Sullivan, 1972).

Several studies have systematically addressed cognitive function in small groups of affected individuals. Three different studies describing cognitive function in a total of 31 patients have revealed composite IQ scores of approximately 60, though individual scores varied widely, from 25 to 101 (Christie et al., 1982; Matthews, Solan, & Barabas, 1995; Schretlen, Harris, Park, Jinnah, & del Pozo, 2001). Follow-up studies of one cohort revealed little developmental progress over 2–4 years, suggesting an upper limit to cognitive development (Matthews, Solan, Barabas, & Robey, 1999; Solan, Matthews, Barabas, & Robey, 1997). Other studies, however, have suggested that individuals with LND may be less cognitively impaired than they appear to be, as they seem to function at higher levels than expected from standardized test scores (Anderson, Ernst, & Davis, 1992; Nyhan, 1978). Moreover, a few patients with classic LND but apparently normal intelligence have been reported (Evans, Sirikumara, & Gregory, 1993; Kenney, 1991; Lynch & Noetzel, 1991; Scherzer & Ilson, 1969). However, these observations should be interpreted with caution, since they are often based on clinical impressions rather than formal testing.

Both the large individual differences in cognitive test performance between patients with LND and the discrepancies between cognitive test scores and everyday functioning might result, at least in part, from difficulty in eliciting reliable test performance from such patients. Several reasons might account for this problem. First, the severe neurological and behavioral abnormalities in patients with LND significantly restrict both their educational opportunities and their amenability to formal testing. Second, the motor and speech impairments together with the behavioral abnormalities can make responses difficult to interpret, as many patients with LND exhibit reduced attention, persistent oppositional behavior, and poor cooperation in formal testing situations. Finally, standardized IQ testing yields composite scores that may obscure important variations in abilities across different cognitive domains, and may provide only limited insight into an individual's functional capacity.

Indeed, some have suggested that patients with classic LND do not show a general deficit in a wide variety of cognitive abilities (Anderson et al., 1992). The concept of a possible selective cognitive deficit has been confirmed by a longitudinal series of neuropsychological reports on six patients, showing that performance was mostly impaired by a decrease in attentiveness and loss in mental flexibility. The major difficulty involved working simultaneously with multiple aspects of a problem (Matthews et al., 1995, 1999; Solan et al., 1997). Another recent neuropsychological study demonstrated relatively severe difficulties with attention, working memory, and delayed recall in LND, with near-normal orientation and retention of newly acquired information (Schretlen et al., 2001). Both studies seem to confirm the concept that the patients do not have global mental retardation, but rather have impairments in specific cognitive domains.

Overt cognitive deficits have not been widely recognized as accompaniments of partial HPRT deficiency. Several reports have described LNVs involving apparently grossly normal cognitive function (Adler & Wrabetz, 1996; Bakay et al., 1979), but often formal cognitive testing has not been performed. Although many of these patients function as productive members of society, formal cognitive testing may reveal subnormal function. A recent study including nine patients with LNVs revealed a profile of cognitive performance

similar to that of patients with classic LND; several patients scored in the mental retardation range (Schretlen et al., 2001). Most patients with partial HPRT deficiency performed better than those with classic LND and worse than healthy controls, as an intermediate phenotype (Figure 21.3). These results suggest that cognitive disabilities associated with HPRT deficiency also occur as a continuum of severity, similar to the motor disorder and hyperuricemia.

Aberrant Behavior

Behavioral abnormalities are a defining aspect of the LND phenotype. In fact, LND was one of the first conditions used to demonstrate that abnormal patterns of behavior could define a "behavioral phenotype" analogous to the dysmorphic patterns already recognized for genetic diseases (Nyhan, 1972a). Specifically, self-injury has been considered to define the behavioral phenotype of LND, although other behavior anomalies have often been described anecdotally. For example, patients with LND have frequently been reported as being aggressive (Anderson & Ernst, 1994; Christie et al., 1982; Dizmang & Cheatham, 1970; Mizuno & Yugari, 1975; Nyhan, 1976) and manipulative (Bull & LaVecchio, 1978), but also as remarkably good-humored and unusually engaging (Nyhan, 1972b, 1973, 1976).

Self-injurious behavior emerges in nearly all cases within the first few years of life—usually at about 2–3 years of age, but with a wide range of 6 months to 18 years (Jinnah & Friedmann, 2001). In contrast, it does not occur in patients with HRND or HRH. The most common form of self-injury involves biting, mostly the lips and fingers, but sometimes the tongue, arms, shoulders, or even toes (Anderson & Ernst, 1994; Robey, Reck, Giacomini, Barabas, & Eddey, 2003). Many other forms of self-injury have also been observed, including banging or snapping the head backward, injuring hands or feet on sharp objects, and poking the eyes with the fingers (Table 21.2). Caregivers must always be on

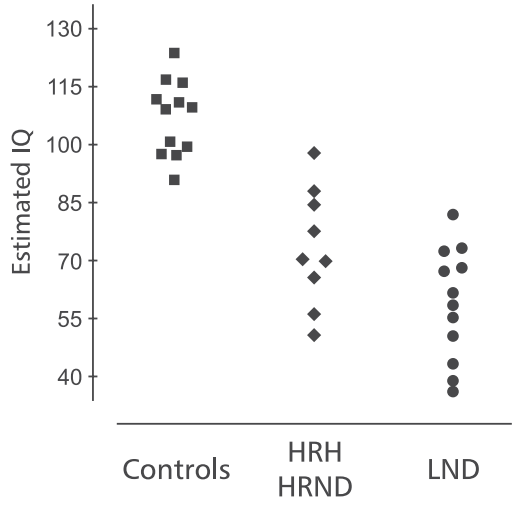

FIGURE 21.3. Cognitive impairment due to HPRT deficiency. Correlation of IQ estimates with partial HPRT deficiency (HRH and HRND) and complete HPRT deficiency (classic LND), compared to controls. Each symbol represents a single case. Data from Schretlen, Harris, Park, Jinnah, and del Pozo (2001).

TABLE 21.2. Self-Injurious Behavior in LND

Feature	Anderson & Ernst (1994) (n = 40)	Hall et al. (2001) (n = 64)
Biting		
Lips, mouth	83% (33)	77% (49)
Fingers	73% (29)	78% (50)
Arms	40% (16)	
Tongue	35% (14)	
Shoulders	20% (8)	
Other injurious behaviors		
Head snapping	85% (34)	
Head banging	75% (30)	56% (36)
Eye poking	33% (13)	31% (20)
Rubbing head		27% (17)
Rubbing arms		17% (11)
Risky behaviors often resulting in injury		
Extending arms in doorways	88% (35)	66% (42)
Feet under wheelchair	58% (23)	
Finger in wheelchair spokes	43% (17)	30% (19)
Tipping wheelchair	3% (1)	33% (21)

Note. Types of self-injury in LND, as reported in two studies of 40 and 64 subjects, respectively (Anderson & Ernst, 1994; Hall, Oliver, & Murphy, 2001). The numbers in parentheses indicate the actual number of patients in each group.

the alert when traveling, as many patients will unexpectedly thrust an arm or leg out when being wheeled through a narrow doorway or placed near a closing door.

This behavior can wax and wane over time, with wide variations in severity. As patients age, the intensity and severity of their self-injury can decline; in rare cases, it can disappear for months or even years (Mizuno, 1986). However, in the more severe cases, self-injurious behavior occurs daily and can lead to severe tissue loss and major medical complications. Self-injury resulting in partial amputation of lips or fingers, major infections, or near-blindness is not uncommon (Christie et al., 1982; Jinnah & Friedmann, 2001; Nyhan, 1972b).

Self-injurious behavior in LND is frequently exacerbated by psychological stressors, such as formal medical evaluation, medical procedures, the presence of a stranger, or changes in environment. It may also be exacerbated by physical discomfort (e.g., an upper respiratory infection, or painful arthritis or nephrolithiasis). The behavior tends to be least severe when patients are actively engaged in a comfortable and familiar environment. Some affected individuals develop techniques to reduce self-injury, such as sitting on their hands or wearing thick, soft gloves. However, most individuals require some form of physical restraint at least a portion of the time.

Individuals with LND clearly do not wish to injure themselves, and often call for help when they feel that self-injury is imminent. However, the reasons *why* these patients hurt themselves remain unclear. Those who can communicate will most frequently express that they just don't know why they injure themselves. Others report that "it just happens" or refer to an offending body part as if it is not under their own control (Dizmang & Cheatham, 1970). Patients with LND generally do not seem to identify a specific urge, thought process, or emotion as a precipitant.

In addition to self-injurious behavior, patients with LND are often labeled as aggressive (Anderson & Ernst, 1994; Christie et al., 1982; Dizmang & Cheatham, 1970; Mizuno & Yugari, 1975; Nyhan, 1976). Many patients will strike out at those around them, say or do things to upset people, use obscene language, or spit at people (Anderson & Ernst, 1994; Nyhan, 1976). Although many of these behaviors appear aggressive, it is important to note that these behaviors are not synonymous with purposeful aggression intended to harm another person. In LND, it seems equally likely that the behaviors reflect either a failure of impulse control or a compulsion (Visser, Bär, & Jinnah, 2000). Although they will indeed strike at nearby individuals, they often do not intend harm. Many of them will warn potential victims if they are close enough to be hit. They usually apologize afterward, express feelings of guilt, or even appear embarrassed by the act. These aggressive behaviors can be triggered by excitement, by displeasure, or by the awareness that the behavior provokes a negative reaction. For example, spitting and cursing are most prominent in the presence of individuals who seem most bothered by them, whereas these behaviors tend to be extinguished if they are ignored.

In addition to these behaviors, individuals with LND often exhibit personality features revealing a contrariness that resembles oppositional defiant behavior in many settings. For example, when asked to read a word from a card, some affected children will give a wrong answer although they know the correct one. Or, when asked the color of grass, they may recite many different colors with the selective exclusion of green. They tend to disagree persistently with others—or even with themselves, as expressed in very changeable statements.

In marked contrast to the frequency of aggressive and negative behaviors, Nyhan (1972b, 1973, 1976) has commented that children with LND are unusually engaging and gentle. Despite their difficult behaviors, they are often the favorites of nurses and caregivers. They like to be where the action is, and they like to be the center of attention. Our personal experience with more than 40 affected individuals confirms that most of them are interactive and happy children when their neurological and behavioral problems are properly managed. This general complacency is remarkable in the view of their severe disability, and is not concordant with the interpretation that individuals with LND are invariably aggressive and contrary.

Although not universal, both the positive and negative behavioral characteristics seem sufficiently common to be considered typical behavioral features of the disease. This issue has recently been addressed in a study based on informant rating scales, confirming that LND is associated with a characteristic behavioral phenotype (Schretlen et al., 2005). In addition to self-injury and aggressive behaviors, patients with LND showed more anxious or depressive behaviors, thinking and attentional problems, stereotyped and hyperactive behavior, and disturbing interpersonal behaviors.

Patients with HRND and HRH have generally been considered to be free of self-injurious or other aberrant behaviors. However, some abnormal behaviors have been reported in this population, including compulsive trichotillomania (Benke & Herrick, 1972), impulsively engaging in high-risk behaviors (Geerdink et al., 1973), or prominent onychophagia (Emmerson & Thompson, 1973). In addition, in the recent study of the extended behavioral phenotype, patients with partial HPRT deficiency were rated as intermediate between healthy controls and patients with classic LND on several behavioral scales. Furthermore, these patients demonstrated inattention and distractibility that were just as severe as those shown by patients with classic LND. These results suggest that the characteristic behavioral abnormalities due to HPRT deficiency, while not always obvious, exist along a continuous spectrum as the other clinical features do.

Other Manifestations

Megaloblastic anemia is an occasional finding in LND of uncertain origin, because serum B12, folate, and thyroid function tests are normal, and folate and B12 supplements are not routinely effective (Mizuno, 1986; van der Zee, Lommen, Trijbels, & Schretlen, 1970; van der Zee, Schretlen, & Monnens, 1968; Watts et al., 1982). It has been suggested that bone marrow stem cells are particularly dependent on purine salvage, and HPRT deficiency subverts hematopoiesis (Hakoda et al., 1995; McKeran, 1977). In addition, growth retardation is frequently reported in LND, with height and weight falling often 2 or more standard deviations below age-adjusted normative data (Christie et al., 1982; Mizuno, 1986; Skyler, Neelon, Arnold, Kelly, & Lebovitz, 1974; Watts, Harkness, Spellacy, & Taylor, 1987). Finally, testicular atrophy, undescended testes, and the absence of testicular tissue have been described in a number of cases (Mizuno, 1986; Reed & Fish, 1966; Watts et al., 1982, 1987). Megaloblastic anemia (Kelley et al., 1969) and testicular dysfunction (Geerdink et al., 1973; Snyder et al., 1984) have been described in patients with partial HPRT deficiency as well.

DIAGNOSIS

Differential Diagnosis

The most common presenting features for LND are hypotonia and developmental delay, followed by the appearance of extrapyramidal and sometimes pyramidal motor signs. The differential diagnosis for developmental delay is extensive (Fenichel, 2000). LND should be suspected if delayed development is accompanied by self-injurious behavior or evidence for excessive production of uric acid.

Although the occurrence of self-injurious behavior often leads to the suspicion of LND, self-injury may occur in many different clinical conditions. Most commonly, it occurs in severe mental retardation and autism (King, 1993; Winchel & Stanley, 1991). In addition, self-injury is reported in several genetic conditions, including Rett syndrome (Jankovic, 1988), Cornelia de Lange syndrome (Berney, Ireland, & Burn, 1999), Prader–Willi syndrome (Symons, Butler, Sanders, Feurer, & Thompson, 1999), Smith–Magenis syndrome (Smith, Dykens, & Greenberg, 1998), fragile X syndrome (Symons, Clark, Hatton, Skinner, & Bailey, 2003), *cri du chat* syndrome (Collins & Cornish, 2002), propionic acidemia (Nyhan, Bay, Beyer, & Mazi, 1999), and neuroacanthocytosis (Hardie, 1989; Jankovic, 1988). It has also occured in other conditions, such as amphetamine use (Kratofil, Baberg, & Dimsdale, 1996; Sokol, Campbell, Goldstein, & Kriechman, 1987), Tourette syndrome (Comings & Comings, 1985; Robertson, Trimble, & Lees, 1989), dementia (Shua-Haim & Gross, 1997), and various other psychiatric disorders (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004; Paul, Schroeter, Dahme, & Nutzinger, 2002).

The self-injury of LND can often be distinguished from that appearing in these other diseases on clinically perceptible grounds. First, self-injury in LND is usually much more severe than in these other conditions, in which it might result from highly stereotyped behavior or accidental injury. Second, the prominent topographic preference for mouth and fingers is not frequently seen in other conditions. Third, self-injurious behavior in LND is always accompanied by the profound motor impairment. LND should be suspected when self-injurious behavior is associated with the typical motor dysfunction, especially if it is also associated with hyperuricemia.

Uric acid overproductions and its consequences are infrequently the presenting features of classic LND, accounting for only 8.3% of cases (Jinnah & Friedmann, 2001). Some

patients, however, do present with mild or severe complications of hyperuricemia. Many parents of patients with LND can recall "orange sand" in the children's diapers before any neurological or behavioral symptoms were recognized—an indication of otherwise subclinical urinary uric acid crystals and microhematuria (Christie et al., 1982; Mizuno, 1986). A few patients with LND presenting with overt renal failure or hematuria caused by nephrolithisasis have been reported (Ankem, Glazier, & Barone, 2000; Erhard, Herkenrath, Benz-Bohm, & Querfeld, 1997; Holland, Dillon, Pincott, Simmonds, & Barratt, 1983; Marcus, Christensen, & Malm, 1993; Nyhan, Oliver, & Lesch, 1965; Roscioni et al., 1994).

In contrast to classic LND, patients with HRND and HRH do frequently present with complications from uric acid excess, accounting for 63.6% and 95.7% of cases, respectively (Jinnah & Friedmann, 2001). The absence of obvious neurological abnormalities in HRND and HRH provide no clue to the diagnosis before hyperuricemia-related complications become apparent. Although gout is a relatively common disorder in the general population, partial deficiency of HPRT is an infrequent cause. In two large studies, HPRT deficiency accounted only for 1.6% and 4.5% of patients, many of them being relatives (Kelley et al., 1969; Yu et al., 1972). Therefore, HPRT deficiency as the underlying cause of gout may not be detected unless patients are screened rigorously.

Confirmatory Testing

The majority of patients with LND have elevated serum uric acid levels. However, increased serum and urinary uric acid values are neither sufficiently sensitive nor specific to serve as reliable diagnostic tests (see Table 21.1).

The measurement of HPRT enzyme activity, conducted in blood or in fibroblast or lymphocyte cell cultures, has been the most commonly used diagnostic test for LND. HPRT activity measured in cultured whole cells is more accurate and may also provide reliable predictive value concerning severity of disease (Jinnah, Harris, Nyhan, & O'Neill, 2005).

The diagnosis can also be confirmed by HPRT gene mutation analysis, which is increasingly used as a diagnostic tool. The characterization of a genetic mutation in an affected index patient facilitates the subsequent identification of relatives carrying the mutation or of at-risk pregnancies by molecular genetic methods. In addition, genetic mutation analysis may help to clarify the molecular basis for the resulting residual enzyme activity (Jinnah et al., 2000).

TREATMENT

HPRT deficiency is associated with metabolic, neurological, and behavioral abnormalities. Treatment attempts have often been focused on one of these clinical entities, and they include pharmacological as well as psychological and physical methods.

Hyperuricemia

Allopurinol reduces the risk of hyperuricemia-associated urological and articular complications (Edwards, Puig, & Mateos, 1986). It reduces serum acid levels by inhibiting the conversion of xanthine and hypoxanthine to uric acid. However, the normalization of serum

uric acid values may not entirely protect against the formation of kidney stones. Allopurinol is metabolized to oxypurinol, which together with an increase in xanthine and hypoxanthine may also contribute to stone formation (Kranen et al., 1985). Nephrolithiasis is best prevented by allopurinol in combination with generous hydration at all times.

Although renal stones are often identified after the development of clinical signs such as renal colic or urinary obstruction, patients may develop extensive nephrolithiasis without overt symptoms. Therefore, it is important to maintain a high index of suspicion for kidney stones, even among those under treatment. In fact, some have recommended regular ultrasound evaluations to avert the development of long-term renal complications (Morino, Shiigai, Kusuyama, & Okada, 1992).

Movement Disorder

Effective therapies for the neurobehavioral features of LND are currently lacking. Several drugs have been tested in small trials, but none has consistently demonstrated effectiveness. Although most drug trials have focused on behavioral problems, a few have focused primarily on the neurological abnormalities. Because basal ganglia dopamine is markedly depleted in LND, attempts have been made to treat dystonia by restoring dopamine. After treatment with the dopamine precursor levodopa, the motor disorder was reported to remain unchanged in two patients (Hunter et al., 1996; Manzke, Gustmann, Koke, & Nyhan, 1986), to improve modestly in two patients (Manzke et al., 1986; Mizuno & Yugari, 1974), and to worsen in four patients (Jankovic, Caskey, Stout, & Butler, 1988; Watts et al., 1982). The dopamine agonist bromocriptine improved motor function in one patient and worsened it in another (Jankovic et al., 1988). Choreiform and ballismic movements, which typically respond to dopamine receptor antagonists or drugs that deplete dopamine stores, were not consistently improved by fluphenazine, pimozide, and tetrabenazine (Goldstein, Anderson, Reuben, & Dancis, 1985; Jankovic et al., 1988; Watts, McKeran, Brown, Andrews, & Griffiths, 1974; Watts et al., 1982).

Neurosurgical interventions aimed at the extrapyramidal features in LND have been tried as well. Two patients were treated with thalamotomy, with no obvious benefit (Bunn et al., 1975; Michener, 1967). Another subject received bilateral deep brain stimulation (DBS) in the globus pallidus pars interna, which improved the dystonia by 33% (Taira, Kobayashi, & Hori, 2003). Although this technique is still experimental, its potential benefits deserve further attention.

We have found that symptomatic treatment of severe dystonia in LND—for example, to improve hand function or prevent contractures—can be performed by botulinum toxin injections in selected muscles. Pyramidal manifestations such as spasticity can be managed with baclofen or benzodiazepines. Benzodiazepines have the added advantage of reducing anxiety, which can often exacerbate the extrapyramidal and behavioral features of the disease (Jinnah & Friedmann, 2001).

Finally, a properly designed wheelchair is essential for any patient with HPRT deficiency and severe motor impairment. It provides physical support, enhances mobility, and increases opportunities for social interaction. A soft but firm support should stabilize the head, because frequent opisthotonic spasms and extreme backward head thrusts may lead to cervical spine injury (Watts et al., 1982). In addition, physical therapy can be helpful in LND—for example, to stimulate motor development, facilitate motor function, and prevent contractures.

Aberrant Behaviors

Various medications have been tested for controlling the neurobehavioral abnormalities in LND, but no agent has consistently demonstrated effectiveness in managing this aspect of the disease.

Approaches have included reducing hyperuricemia by allopurinol; restoring purine depletion by adenine; supplying intermediate agents, such as folate and glutamine; administering artificially large amounts of substrates or cofactors of HPRT to drive maximal activity; using dopamine receptor antagonists to treat a alleged dopamine receptor hypersensitivity; increasing brain serotonin levels with the serotonin precursors 5-hydroxytryptophan and tryptophan or the serotonin reuptake inhibitors clomipramine and fluoxetine; and using several other agents, such as inosine, diaminopurine, nicotinamide, tetrahydrobiopterin, adenosine monophosphate, guanosine monophosphate (GMP), and chlordiazepoxide (Jinnah & Friedmann, 2001). Some treatments have serious side effects and are discouraged. For example, adenine, glutamate supplements, and dopamine receptor antagonists can lead to 2,8-dihydroxyadenine nephrolithiasis and renal failure, glutamate neurotoxicity, and tardive dyskinesia, repectively.

In LND, stress and anxiety exacerbate self-injury, so anxiolytic drugs (including benzodiazepines) may be useful on a temporary basis. Several other drugs have been suggested to be effective in treating self-injurious behavior in LND, and these deserve further attention. In one uncontrolled study investigating the hypothesis that dysesthesias due to sensory neuropathy contribute to self-injury in LND, the anticonvulsant carbamazepine diminished self-injury in three patients and had a temporarily modest effect in one (Roach, Delgado, Anderson, Iannaccone, & Burns, 1996). Because no sensory neuropathy could be demonstrated, it is thought that carbamazepine works via another yet unknown mechanism, perhaps at the level of the central nervous system. Gabapentin, another antiepileptic drug, has been reported to reduce self-injury in one patient with LND, although follow-up was only limited to several weeks (McManaman & Tam, 1999). Finally, a significant reduction of self-injury by the atypical neuroleptic risperidone has been described in one patient (Allen & Rice, 1996). It should be noted that these drugs have not been systematically studied, and additional investigations with prolonged follow-up are necessary to evaluate their ultimate effectiveness.

Nonpharmacological treatments for LND include globus pallidus DBS for the treatment of dystonia in one patient, as mentioned earlier. In this case, the treatment had the unexpected side effect of eliminating self-injurious behavior for at least 2 years (Taira et al., 2003). Again, further studies are warranted to determine whether this approach is successful in other cases for extended periods of time.

Psychologically based techniques have been used to manage self-injury and other unwanted behaviors in LND. Extinction methods, consisting of actively ignoring an unwanted behavior to prevent the patient from receiving positive reinforcement in terms of added attention, have proven to be among the most effective behavior modification tools currently available for LND (Anderson, Dancis, Alpert, & Herrmann, 1977; Bull & LaVecchio, 1978; McGreevy & Arthur, 1987). Negative reinforcement in LND is ineffective and may even increase undesirable behavior (Anderson et al., 1977). In most patients, a combination of ignoring unwanted behaviors and positive reinforcement for alternative behaviors leads to the desired behavioral modification.

As noted earlier, one of the most critical supportive elements for the management of self-injurious behavior in a patient with LND is a wheelchair (Letts & Hobson, 1975). It should be individually adapted, comfortable, and fully padded without any sharp parts

within reach. In addition, it should be impossible for the patient to put fingers into the wheel spokes or abrade the ankles on the sides of foot supports. Restraints for arms and legs should also be applied, to prevent self-injury such as hitting, biting fingers, and poking the eyes. Flexible arm splints (Ball et al., 1985) or helmets with retractable mouth barriers (Eguchi, Tokioka, Motoyoshi, & Wakamura, 1994) may provide alternatives to protective straps. Other patients find that covering their hands with gloves or socks provides enough of a deterrent to prevent self-injury (Nyhan, 1976).

Of all forms of self-injury in LND, biting the lips and tongue may be the most difficult to manage, and often causes desperate feelings of powerlessness in family members and caretakers. Dental devices, constructed to prevent self-biting while preserving the teeth, have rarely provided a safe and consistent means for preventing self-biting (Jinnah & Friedmann, 2001). The prevention of self-inflicted tissue damage often requires tooth extraction. Although this is a drastic procedure, patients are often very relieved once the procedure is completed. Sometimes a partial set of teeth can be left *in situ* without causing too much trouble, and this can be desirable to try for functional and esthetic reasons. However, any tooth causing damage should be extracted without delay when behavior therapy and other conservative measures fail.

Prevention

Since there are currently no effective therapies for the devastating neurobehavioral features of LND, prevention remains the cornerstone of effective medical intervention. Genetic counseling and carrier testing of a patient's mother, sisters, and other female family members play an important role in identifying potentially affected subjects. In addition, the identification of carrier status mandates the monitoring of all subsequent pregnancies if abortion is an option.

PATHOGENESIS

Molecular Genetics

The normal human HPRT gene consists of nine exons spanning about 45 kb at Xq26–q27 on the distal end of the long arm of the X chromosome (Francke & Taggart, 1980). The entire gene has been fully sequenced (Edwards et al., 1990), and the regulation of its expression has been carefully studied (Jiralerspong & Patel, 1996).

HPRT deficiency is inherited as an X-linked recessive disease, and the incidence of classic LND has been estimated at 1 in 380,000 births (Crawhall, Henderson, & Kelley, 1972). Although virtually all patients with LND are male, due to the mode of inheritance, several female patients have been described to date (Aral, de Saint, Al Garawi, Kamoun, & Ceballos-Picot, 1996; De Gregorio, Nyhan, Serafin, & Chamoles, 2000; Hara et al., 1982; Hooft, Van Nevel, & De Schaepdryver, 1968; van Bogaert et al., 1992; Yukawa et al., 1992). Two female patients demonstrated nonrandom inactivation of the paternally derived X chromosome (De Gregorio et al., 2000; Ogasawara et al., 1989), and two were determined to have a point mutation in one allele and markedly reduced messenger RNA expression from the other allele (Aral et al., 1996; Yamada, Goto, Yukawa, Akazawa, & Ogasawara, 1994).

A meta-analysis of 271 mutations causing LND and partial phenotypes, and a subsequent update of another 31 cases, demonstrated a wide variety of different mutations (Jinnah

et al., 2000, 2005). Single-base substitutions leading to alteration of one amino acid constituted the most common type of mutation. Less common mutations included single-base substitutions leading to premature stop, single-base substitutions leading to splicing errors, deletions, duplications or rearrangements, and double mutations (Table 21.3). Mutations causing disease appear throughout the HPRT gene, with some minor mutational hot spots. Studies of genotype–phenotype correlations have provided two important lessons (Jinnah et al., 2000, 2005). First, the location of the mutation within the gene does not appear to determine the overall severity of the disorder or to govern which clinical manifestations will occur. Second, the type of mutation is related to severity, as those predicted to cause complete HPRT deficiency are more likely to be associated with classic LND than with milder LNVs.

Biochemical Background

Purine nucleotides are important players in many biochemical processes, such as nucleic acid synthesis, chemical energy transport, coenzymatic reactions, and inter- and intracellular signaling. The pathways for synthesis, metabolism, and degradation of purines are shown in Figure 21.4. Purine nucleotides can be obtained through either (1) synthesis de novo, (2) salvage of purine bases, or (3) uptake from the extracellular environment. In humans, about 90% of free purine bases generated during intracellular metabolism are recycled rather than degraded or excreted (Murray, 1971). HPRT mediates the recycling of the purine bases hypoxanthine and guanine into the usable nucleotide pools. In particu-

TABLE 21.3. Gene Mutations in HPRT Deficiency

Mutation type	HRH or HRND (n = 71)	LND (n = 220)	Unknown phenotype (n = 8)	Total (n = 302)
Single-base substitution				
• Missense	54	69	4	127
• Nonsense	1	23	1	25
• Splice error	7	36	0	43
Deletion				
• Coding sequences	2	61	3	66
• Splice error	0	5	0	5
Insertion				
• Coding sequences	1	18	0	19
• Splice error	0	1	0	1
Others				
• Duplication	3	3	0	6
• Substitutions	0	2	0	2
• Females	1	5	0	6
• Double mutants	2	0	0	2

Note. Overview of mutation types in 271 cases of HRH, HRND, and classic LND, as reported by Jinnah, De Gregorio, Harris, Nyhan, and O'Neill (2000) and Jinnah, Harris, Nyhan, and O'Neill (2005). Cases with less severe manifestations typically have (missense) mutations that are predicted to permit some degree of residual enzyme activity, while mutations predicted to cause complete HPRT deficiency are more likely to be associated with classic LND.

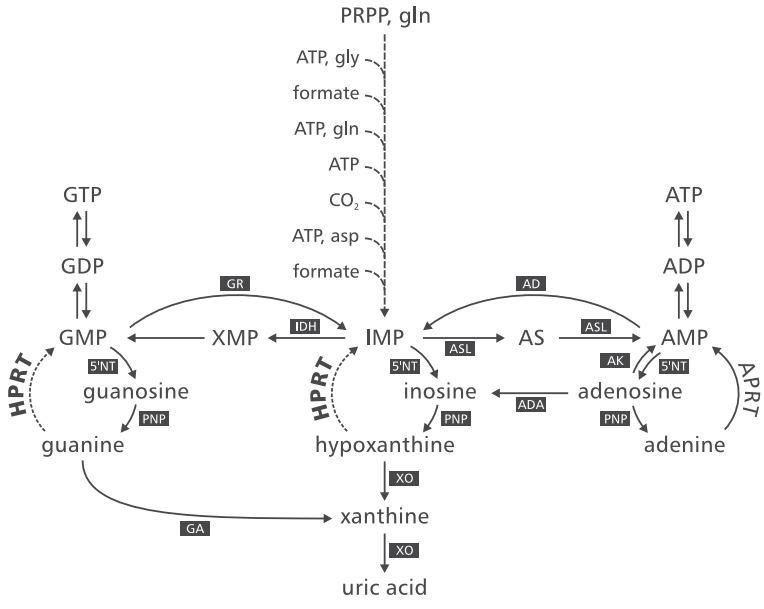

FIGURE 21.4. Purine metabolism. Metabolic pathways for synthesis, metabolism, and degradation of purines, including salvage reactions by HPRT. Abbreviations: 5'NT, 5'-nucleotidase; AD, adenylate deaminase; ADA, adenosine deaminase; ADP, adenosine diphosphate; AK, adenosine kinase; AMP, adenosine monophosphate; APRT, adenine phosphoribosyltransferase; AS, adenylosuccinate; ASL, adenine succinate–synthetase/lyase; asp, aspartic acid; ATP, adenosine triphosphate; GA, guanase; GDP, guanosine diphosphate; gln, glutamine; gly, glycine; GMP, guanosine monophosphate; GR, GMP reductase; GTP, guanosine triphosphate; HPRT, hypoxanthine–guanine phosphoribosyltransferase; IDH, IMP dehydrogenase; IMP, inosine monophosphate; PNP, purine nucleoside phosphorylase; PRPP, phosphoribosylpyrophosphate; XMP, xanthylate; XO, xanthine oxidase.

lar, HPRT catalyzes the transfer of the 5-phosphoribolsyl group from PP-ribose-P to hypoxanthine or guanine to form their respective nucleotides, inosinic acid and GMP.

The consequences of the absence of HPRT include (1) accumulation of its substrates hypoxanthine and guanine, which are not reutilized but degraded to uric acid; (2) increased PP-ribose-P due to underuse and increased synthesis; and (3) accelerated de novo purine synthesis (Jinnah & Friedmann, 2001). Although it seems likely that impaired purine salvage would lead to purine depletion, no consistent loss of purines has been demonstrated either in humans or in animal models of LND. The reduced purine salvage, together with the increase in purine synthesis, is the basis for marked overproduction of uric acid in LND (Jinnah & Friedmann, 2001).

Although the primary biochemical defect causing LND has been known for a long time, the pathophysiological mechanisms by which the HPRT deficiency leads to the neurobehavioral disturbances in LND have not yet been clarified. Following is a summary of some of the key aspects of pathogenesis.

Neuropathology

A review of autopsy studies has not revealed any consistent neuroanatomical or histological abnormalities in the brains of patients with LND (Visser et al., 2000). In addition, early

neuroimaging studies, including computed tomography and magnetic resonance imaging (MRI), showed no obvious structural changes, although mild diffuse atrophy was noted in several patients. Quantitative MRI confirmed these findings, and demonstrated smaller total brain volumes in patients with LND than in age-matched controls (Harris et al., 1998). In this study, basal ganglia volumes were disproportionately affected, averaging 66% of control volumes; this finding suggested selective structural brain changes in LND.

Postmortem neurochemical analyses of brain tissue have revealed additional evidence for brain dysfunction in LND. A profound loss of dopamine among all regions of the basal ganglia has been demonstrated in five patients with LND (Lloyd et al., 1981; Saito et al., 1999). Levels of dopamine and its metabolite homovanillic acid were reduced by 60–90% in the caudate, putamen, globus pallidus, and nucleus accumbens. In the substantia nigra, however, the dopamine content was minimally reduced. In contrast, other neurotransmitter systems appeared relatively spared.

To address the issue of dysfunction of dopamine systems *in vivo*, dopamine axon integrity was measured in seven patients via positron emission tomography (PET) (Wong et al., 1996). This study showed a reduction of binding of the dopamine transporter ligand WIN 35,428 by 73% and 56% in putamen and caudate, respectively. Another PET study, including 11 patients, showed reduced accumulation of the levodopa analogue [^{18}F]fluorodopa into fibers in the putamen and caudate, by 69% and 61%, respectively (Ernst et al., 1996). These results provide important correlative evidence for dysfunction of nigrostriatal dopaminergic pathways *in vivo*.

These biochemical and neuroimaging studies have led to suggestions that nigrostriatal dopamine axons are reduced in the LND-affected brain. However, empirical support for these suggestions has been lacking. An immunohistochemical study of two LND-affected brains provided no evidence for consistent reduction of nigrostriatal dopamine axons or neurons (Saito et al., 1999). Furthermore, detailed studies of an HPRT-deficient knockout mouse model have demonstrated a similar loss of dopamine content without loss of dopamine axons or neurons (Jinnah et al., 1994). Others have shown a profound loss of dopamine content in HPRT-deficient subclones of the rat PC12 pheochromocytoma cell line, in the absence of any apparent morphological correlate in these cells (Bitler & Howard, 1986; Yeh, Zheng, & Howard, 1998). Therefore, the loss of dopamine in the neurochemical studies and the apparent loss of dopamine transporters in the PET studies could have a metabolic rather than an anatomical basis.

HPRT–Dopamine Connection

Although there is strong evidence for an important connection between HPRT and dopamine neurons, the nature of this relationship remains enigmatic. The functions of HPRT have no apparent direct relationship to dopamine neurotransmission, so it is likely that HPRT deficiency influences the dopamine systems indirectly, through secondary changes in purine metabolism.

Several hypotheses that account for the HPRT–dopamine relationship have been presented, and these have been reviewed in detail elsewhere (Visser et al., 2000). These theories include presumed regional differences in brain HPRT, indicating a relatively high dependence of the basal ganglia on HPRT-mediated purine salvage; HPRT deficiency's leading to selective nigrostriatal dopamine fiber loss, while cell bodies remain intact; HPRT deficiency's inducing metabolic toxicity by accumulation of a toxic metabolite; HPRT deficiency's causing depletion of purine metabolites; HPRT deficiency's leading to exces-

sive production of oxygen free radicals and subsequent oxidative stress; and depletion of intermediary molecules that are required for other neural function by the accelerated purine synthesis. However, to date, many of these hypotheses have not been empirically verified. Several theories recently investigated in a mouse model of LND have been reported to be unlikely to account for the pathophysiological mechanism by which HPRT deficiency causes dopaminergic dysfunction; these theories include increased oxidative stress (Visser et al., 2002) and tetrahydrobiopterin deficiency (Hyland, Kasim, Egami, Arnold, & Jinnah, 2004).

LND and the Basal Ganglia

Although the exact nature of the relationship between HPRT and the dopamine systems remains to be determined, results from biochemical and neuroimaging studies are consistent with dysfunction of basal ganglia dopamine systems. Based on anatomy and physiology of the basal ganglia, distinct circuits have been recognized; these connect distinct cortical areas, through the basal ganglia and thalamus, back to the cortex. It has been proposed that these circuits contribute to motor, cognitive, motivational, and emotional aspects of behavior. It appears that many clinical features of LND can be attributed to dysfunction of these neural circuits involving the basal ganglia (Visser et al., 2000). This concept, summarized in Table 21.4, is discussed in this section.

The motor features associated with HPRT deficiency include dystonia, chorea, and ballismus. These are all typically considered hyperkinetic manifestations of disturbances in the subcortical motor circuits through the basal ganglia. The oculomotor abnormalities observed (including an impairment in the initiation of voluntary saccades, with failure to suppress reflexive saccades) are also found in other basal ganglia diseases, such as Huntington disease (Lasker, Zee, Hain, Folstein, & Singer, 1987; Leigh, Newman, Folstein, Lasker, & Jensen, 1983). In addition, the nature of the dysarthria in LND has never been studied in detail, but has been described as "athetoid" dysarthria typical of basal ganglia disease (Nyhan, 1972b, 1973).

It is, however, unlikely that basal ganglia dopamine depletion is directly responsible for the clinical features suggestive of corticospinal tract involvement in some affected patients. To account for these findings, it has been proposed that patients with LND are

TABLE 21.4. Clinical–Pathological Correlation in LND

Clinical feature	Proposed basal ganglia circuit
• Dystonia	• Motor and oculomotor circuits
• Chorea	
• Ballismus	
• Dysarthria	
• Ocular dysmotility	
• Cognitive disability	• Dorsolateral prefrontal circuit
• Aggressive, compulsive, and impulsive behaviors	• Lateral orbitofrontal and anterior cingulate circuits
• Self-injury	

Note. Proposed correlation between clinical features in LND and dysfunction of specific neuronal circuits through the basal ganglia. Data from Visser, Bär, and Jinnah (2000).

susceptible to a mechanical or ischemic cervical myelopathy, due to chronic cervical dystonia and violent retrocollis (Watts et al., 1982). Forceful neck movements in LND are illustrated by the reports of an atlantoaxial dislocation as a result of violent retrocollis in one patient (Hoefnagel et al., 1965), and an unexplained high cervical fracture and an os odontoideum in two brothers (Shewell & Thompson, 1996).

Although patients with LND and those with partial HPRT deficiency may suffer from a certain degree of cognitive impairment, as stated before, they show a characteristic profile of cognitive abilities, including prominent difficulties with attention, working memory, and flexible thinking (Matthews et al., 1995, 1999; Schretlen et al., 2001; Solan et al., 1997). This profile of cognitive strengths and weaknesses suggests that subcortical executive functions are more disrupted than those where cortical areas are primarily involved. This view is compatible with dysfunction of the cognitive circuits of the basal ganglia, involving the caudate and prefrontal cortex (Visser et al., 2000). However, more extensive studies will be required to develop a more complete understanding of cognitive function in LND.

The negative behaviors in LND, including aggressive behavior and self-injury, have been interpreted as compulsions or impulsions (Dizmang & Cheatham, 1970; Nyhan, 1972b), and have been proposed to lie along a continuum of behaviors that include obsessive–compulsive and stereotypic behaviors (Visser et al., 2000). Although the neurobiology of self-injury in LND is incompletely understood, it has been suggested that the basal ganglia and connections with the limbic system are involved, similar to those proposed for Tourette syndrome (Mathews et al., 2004; Palumbo, Maughan, & Kurlan, 1997). Additional insight into the effects of basal ganglia dopamine dysfunction on self-injurious behavior has been obtained from animal models for LND, as will be discussed in the next section.

EXPERIMENTAL MODELS

In Vitro Models

Many investigators have attempted to model the metabolic defects associated with HPRT deficiency in cultured cells. Many different types of cells have been investigated, including fibroblasts, lymphoblasts, primary neuronal or astrocyte cultures, neuroblastomas, gliomas, and pheochromocytomas (Jinnah & Friedmann, 2001).

Of particular relevance to the proposal that nigrostriatal dopamine dysfunction contributes to the neurobehavioral phenotype of LND are studies of PC12 cells, a rat pheochromocytoma cell line that makes dopamine. Dopamine content and dopamine uptake are markedly reduced in the majority of a series of different HPRT-deficient PC12 lines (Bitler & Howard, 1986; Yeh et al., 1998). This loss of dopamine occurs in the absence of any overt defect in growth habits or morphological appearance. These findings emphasize again an important connection between aberrant purine metabolism and dopamine transmitter dysfunction.

Many additional abnormalities have been reported, albeit with less consistency. Some studies have shown increases or decreases in various purine and pyrimidine metabolites, as well as changes in amino acid metabolism or other processes. Although studies of cultured HPRT deficiency cells are attractive because of the feasibility of performing detailed studies under strictly controlled conditions, they also suffer from a number of limitations. First, the lack of consistency among the many studies makes it difficult to determine which abnormalities are most significant. Second, the foreign environment and culture conditions may result in the expression of anomalies that do not occur in the brain or are otherwise not relevant to the pathogenesis of the disease. Finally, cultured cells tend to be structur-

ally less complex than those in the brain, thereby increasing the likelihood of missing relevant abnormalities.

Animal Models

To study the pathophysiological mechanisms associated with HPRT deficiency *in vivo* in more detail, and to overcome several of the limitations of *in vitro* models for LND, two knockout mouse models have been developed. One strain of mutant mice was produced by selecting stem cells for spontaneous mutations in the HPRT gene (Hooper, Hardy, Handyside, Hunter, & Monk, 1987); the other carries a retrovirus-mediated disruption of the HPRT gene (Kuehn, Bradley, Robertson, & Evans, 1987). Both mutations result in complete absence of HPRT enzyme activity, but the mouse strain carrying the HPRT deletion mutation has been studied in more detail.

As in patients with LND, the absence of HPRT in mice is associated with activation of purine synthesis via the de novo pathway (Jinnah, Page, & Friedmann, 1993; Pelled, Sperling, & Zoref-Shani, 1999). In addition, these mice have significant deficits in brain dopamine levels (Dunnett, Sirinathsinghji, Heavens, Rogers, & Kuehn, 1989; Finger, Heavens, Sirinathsinghji, Kuehn, & Dunnett, 1988; Jinnah et al., 1994, 1999; Jinnah, Langlais, & Friedmann, 1992; Williamson et al., 1991), similar to those found in patients with LND. Biochemical surveys have revealed 50–60% dopamine loss in the striatum, while other brain regions and neurotransmitter systems appear relatively spared (Jinnah et al., 1994, 1999). Other markers associated with the dopamine systems, including homovanillic acid, tyrosine hydroxylase, and aromatic amino acid decarboxylase, were also reduced in the striatum of these mutant mice. Interestingly, the abnormality in dopamine content appears to develop 3–6 weeks after birth. This coincides with the development and maturation of the basal ganglia, and suggests a late developmental or early degenerative process. Despite the profound reduction in basal ganglia dopamine, no apparent reduction in the number of midbrain dopamine neurons is apparent (Dunnett et al., 1989; Jinnah et al., 1994). Biochemical measures of other neurotransmitter systems, including norepinephrine, serotonin, gamma-aminobutyric acid, and acetylcholine systems, appear normal. These studies provide further support for the concept that basal ganglia dopamine systems are abnormal in the HPRT-deficient brain.

Despite the existence of genetic, metabolic, and neurochemical abnormalities similar to those of LND, the knockout mice also differ from their human counterparts in several respects. First, they do not develop hyperuricemia, because in mice uric acid is degraded to allantoin by the enzyme uricase. In addition, HPRT-deficient mice do not exhibit any overt neurobehavioral anomalies, such as self-injury, motor dysfunction, or cognitive behavior. The absence of an analogous neurobehavioral phenotype suggests that a key element of pathophysiology is missing from the HPRT-deficient mouse brain. Various explanations have been provided, including differences in the relative importance of purine salvage by HPRT, differences in purine metabolism, differences in the response of the rodent brain to the loss of HPRT, or different compensatory mechanisms (Jinnah & Friedmann, 2001).

In addition to genetic mouse models, several pharmacological models have been developed. Specific drugs can cause self-injurious behavior under certain circumstances in animals, including methylxanthines, clonidine, amphetamine, methamphetamine, pemoline, dopamine uptake inhibitors, and BayK 8644 (Jinnah & Friedmann, 2001). These have been used as pharmacobehavioral models for LND, but are more properly considered

models for self-injurious behavior in general. Interestingly, many of the drugs that provoke self-injurious behavior in rodents stimulate the dopamine system.

Another model for self-injury in LND involves the pharmacological destruction of brain dopamine system in neonatal rats, resulting in a hyperactive phenotype. Treatment of these animals with the dopamine precursor levodopa exacerbates the hyperactivity and induces self-biting (Breese et al., 1984; Moy, Criswell, & Breese, 1997). Direct intracerebral microinjection of dopamine agonists into the caudoputamen elicits similar behavior (Breese, Napier, & Mueller, 1985). These findings provide additional evidence that a disorder of dopaminergic pathways is important in the pathogenesis of self-injurious behavior. However, neurotransmitter systems other than the dopamine system may also contribute to self-biting after neonatal destruction of dopamine neurons, and the involvement of serotonin systems and of adenosine has been suggested (Jinnah & Friedmann, 2001).

Another important lesson learned from the neonatally lesioned rat model is the fact that the age at which the basal ganglia are disrupted has a profound influence on motor outcomes. Whereas patients with Parkinson disease display a *hypo*kinetic syndrome, individuals with LND display a *hyper*kinetic motor syndrome. The destruction of brain dopamine systems in *adult* rats results in a *hypo*kinetic behavioral phenotype characterized by akinesia and bradykinesia. However, the same lesion in neonatal animals causes the development of spontaneous hyperactivity as they grow to adults, including learning defects and unusually aggressive behavior (Breese et al., 1984, 1985; Erinoff & Snodgrass, 1986). Although the reasons for the marked differences in neurobehavioral outcome following lesions of brain dopamine systems at different ages have not yet been fully explained, the absence of a hypokinetic phenotype after dopamine lesions during early development probably results from compensatory developmental changes that may not operate with the same fidelity as the mechanisms controlling motor behavior in the normal brain (Jinnah & Breese, 1997; Joyce, Frohna, & Neal-Beliveau, 1996; Moy et al., 1997; Zigmond, Abercrombie, Berger, Grace, & Stricker, 1990).

CONCLUSION

HPRT deficiency is associated with both a qualitative and quantitative spectrum of abnormalities. Patients may exhibit (1) hyperuricemia due to uric acid overproduction; (2) motor dysfunction, including dystonia and hypotonia; (3) selective cognitive impairments; (4) aberrant behaviors, including compulsive self-injurious behavior and aggressiveness toward others; and (5) other manifestations, such as growth retardation and anemia. Residual HPRT activity seems to determine the pattern of abnormalities present in patients, as well as the severity of their symptoms. Patients with virtually no residual enzyme activity exhibit the full spectrum of LND, while partial HPRT deficiency may result in hyperuricemia with or without neurological symptoms.

There is emerging evidence from clinical observations and from *in vitro* and *in vivo* models that HPRT deficiency is associated with dysfunction of the dopamine system in the basal ganglia, which may account for many of the neurobehavioral features present in LND. However, the exact effect of HPRT deficiency on dopaminergic neurons, as well as the mechanism by which basal ganglia dysfunction causes the neurobehavioral phenotype, remains enigmatic. Research should focus on these pathophysiological "black boxes," in order to gain a more complete understanding of basal ganglia function, and to facilitate the development of more effective treatments for LND.

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PRADER–WILLI SYNDROME

ELISABETH M. DYKENS
KAREN SUMMAR
ELIZABETH ROOF

Prader–Willi syndrome (PWS) is a genetic disorder involving infantile hypotonia, short stature, hypothalamic hypogonadism, hyperphagia, obesity, mild levels of mental retardation, and a characteristic behavioral phenotype. For good reasons, research on persons with PWS has focused primarily on babies and children. Affected individuals are increasingly diagnosed in infancy or early childhood, and more and more infants with hypotonia (a hallmark of the syndrome) are routinely evaluated for PWS today than even a decade ago. Families with newly diagnosed infants typically need information and much support, especially if the babies fail to thrive and require gavage or other specialized feeding techniques. For diagnosticians, early interventionists, and families, then, infancy remains a time of heightened concern.

Childhood has also been of keen interest. The syndrome's most striking and life-threatening characteristics—hyperphagia and food seeking—invariably begin in the preschool years, between 2 and 6 years of age. Families must shift their daily routines and eating habits to accommodate these children's lifelong needs for a specialized low-calorie diet and for close supervision around food. Repetitive, compulsive behaviors and temper tantrums, all highly characteristic of the syndrome, also begin in early childhood. With the onset of both medical and behavioral complexities, then, the early childhood years have understandably dominated the PWS research scene.

In sharp contrast, data are scarce on adults with PWS, especially adults in their middle and older years. Until recently, the behavioral literature had reported only a dozen or so adults over the age of 30 years who had been examined with standardized assessment tools. To some extent, this lack of emphasis on adults with the syndrome is a by-product of the intense focus on childhood. But it is also the case that until recently, few adults with PWS lived into middle or old age.

Using a population-based cohort in the United Kingdom, Whittington, Holland, Webb, and Boer (2001) estimated a 3% annual death rate overall for persons with PWS, and a 7% death rate for adults age 30 years and older. Different death rates across age cohorts raise the possibility that those who do survive into adulthood differ from those who do not; they may be healthier (Widaman, Borthwick-Duffy, & Powers, 1994). While such

selective survival issues have yet to be formally studied in PWS, some persons with the syndrome are now surviving well into adulthood, including those who are relatively obese and at risk for obesity-related medical complications (Dykens, 2004).

Although data are relatively scarce, this chapter summarizes findings to date on adults with PWS from both the medical and behavioral literature. Before reviewing medical and behavioral issues in adults, we first provide a brief summary of the genetics of PWS. This background information is particularly important, because the genetic subtypes of PWS have emerged as robust predictors of some aspects of the PWS behavioral phenotype.

In addition, some of the chapter draws upon our collective clinical experiences in working with adults with PWS and their families and caregivers in psychiatric or medical clinics, and in advocacy and support groups. Whenever possible, we integrate these clinical observations with research data, or specify areas in need of future study. Our ongoing research program also aims to identify why some adults with PWS have more successful outcomes than others. This chapter thus identifies problems and areas of difficulty for adults, as well as positive attributes and areas of relative strength. This more balanced research perspective—one that examines both problems and strengths—paves the way for interventions that optimize the quality of life for adults with PWS and their families.

GENETICS

PWS occurs in approximately 1 in 20,000 births, and is equally distributed between females and males and among all ethnic groups. PWS is caused by a lack of paternally derived imprinted information on a specific region on the long arm of chromosome 15 (15q11–q13). PWS is the first known genetic disorder to show the effects of differential genomic imprinting—that is, the differential expression of genes derived from mothers versus fathers (see Nicholls, 1993, for a review). "Imprinting" refers to the addition of methyl groups to DNA, which renders the DNA inactive. This imprinting is specific to the sex of the parent of origin (i.e., DNA from the mother is differently methylated than DNA from the father).

In approximately 70% of cases, PWS is associated with a paternally derived deletion at 15q11–q13. Recently, this large class of deletions was further classified into two types, with type I deletions being about 500 kb larger than type II deletions (Butler, Bittel, Kibiryeva, Talebizadeh, & Thompson, 2004). Although Butler and colleagues' data are preliminary, individuals with larger deletions appear to have lower adaptive functioning, and they may also have more compulsive and other problematic behavior.

In about 25% of patients, PWS is associated with maternal uniparental disomy (UPD), or the derivation of both copies of chromosome 15 from the mother. This situation is thought to arise from a rescue of an embryo with a trisomy 15 (the most common trisomy in fetuses), in which the third chromosome 15 is lost and this is the one of paternal origin. The effects of imprinting are also operating in UPD, since genes turned off in the mother have no active counterparts from a paternally derived chromosome. As detailed later in the chapter, persons with maternal UPD share much of the classic PWS phenotype, but also differ in important ways from those with paternal deletions.

In a few, rare cases, PWS is caused by an anomaly in the imprinting process. Some of these imprinting defects involve small deletions in the center controlling the imprinting process within 15q11–q13 (Saitoh et al., 1997). Although the numbers of cases with imprinting deletions are small, they include all cases in which there has been a familial recurrence of PWS.

PWS, then, is associated with a lack of paternally derived information—either through paternal deletion or through maternal UPD—to the PWS critical region on chromosome 15. When the opposite pattern occurs, and there is a lack of *maternally* derived information to the same 15q11–q13 region, persons have a different disorder, Angelman syndrome (AS). Despite their close genetic relationship, the clinical features of AS and PWS are dramatically different. Those with AS typically have microcephaly, seizure disorders, limited or absent expressive language, bouts of laughter, and an ataxic gait (Williams et al., 1995). In both AS and PWS, advances in the underlying genetics of the 15q11–q13 region have led to more refined studies of behavior. Throughout the chapter, new studies are mentioned that identify differences in behavior among persons with PWS that are due to paternal deletion versus maternal UPD.

PHYSICAL AND MEDICAL CONCERNS

In the past, prevalence rates of problems associated with PWS were based on clinical samples or best estimates. Problems with ascertainment, correct diagnosis, and an adequate control group led to overestimations of some conditions and to missed cases of others. Recently, however, Whittington, Holland, and their colleagues in the United Kingdom reported the first population-based estimates of medical problems in PWS. In addition to increased risks of obesity, their findings both corroborate and extend previous work. Specifically, these researchers document common physical disorders involving endocrine functioning (e.g., diabetes mellitus, osteoporosis, hypothalamic hypogonadism, growth hormone insufficiency), as well as problems in other body systems (e.g., cardiovascular functioning, respiration, the central nervous system [CNS], and orthopedics).

Endocrinology

Diabetes mellitus has been observed in PWS for many years. Early papers included type 2 diabetes (non-insulin-dependent diabetes mellitus) as a primary feature of PWS. The prevalence of diabetes in PWS is 12–25% in all age groups, from 2 to 4 times greater than the 6.3% found in the general U.S. population (American Diabetes Association, 2004; Butler et al., 2002). For adolescents and children, there is a 10-fold increased risk of diabetes in PWS (American Diabetes Association, 2004; Whittington & Holland, 2004). As in the general population, obesity is the major risk factor for type 2 diabetes; also as in the general population, truncal obesity is associated with both diabetes and hypertension in PWS. Individuals with PWS who develop diabetes, then, are at increased risk of hypertension, coronary artery disease, kidney failure, blindness, and stroke. These possible morbidities underscore the importance of sustained weight management in adults with PWS.

Alterations in the hypothalamus are responsible for the delay of gonadal maturation seen in PWS. These alterations in turn are responsible for the clinical finding of cryptorchidism in virtually all males with PWS, as well as that of absent, delayed, or irregular menarche in females (Crino et al., 2003). For many years, these individuals were thought to be sterile. In the past decade, however, two women with PWS have given birth to live children (Akefeldt, Tornhage, & Gillberg, 1999). One woman had PWS resulting from a deletion in the 15q11–q13 region, and she delivered an infant with AS, as expected. The second woman was diagnosed with PWS due to maternal UPD, and she delivered an unaffected baby. In one of these women, treatment with a selective serotonin reuptake inhibitor was

implicated in inducing gonadotropin release and the hormonal conditions required for pregnancy. Although the data are preliminary, this case provides a new cautionary note about using this class of psychotropic medications in adults with PWS.

Decreased growth hormone secretion, which is another effect of the hypothalamic dysfunction in PWS, is felt to be responsible for the short stature seen in individuals with PWS (Grugni et al., 1998). Deficiency in growth hormone in PWS results in a shorter birth length, decreased growth velocity, and a lack of growth spurt prior to the onset of puberty. Replacement therapy with growth hormone has resulted in increased growth velocity, decreased percentage of body fat, and increased lean body mass (Carrel, Myers, Whitman, & Allen, 2001, 2002). The use of this therapy in children has been so beneficial that studies are now being conducted to study its effects on adults and infants with PWS. Anecdotally, we have observed that adults on growth hormone show increased muscle mass, thereby burning more calories.

Sexuality

Of concern is that issues related to sexuality have not yet been even informally studied in adults with PWS. Because incomplete sexual development and a lack of secondary sexual characteristics are features of the syndrome, many families and practitioners have assumed that these individuals remain relatively immature in their sexual functioning, and that adults are infertile. But as the cases described above prove, when the conditions are right, women with PWS can become pregnant. Anecdotally, we find as well that adults engage in exploratory and other sexual behavior with others.

Men and women with PWS can benefit from the same education about sexuality offered to other individuals with developmental or cognitive disabilities. Most adults need information about privacy, abuse, responsible sexual behavior, routine gynecological care, and general awareness of body parts and functions. Some women with PWS have been known to trade sexual favors for food, and these women are at heightened risk for sexually transmitted diseases and sexual abuse.

Cardiovascular Functioning

Since obesity is a major feature of PWS, these individuals would presumably be at increased risk for coronary artery disease, hypertension, and other cardiovascular dysfunction. Cardiac data, however, are somewhat scarce in adults with PWS. Of note, when individuals with type 2 diabetes are excluded from studies, there may actually be a decreased incidence of hypertension in adults with PWS (Whittington & Holland, 2004). Additional studies are needed on the prevalence and correlates of cardiovascular disease in adults with PWS.

Respiration

Several recent anecdotal case reports suggest an increased frequency and severity of respiratory illness in PWS; such problems are expected in persons with PWS, in light of their obesity and hypotonia (Stevenson et al., 2004). Hypotonia leading to hypoventilation could lead to increased risk of respiratory illness, as well as an increased risk of adverse outcome

in situations requiring mechanical ventilation. Unterborn (2001) demonstrated altered pulmonary function testing in individuals with PWS.

Another respiratory problem in PWS is sleep apnea. Obstructive sleep apnea is a well-known complication of obesity, and it comes as no surprise that this is a common problem in adults with PWS. Symptoms of obstructive sleep apnea include irritability, daytime sleepiness, and disrupted sleep. When the problem is left untreated, the body remains chronically hypoxic at rest; this increases the demands on the right side of the heart, which eventually fails. This condition, known as cor pulmonale, is an irreversible form of heart failure for which there is no adequate treatment. Because of their obesity, as well as the adenoid and tonsillar hypertrophy commonly seen in all children (Erler & Paditz, 2004), children with PWS are at particularly high risk for obstructive sleep apnea.

Central Nervous System

In general, seizures are more common in persons with syndromes associated with cognitive disabilities. Seizures are not as common in PWS as in other such syndromes, but they are more commonly seen in PWS than in the general population (Cassidy & Schwartz, 1998). Furthermore, it is well known that individuals with PWS have a relatively high pain threshold; this feature is not well understood and is probably related to CNS dysfunction.

Two types of temperature abnormalities have also been described in PWS, and are likely to be related to hypothalamic dysfunction. The first is abnormal regulation of body temperature, and the second is an altered perception of temperature. As described later in this chapter, the CNS is also implicated in much of the behavioral phenotype of PWS, as well as in the increased risks of psychiatric disease among adults with the syndrome.

Orthopedics

It has been known for some time that osteoporosis is a common problem in PWS (Cassidy, Rubin, & Mukaida, 1985). The frequency of fractures is a measure used to assess the risk for osteoporosis, and individuals with PWS have an increased rate of bone fractures (Butler et al., 2002). Vestergaard and colleagues (2004) found decreased bone mineral density in adults with PWS, compared to controls matched on gender and body mass index (BMI). These findings implicate an underlying abnormality of bone metabolism in adults with PWS, as well as an increased risk of osteoporosis.

West and Ballock (2004) recently reported increased rates of orthopedic conditions in PWS, based on reports from parents or caregivers of over 500 individuals with the syndrome. This association is explained in part by the obesity that is common in PWS, as well as by the underlying endocrine disorders that affect bone metabolism. West and Ballock found that 47% of the sample had flat feet, 41% scoliosis, 19% valgus genu, 10% hip dysplasia, 9% osteoporosis, 7% femoral patellar instability, 2% clubfeet, 2% nursemaid's elbow, and 2% leg length inequality; however, just one person (0.2%) had slipped capital femoral epiphysis (SCFE). Although obesity is a well-documented risk factor for SCFE, the prevalence of SCFE in PWS is *not* increased over the general population. It should be kept in mind, however, that the administration of growth hormone may increase the risk

of SCFE in persons with PWS. Early in the treatment of PWS with growth hormone replacement therapy, there were concerns that scoliosis might be aggravated by growth hormone administration. Although very few reports of this have occurred, persons on hormonal replacement therapy are typically assessed for this risk.

Malignancies

A survey conducted by Davies and colleagues (2003) evaluated the risk of malignancies in PWS in over 1,000 respondents recruited through the PWS Association (USA). The total number of cancers for individuals with PWS was 8 (per 1,000), as contrasted with 4.8 in the general population; in particular, there were 3 cases of myeloid leukemia per 1,000 in the sample with PWS, versus 0.075 in the general population. The total number of cancers in the sample with PWS was not statistically different from that in the general population, but the difference in myeloid leukemia was statistically important; the implication is that individuals with PWS have no increased risk of cancer except of the myeloid leukemia variety. This is an interesting finding, as it is well known that myeloid leukemia occurs with increased frequency in genetic syndromes caused by chromosomal trisomy (e.g., Down syndrome).

Altogether, then, adults with PWS show a host of medical concerns; some of these are likely to be associated with aberrant functioning of the hypothalamus, including hyperphagia and complications of obesity (see Table 22.1 for a summary). Many of these problems lead to compromised overall quality of life, and some problems, such as obstructive sleep apnea, relate as well to everyday cognitive functioning.

COGNITIVE, BEHAVIORAL, AND PSYCHIATRIC CONCERNS

Compared to others with genetic mental retardation syndromes, adults with PWS have relatively well-developed cognitive skills, with average IQ scores in the middle to upper 60s (Dykens, Hodapp, Walsh, & Nash, 1992a; Whittington & Holland, 2004). Due to significant interference from their food-seeking and maladaptive behaviors, however, these adults often function adaptively at a level considerably below their measured IQ.

TABLE 22.1. Salient Medical Concerns in Adults with PWS

Increased risks of . . .
• Complications of obesity
• Diabetes
• Osteoporosis
• Absent or irregular menarche
• Cryptorchidism
• Growth hormone deficiency
• Short stature
• Obstructive sleep apnea
• Orthopedic concerns

Cognitive Functioning

Cognitive studies have focused primarily on children or adolescents with PWS. This work describes many with the syndrome as having a cognitive profile characterized by relative strengths in expressive vocabulary and visual–spatial functioning, including solving jigsaw puzzles and "word find" puzzles. These interests in jigsaw puzzles and word searches were informally observed for many years by parents and clinicians, but have only recently been studied in a formal manner. Dykens (2002) found that youngsters with PWS placed, on average, three times as many jigsaw puzzle pieces in a 3-minute period than age- and gender-matched typically developing controls with average IQs.

Recent work further specifies that youngsters with PWS due to maternal UPD have better-developed verbal skills then their counterparts with paternal deletions (Roof et al., 2000). Those with maternal UPD, however, perform much worse on standardized visual–spatial tasks, and they also perform significantly worse than those with deletions on jigsaw puzzles (Dykens, 2002).

It remains unknown, however, how (or even whether) these distinctive profiles change in older adults with PWS. Age is modestly associated with puzzle proficiency in youngsters with PWS (Dykens, 2002), but it is unclear whether adults become even more proficient at puzzles with increased exposure and practice. Anecdotally, we find that adults seem more motivated than children to work on puzzles, perhaps because they have fewer competing, school-based activities than their younger counterparts. Of note as well is the trend for many adults with PWS to carry their word search books with them, so as to solve these puzzles whenever the occasion arises. Our group has worked with several adults who successfully complete word searches despite the fact that they cannot read. Studies are currently underway to assess the possibility that adults are using similar visual matching strategies in word search and jigsaw puzzles, and to hone in on specific facets of visual–spatial functioning involved in these skills.

Finally, while longitudinal data are scarce, findings to date suggest relative stability in IQ over the course of time in children and young adults with PWS (Dykens et al., 1992a). Studies have yet to examine possible changes or shifts in IQ or in specific cognitive domains in adults with PWS in their middle or older years. Such studies are particularly important, because findings from other genetic syndromes suggest increased risks of cognitive and adaptive declines, as well as of premature aging (see Zigman, Silverman, & Wisniewski, 1996, for a review).

Adaptive and Academic Achievement Skills

Adults with PWS generally perform at a lower level of adaptive skills than would be predicted from their IQs alone. When assessed with the Vineland Adaptive Behavior Scales, many adolescents and adults show relative strengths in daily living skills that involve repetition and rote performance, especially grooming and domestic skills such as cooking (Dykens, Hodapp, Walsh, & Nash, 1992b). Relative weaknesses are found in the Vineland Socialization domain, especially in coping skills—a finding consistent with being easily slighted and showing a low tolerance for frustration (Dykens & Rosner, 1999). The trajectory of adaptive skills in older adults with PWS remains unknown.

Academically, youngsters with PWS may show an uneven profile. Among a sample of 90 participants with PWS who had a mean age of 20 years, Whittington and Holland (2004) found lower levels of achievement than would have been predicted on the basis of IQ alone.

Relative weaknesses in arithmetic and strengths in reading were found in 21 young adults with PWS (Dykens et al., 1992a). Although differences in academic skills across genetic subtypes of PWS may be subtle, those with maternal UPD may have reading skills that are consistent with their levels of measured IQ (Whittington et al., 2004). Informally, we observe that many adults with PWS are avid readers, but it is unclear whether their level of reading comprehension is on a par with their reading decoding skills.

Hyperphagia and Food-Related Psychopathology

Although the exact etiology remains unknown, hyperphagia in Prader–Willi syndrome is thought to stem from an impaired satiety response, specifically with a significant delay in the satiety response (Holland, Treasure, Coskeran, & Dallow, 1995). When the 13 adults they studied were given free access to food, Holland and colleagues (1995) found that most of them eventually indicated that they were full—but only at a much later time than controls, and after eating very large amounts of food. In addition, the participants with PWS stated that they were hungry again much sooner than typical controls.

Such observations have led to questions of whether persons with PWS are so hungry that they eat indiscriminately. As others in the general population do, however, people with PWS have distinct food preferences. Although early studies found a preference for sweet foods (Taylor & Caldwell, 1985), more recent work finds that persons with PWS prefer high-carbohydrate foods. This preference is different from those of typical or obese controls, who are less inclined to prefer high-carbohydrate items (Fieldstone, Zipf, Schwartz, & Berntson, 1997).

In addition, although some individuals with the syndrome "just eat," others have rituals or rules that govern their eating (Dykens, Leckman, & Cassidy, 1996). Many such rituals involve eating all of one food type before moving on to the next, based on various criteria: color (e.g., all green food first, then brown), texture (e.g., hardest to softest), caloric content (e.g., highest to lowest), type (e.g., meat followed by vegetables), or desirability (most to least preferred). Some individuals need to have their food cut or served in particular ways, or their utensils arranged in "just the right spot" before eating.

Yet food preferences or rituals do not necessarily prevent many with the syndrome from making poor food choices. Clinically, we see examples of adults with the syndrome who eat food from the floor or garbage can, or who eat unusual or unpalatable items, such as frozen meat or pet food. Dykens (2000) administered food choice pictures and tasks to 50 adults with PWS and to controls with and without mental retardation. Most adults with PWS held understandings similar to those of typical controls about the fate and purpose of food. Despite these well-developed perceptions, adults with PWS were more likely than either comparison group to endorse eating contaminated food (e.g., cake with a bug on it) or unusual food combinations (e.g., pizza with chocolate sauce). All participants rejected nonfood substances when they were presented alone (e.g., grass), but some of those with PWS were willing to eat inedible substances when they were paired with a desired food (e.g., grass on cake).

These findings suggest limited understandings in adults with PWS of germs and invisible particles, and point up possible interventions that teach these concepts, as well as the emotion of disgust for certain items. In the meantime, however, interventions continue to rely on a reduced-calorie diet, restricted access to food (e.g., locking the kitchen cabinets and refrigerator), close supervision around food, and regular physical activity or exercise (see Dykens, Hodapp, & Finucane, 2000, for a review).

Possible mechanisms that underlie hyperphagia in PWS are currently under intense study. Preliminary functional magnetic resonance imaging studies with eight young adults with PWS suggest alterations in circuitry involving the hypothalamus, amygdala, and frontal cortex (Dimitropolous & Schultz, 2004). Previous findings implicate anomalies in a specific set of oxytocin-secreting neurons in the paraventicular nucleus of the hypothalamus. It is thought that these neurons are related to satiety (Swaab, Purba, & Hofman, 1995).

In addition to these findings, recent breakthroughs implicate abnormalities in a novel hormone, ghrelin, which is secreted by the stomach and is a powerful stimulant of appetite and food consumption. Compared to obese and lean controls, both children and adults with PWS have markedly high plasma levels of ghrelin (Cummings et al., 2002; Delparigi et al., 2002; Haqq et al., 2003). Whereas typical individuals show a drop in ghrelin levels in response to a caloric load, ghrelin levels remain high in persons with PWS even after food consumption (Delparigi et al., 2002). The elevated levels of ghrelin in PWS are similar to those found during starvation states, including the states brought on by anorexia nervosa (Delparigi et al., 2002). Tauber and colleagues (2004) suggest that resistance of the hypothalamus to ghrelin may be the reason for the constantly elevated levels in PWS.

To date, anorexic agents or other medications have not been successful in curbing the drive for food in persons with PWS, especially over the long term. In a preliminary study, Tan and colleagues (2004) administered somatostatin, a ghrelin blocker, to four adults with PWS. Ghrelin was reduced to normal levels in these adults, yet no reduction was seen in their appetite or food consumption. Because somatostatins also lower anorexigenic gastrointestinal hormones (e.g., PYY3-36), it may be that any anorexegenic effects of lowered ghrelin were counteracted by reduced PYY-36. Alternatively, perhaps longer trials of somatostatins are necessary. Although families and individuals with PWS often hope for a "magic bullet" solution, the most effective interventions to date remain increased activity, low-calorie diets, and supervision around food (Dykens et al., 2000).

Other Maladaptive Behaviors

Hyperphagia and the lifelong need for a specialized diet are often assumed to be highly problematic for families and teachers, as well as for individuals with PWS. Although food-related concerns are indeed major, families, teachers, job coaches, and group home care providers generally report that other behavior problems are even more time-consuming and difficult to manage than food-related issues. Indeed, these maladaptive behaviors are often clinically meaningful and demand specialized programming and intervention (Dykens & Kasari, 1997).

Behavior problems such as temper tantrums, stubbornness, and impulsivity are so common in PWS that they have earned a place as minor diagnostic criteria in the consensus clinical criteria for PWS (Holm et al., 1993). Frequent problems seen in over 100 persons with PWS ages 4–46 years include (in addition to overeating) skin picking, stubbornness, obsessions, tantrums, disobedience, impulsive lability, excessive sleepiness, talking too much, compulsions, and being anxious and worried. These findings are remarkably similar to the frequency and severity of problems in other samples with PWS (e.g., Clarke, Boer, Chung, Sturmey, & Webb, 1996; Dykens & Kasari, 1997; Einfeld, Smith, Durvasula, Florio, & Tonge, 1999). Because compulsions are often particularly problematic in persons with PWS, they are discussed in detail next.

Compulsions

Many children and adults with PWS show repetitive, compulsive behaviors that are not related to food. Dykens and colleagues (1996) found high rates of compulsive behaviors on the Yale–Brown Obsessive–Compulsive Behavior Scale in a sample of 91 individuals with the syndrome. Frequent symptoms included hoarding (toiletries, paper, and pens); ordering and arranging items by color, shape or size, or until they were "just right"; needing to tell or say things (repeated questioning); being concerned with symmetry and exactness; and redoing things (e.g., tying and untying shoes, rewriting homework, recutting coupons until the lines were perfect). For 45–80% of the sample, these symptoms were time-consuming, distressful, or caused adaptive impairment, suggesting high risks of obsessive–compulsive disorder (OCD). Increased compulsivity in PWS has also been found in other samples, including a population-based sample in the United Kingdom (Clarke et al., 2002).

Compulsivity is high in persons with PWS relative to others with mental retardation, including those with and without other genetic syndromes (Dykens & Kasari, 1997; Dykens & Smith, 1998; State, Dykens, Rosner, Martin, & King, 1999). In a study comparing adults with PWS to age- and gender-matched adult patients with OCD (Dykens et al., 1996), the two groups showed the same number and severity level of symptoms. Several studies, then, show increased compulsivity in both children and adults with PWS, above and beyond the stereotypical behavior often seen in persons with mental retardation in general.

Yet, for all the similarities with OCD, compulsive features in those with PWS differ from those with OCD in several ways. Whereas those with OCD often have such compulsions as hand washing and checking, compulsive behaviors in PWS are more apt to include sameness, exactness, symmetry, hoarding, ordering, arranging, and skin picking (Clarke et al., 2002; Dykens et al., 1996; Feurer et al., 1998). Moreover, compulsive and self-injurious behaviors, such as skin picking, appear to begin at an earlier age in PWS than in persons with OCD (Dimitropolous, Feurer, Butler, & Thompson, 2001; Wigren & Heimann, 2001).

Indeed, compulsive behaviors in PWS seem to emerge in the toddler years, and to coincide with the onset of hyperphagia; the severities of hyperphagia and compulsions also seem related in this age group (Dimitropolous et al., 2001). Adolescence and early adulthood appear to be the critical periods for an increase in behavioral and emotional disturbances in persons with PWS (Dykens, 2004; Steinhausen, Eiholzer, Hauffa, & Malin, 2004). Examining 240 persons with PWS ages 4–49 years, Dykens found that young adults in their 20s ($n = 58$) had the highest levels of maladaptive and compulsive behaviors, even as compared to the adolescent period ($n = 81$).

Dykens (2004) found that, in striking contrast to young adults, adults ages 30–50 years ($n = 45$) had markedly reduced rates of compulsions, skin picking, and other maladaptive behaviors (including externalizing problems). The reasons for this "mellowing" among older adults remain unknown. Gender and BMI accounted for a modest amount of the variance in maladaptive levels in this older age group, while residential status (living at home or in placement) was associated with reduced obesity and BMI, but not necessarily with maladaptive behavior. Approximately one-half of this older sample was obese and at risk for obesity-related medical complications. Longitudinal studies are needed that assess possible medical, hormonal, and environmental factors associated with the drop in compulsive and other maladaptive behaviors in older adults.

Genetic Subtypes and Psychopathology

On average, persons with PWS due to maternal UPD as opposed to paternal deletions have slightly lower overall levels of compulsive and other maladaptive behaviors, including skin-picking (Dykens, Cassidy, & King, 1999; Symons, Butler, Sanders, Feurer, & Thompson, 1999). A robust and relatively recent finding, however, is that individuals with PWS due to maternal UPD are at heightened risk for severe psychopathology as they enter young adulthood. Although young adulthood in general is a vulnerable time for the onset of psychosis and other major psychopathology, this trend seems particularly true for those with maternal UPD. Previous case reports described psychotic episodes with sudden onset, and at times with a severe depressive component as well, in a few young adults with PWS. Most, but not all, of these cases had the UPD genetic subtype (Beardsmore, Dorman, Cooper, & Webb, 1998; Clarke et al., 1998).

More recently, Vogels and colleagues (2004) conducted a retrospective chart review of 60 individuals with PWS followed over a 15-year period and found that of the 6 who developed psychosis, 5 had maternal UPD and one had an imprinting center mutation. Of these 6 persons, 4 had autistic-like traits in childhood; common psychotic features in adulthood included restricted affect, excessive sleeping, and poor appetite with food refusal. The authors postulated that strict diet and good control of weight might trigger the onset of psychotic symptoms in persons with PWS and a predisposition for psychiatric illness. In addition, the onset of psychotic symptoms was acute or abrupt, with symptoms appearing "like a bolt from the blue" (Clarke et al., 1998; Verhoeven, Curfs, & Tuinier, 1998).

These finding are consistent with those of Boer and colleagues (2002), who screened eight counties in the United Kingdom and found five cases of young adults with PWS and psychosis, all of whom had maternal UPD. In addition, compared to those with paternal deletions, Veltman and colleagues (2004) found significantly more autistic symptoms in cases with maternal UPD, especially impairment in social reciprocity and social interaction. Of note is that the 15q region is involved in some cases of autism, including some in persons with isodicentric chromosome 15, previously known as "inverted duplication"; all such cases were maternal in origin (e.g., Wolpert et al., 2000). In PWS, perhaps the abnormality in the expression of maternally imprinted 15q11–q13 genes may lead to a susceptibility to autism spectrum disorders, as well as to an adult onset of psychosis.

In summary, then, the course of maladaptive behaviors and psychiatric problems in adults with PWS has yet to be rigorously studied. Findings to date suggest that persons in their 20s are at high risk for compulsive and other maladaptive behaviors. Those with maternal UPD are at even higher risk for the sudden onset of psychosis, with or without depressive features, especially those with a previous history of autistic-like symptoms (see Table 22.2 for a summary).

The hormonal, neurological, and environmental factors associated with these risks have yet to be identified, and in a similar vein, reasons for the dramatic decline in compulsive and other maladaptive symptoms among older adults have yet to be thoroughly examined. If confirmed, these declines may differ from the aging process in at least some other mental retardation syndromes. In Down syndrome, for example, advancing age is associated with increased risks of depression and Alzheimer-type dementia (e.g., Zigman et al., 1996). Among those with mental retardation in general, age-related increases in some psychiatric problems, such as anxiety and depression, have been found in clinical as well as epidemiological samples (Cooper, 1997; Day, 1987). Although comparative studies are needed, being an older adult

TABLE 22.2. Distinctive Behavioral Features in Adults with PWS

- Increased compulsive and other maladaptive behaviors in young adulthood
- Possible declines in compulsive and other maladaptive behaviors in older adults
- Proneness to psychosis with or without a depressive component in young adults, primarily those with maternal UPD
- Strengths in jigsaw and word search puzzles that persist over time
- Possible nurturant streak and ties to vocational choices
- Some compulsive symptoms that can be reframed as job-related assets
- Need for food supervision across settings
- Tensions between personal rights/independence and diet/food
- Improved dietary and behavioral management in dedicated group homes

with PWS (especially with paternal deletion) may confer some protection against the mental health problems seen in other adults with mental retardation.

VOCATIONAL, RESIDENTIAL, AND QUALITY-OF-LIFE CONCERNS

As adolescents with PWS leave school and become adults, they and their families face renewed concerns regarding how the adults will live, work, and play in their local communities. Adult services are more fragmented, and many parents, previously used to accessing services at school, soon find themselves interacting with several different systems of care in order to meet the needs of their adult offspring with PWS. An additional tension is that adults with PWS have growing desires and needs for autonomy and independence, yet still require supervision and guidance around food. Despite the increased complexities and demands of the adult years, data are remarkably limited on the vocational, residential, and quality-of-life needs of both younger and older adults with PWS.

School-to-Work Transition

Most children with PWS need special education services to address their unique cognitive and behavioral concerns, as well as adjunctive services such as occupational, physical, and speech therapies, and extra adaptive physical education (Levine & Wharton, 1993). Parents uniformly report that they have they been inadequately prepared for their children's transition from school to work (Seguin & Hodapp, 1998). Many are unaware that preparation for this transition ideally begins in high school, and in many states, long waiting lists exist for postgraduation programs in the work, social, or residential arenas. Such inaccessible adult services have culminated in class action lawsuits in several states.

A distinctive concern in PWS is that because many young adults with the syndrome have relatively high IQs (above 70), they are judged ineligible for the services given to their lower-functioning counterparts with IQs that fall below 70. Dykens and Cassidy (1995), however, found no significant behavioral differences between adults with higher and lower cognitive functioning. High IQs do not appear to be a protective factor against the syndrome's characteristic compulsive and other maladaptive behaviors. State and other service delivery systems that use a low IQ score (typically below 70) as an eligibility requirement

may thus exclude persons with higher IQs who have treatment and dietary needs similar to those of adults with lower IQs. Several states have now recognized that in PWS, IQ is a less meaningful entry point into systems of care. In Connecticut, Florida, New York, and Wisconsin, adults with the syndrome are eligible for services from their state departments of mental retardation, regardless of their IQs, as long as they have a confirmed diagnosis of PWS. Parents are advocating for similar legislation in other states.

Employment

Interviewing over 30 families of adults with PWS, Seguin and Hodapp (1998) found that individuals with PWS faced numerous difficulties with both finding and keeping jobs. When these authors compared parents of adults with PWS to those of adults with Down syndrome, the former group noted that their offspring had more difficulties qualifying for supported employment opportunities, and reported less satisfaction with their offspring's actual vocational placement. Many of these parents felt that employment agencies and adult service providers in the community were not adequately educated about PWS and its characteristics. In particular, the parents found it difficult to convince service workers that, despite the relatively high IQs of adults with PWS, they still needed fairly intensive supervision around food, as well as assistance in handling conflict and frustration (Seguin & Hodapp, 1998).

To succeed as employees, adults with PWS need training in basic work skills, as well as support on the job via job coaches or natural supports. Because persons with the syndrome are often easily slighted and prone to angry outbursts (Dykens & Rosner, 1999), they need specific help with managing anger on the job. In addition, many job placements, even those geared for persons with developmental disabilities, do not have adequate supervision around food. Adults with PWS often have difficulty retaining their jobs because of food theft (e.g., stealing other employees' lunches, sneaking off to buy food at break time), or because of poor control over anger and disappointments.

Clinically, we find that chances for vocational success are increased when adults are matched either with jobs that tap their skills, or with ones that reframe their compulsivity into job-related assets. Compulsive symptoms such as the needs for things to be done in a certain way, for counting and recounting, for precision and exactness, for lining things up, for order, and for sameness in daily routine—all could be construed as just the right characteristics for jobs that involve rote tasks, perseverance, precision, and repetition. Examples of such jobs include restacking books in a library, folding laundry at a hotel, counting and collating copies at a copy store, and restocking medical supply cabinets. Such jobs also often rely on visual–spatial functioning, which is an area of relative strength for many with the syndrome. Finally, we find that chances for success on the job are optimized when job coaches are not faded (or are faded very slowly), and when some form of light exercise (e.g., walking at break time) is woven into the work routine, so as to counteract excessive daytime sleepiness that could impair work performance.

Although this observation is largely anecdotal, we note as well that many adults with PWS do well in jobs that tap an unusual nurturant streak shown by some with the syndrome (Dykens & Rosner, 1999). Many of these adults show marked interests in household pets, and strive to work as caretakers for animals in pet stores or veterinarians' offices. Some women with PWS want to work in caretaking roles in day care centers, nursery schools, or nursing homes. We hypothesize that some of these nurturant tendencies may be associated with altered levels of oxytocin in PWS; oxytocin is a neuropeptide associated

with attachment, appetite, and other regulatory processes (Martin, State, North, Hanchett, & Leckman, 1998; Swaab et al., 1995).

Residential Placement

The two most common worries that parents have about their adult offspring with PWS are where their offspring will live, and how they will get along, after the parents die or are no longer able to care for them effectively. Although many adults with PWS reside at home, others are living in group homes or supervised, independent living arrangements. So-called "dedicated" group homes are particularly desirable; in such homes, small groups of adults all diagnosed with PWS live together. Dedicated group homes are often supported by parents, and have at least one advantage over mixed homes: Staff members can use behavioral and dietary management techniques that would be considered too restrictive for adults without PWS.

Although data are sparse, families find that the behavioral difficulties of their adult offspring are often managed better in out-of-home placements (Greenswag, 1987). Furthermore, due to stricter food management and control, persons with PWS often lose weight and maintain a healthy weight over time while living in these structured or supervised settings. Persons in out-of-home placements indeed have significantly lower BMIs than those residing at home (Dykens, 2004), although the behavioral picture may be more complicated across settings. Residential status was not a significant predictor of maladaptive behaviors in older adults (Dykens, 2004), although adults in out-of-home placements did show increased severity of compulsive symptoms. More severe problems may have been a contributing factor in these families' decision to seek placement to begin with, and over time, such individuals may respond well to intervention and structure and become less behaviorally involved. Longitudinal studies are needed to clarify the short- and long-term effects of out-of-home placement. Many other adults with PWS remain at home, and studies are also needed to determine whether adults who remain living with immediate or extended family members are at increased risk for less consistent weight management, as well as medical complications related to obesity.

Yet another concern is this: By 2030, over 1.5 million persons with disabilities are expected to be over 60 years of age, living with elderly parents who can no longer take care of them. Adult siblings of these older persons with disabilities are expected to fill the void; to date, however, the field knows next to nothing about the needs of these siblings as they adjust their work and family lives to become care providers. The extent to which siblings will do this for individuals with PWS remains unknown, as do the types of training and support such siblings will require.

Parents of both children and adults with PWS often need respite care, and, compared to parents of offspring with other types of disabilities, they are more often stressed by their caretaking responsibilities (Hodapp, Dykens, & Masino, 1997; Wigren & Hansen, 2003). In light of this stress, some parents want to avoid placing their adult offspring with PWS with siblings; they are advocating for increased numbers of dedicated group homes or supervised, independent living arrangements that are close enough for frequent visits with family members (Seguin & Hodapp, 1998).

Quality of Life and Future Directions

Although adults with PWS have been much less studied than infants and children, they present a host of unique challenges in both treatment and research. Longitudinal studies

are urgently needed that address selective survival issues. Much like the general population, the population of persons with disabilities is aging. We now need to know the answers to several pressing questions:

- To what extent are adults with PWS living well into adulthood?
- What physiological and environmental factors contribute to longevity?
- Is longevity associated with differences in trajectories of obesity or weight over the years, genetic subtype of PWS, physiological or hormonal factors, place of adult residence, and/or psychiatric disease?
- Are more successful adaptive adult outcomes associated with environmental support; distinctive personality traits; and jobs, hobbies, or activities that persons find engaging or meaningful?
- How can we best support individuals with PWS and their families as they age, and what can successful aging in PWS tell us about aging in others, with or without disabilities?

Furthermore, interventionists have yet to tackle a critical ethical issue: how best to meet the restrictive dietary needs of adults with PWS, along with their desires and rights for independence, societal inclusion, and autonomy. In efforts at optimal community inclusion, flexibility and individualized solutions often work best, as families and care providers try to support adults who are essentially in constant states of starvation but living in "food-enriched" environments and societies (Dykens et al., 1997; Holland, Whittington, & Hinton, 2003).

Adults with PWS themselves often want the same things in life as others, such as getting married and having children. In an interview with five adults who serve as consultants to the PWS Association (USA) (Heinemann, 2004), they indicated that what they wanted most in life included the following: making a lot of friends, being healthy and alive, having more independence, advocating for others with disabilities, obtaining a more challenging job, building more group homes for other adults, being married or having a significant other, and owning a pet so as to feel less lonely.

Although many adults with PWS express sadness and frustration about their inability to attain these types of goals, others set goals and meet them with a more upbeat, "can do" attitude. Examples that come immediately to mind are a young man who has become an active member of his community volunteer fire department, a woman who earns a living taking care of cats, and a man who works as an aide to persons with more severe developmental disabilities. Still other adults report pure enjoyment of hobbies, such as putting together jigsaw puzzles, word searches, and reading. Ultimately, then, future studies need to include the ideas of adults with PWS themselves, especially their ideas on how to be happy, contributing members of their families and communities.

For information on Prader–Willi syndrome, contact the PWS Association on the Web at www.pwsausa.org or email them at national@pwsausa.org. You can write to them at PWS Association, 5700 Midnight Pass Road, Suite 6, Sarasota, FL 34243.

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23

PROGEROID SYNDROMES

SUSAN HOMACK
CRYSTAL RENEÉ HILL
CECIL R. REYNOLDS

Progeroid syndromes are rare genetic disorders characterized by the appearance of accelerated aging. The name for these disorders comes from the Greek word *geras*, meaning "old age." The typical physical appearance for individuals with these disorders is usually associated with old age. However, varying degrees of physical and cognitive complications are evident across syndromes, and even within specific progeroid syndromes there is a high degree of variable expressivity of specific symptoms. For example, most individuals with progeroid syndromes display aged-looking skin, baldness, a loss of subcutaneous fat, and a loss of teeth. Many individuals with these disorders may also display dwarfism or short stature and develop difficulties with joint stiffness, arteriosclerosis, and cardiovascular problems. Currently there is no successful direct treatment for progeroid syndromes, and a multidisciplinary approach involving supportive treatments that focus on alleviating the manifestations and complications of the disorders is usually provided. Unfortunately, because there is no cure and because these syndromes do cause premature aging, individuals with these disorders typically experience premature mortality. However, age of death varies, depending on the specific syndrome diagnosed (Satre, 2003).

There is discrepancy in the literature with regard to how many progeroid syndromes exist. Fossel (2003) reported that perhaps a dozen syndromes have been included in the rubric of progeroid syndromes, whereas Ohashi and colleagues (1993) indicated that at least 30 such syndromes are known. There appears to be a higher incidence of consanguinity (especially first-cousin marriage) among the parents of individuals with progeroid syndromes than is observed in the general population. Hutchinson–Gilford, Bamatter–Franescetti, Berardinelli–Seip, De Barsy, Hallerman–Streiff, Rothmund–Thomson, Von Lohuzien, and Wiedemann–Rautenstrauch syndromes are usually apparent early in life, during the first decade. Werner syndrome, however, appears later in life and may not be diagnosed until adulthood.

PREVALENCE AND ETIOLOGY

Prevalence

Progeroid syndromes are extremely rare. It has been reported that progeroid syndromes occur in approximately 1 per 4,000,000 to 1 per 8,000,000 births; most of them occur equally in both genders and across all ethnic groups (Brown, 2000). However, Hutchinson–Gilford syndrome appears to affect males more often than females, with a 1.5:1 ratio, and 97% of patients appear to be of European descent (Kaiser, 2002). Acrogeria is usually seen in females (de Groot, Tafelkruyer, & Woerdeman, 1980). Several of the progeroid syndromes show a difference in prevalence, depending on the country of origin. For example, Berardinelli–Seip syndrome appears in 1 per 12,000,000 births in the United States, 1 per 1,000,000 births in Norway, 1 per 200,000 births in Lebanon, and 1 per 500,000 births in Portugal (Maldergem, 2003). Werner syndrome appears in 1 per 20,000 to 1 per 40,000 births in Japan (Satoh, Imai, Sugimoto, Goto, & Furuichi, 1999) and 1 per 200,000 births in the United States (Hanson, Martin, & Oshima, 2004).

Genetics

Most of the progeroid syndromes (e.g., Bamatter, Berardinelli–Seip, Bloom, Cockayne, De Barsy, Gottron, Rothmund–Thomson, Soques–Charcot, Werner, Wiedemann–Rautenstrauch) appear to be inherited in an autosomal recessive manner. Therefore, the parents of an affected child are asymptomatic heterozygotes, but obligate carriers of an abnormal gene. This means that at conception the siblings of an individual have a 25% chance of being affected, a 50% chance of being unaffected but carrying the abnormal gene, and a 25% chance of being unaffected and not carrying the gene. However, once an at-risk sibling is known to be unaffected, there is a 67% chance that the individual will carry the gene.

Of the progeroid syndromes that are considered to be inherited in an autosomal recessive manner, only four have clinical testing available for a specific gene. The BSCL2 and the AGPAT2 genes are suspected in Berardinelli–Seip syndrome. Seventy-five percent of cases of Cockayne syndrome appear to have the ERCC6 (chromosomal locus 10q11) gene affected; the CKN1 (chromosomal locus 5) gene appears to be affected in the other 25% of cases (Nance, 2003). Sequence analysis of the RECQL4 gene appears to detect Rothmund–Thomson syndrome in 66% of individuals (Wang & Plon, 2004). Finally, mutations in the WRN gene (chromosome 8p12–p11.2) are found in individuals with Werner syndrome (Hanson et al., 2004).

Although the majority of the progeroid syndromes appear to be inherited in an autosomal recessive manner, several of the progeroid syndromes, including cutis laxa, Hallerman–Strieff syndrome, Hutchinson–Gilford syndrome, and Mulvihill–Smith syndrome, are exceptions. Cutis laxa has four inherited forms, and most cases are inherited in one of two types of autosomal recessive inheritance. However, there have also been reported cases of autosomal dominant inheritance and X-linked inheritance (National Organization for Rare Disorders, 2003). All cases of Hallerman–Strieff syndrome, Hutchinson–Gilford syndrome, and Mulvihill–Smith syndrome appear to be the result of de novo mutations, and therefore the risk of recurrence in siblings is small (Fraser & Friedmann, 1967). Of the syndromes caused by de novo mutations, only Hutchinson–Gilford appears to have an identified gene responsible for the disorder. Approximately 90% of individuals with Hutchinson–Gilford syndrome appear to have an identifiable mutation in the LMNA gene (Brown, Gordon, & Collins, 2003).

MAJOR FEATURES

In the following discussion, we focus on the progeroid syndromes (including Werner syndrome, Cockayne syndrome [type I], Rothmund–Thomson syndrome, Mulvihill–Smith syndrome, acrogeria, Hallerman–Streiff syndrome, Bloom syndrome, and Louis-Bar syndrome) that affect individuals living into the adult years. The major observable feature of each of these disorders is the presence of a physical appearance that appears greatly and prematurely aged. As noted earlier, the physical appearance is typically marked by aged-looking skin, baldness, loss of subcutaneous fat, loss of teeth, and (in many cases) dwarfism or short stature. Many of these disorders are also marked by the presence of medical complications typical of aged individuals (e.g., cardiovascular disease). Mental functioning is not usually impaired, and normal intellectual functioning is expected in most cases (Satre, 2003).

Werner Syndrome

Werner syndrome was first described by Otto Werner, an ophthalmologist in Kiel, Germany (Werner, 1904). Werner syndrome is one of the few progeroid syndromes in which individuals are not affected until the end of the first decade of life. Individuals with Werner syndrome exhibit specific features that include (1) a characteristic bird-like appearance, with decreased subcutaneous facial fat and a body habitus that may include short stature, light body weight, stocky trunk, and spindly extremities; (2) premature senescence, which may include gray hair, baldness, cataracts, hoarse voice, hearing loss, osteoporosis, arteriosclerosis, and malignancy; (3) scleroderma-like skin changes, including atrophic skin, skin sclerosis, skin ulcers, hyperkeratosis, hyper- or hypopigmentation, subcutaneous calcification, and telangiectasia; and (4) endocrine–metabolic disorders, including diabetes, hypogonadism, thyroid dysfunction, hyperuricemia, and hyperlipidemia (Goto, 2000). Cognitive functioning is generally within the average range.

The International Registry for Werner Syndrome has documented more than 100 cases of Werner syndrome (Chen & Oshima, 2002). Cases of this syndrome are reported most frequently in Japan; however, cases also have been documented in the United States and Germany. About 80% of patients with Werner syndrome are of Japanese origin. The frequency of heterozygous healthy individuals carrying the gene for Werner syndrome in Japan is roughly 1 in 100. This can be partly attributed to the high rate of consanguinity among the Japanese population, especially in the mountainous areas of Japan. An awareness of the syndrome among Japanese physicians may also account for the higher number of cases reported in Japan.

Cockayne Syndrome (Type I)

Among the synonyms for Cockayne syndrome are "deafness–dwarfism–retinal atrophy," "dwarfism with renal atrophy and deafness," "Neill–Dingwall syndrome," and "progeroid nanism." Individuals with Cockayne syndrome typically present with the following manifestations: (1) a characteristic physical appearance, with dwarfism, thin hair, deep-set eyes, a jutting nose, thin upper lip, and large ears; (2) growth and neurodevelopmental impairment; (3) cutaneous photosensitivity without an increased risk of cancer; (4) progressive ocular abnormalities; (5) sensory–neural hearing impairment; and (5) dental caries (Linden-

baum et al., 2001; Nance & Berry, 1992). A diagnosis of classic Cockayne syndrome (type I), which includes the majority of individuals with this syndrome, is applied to children who meet these diagnostic criteria beginning after the first year of life. Individuals with this form of Cockayne syndrome can survive into adolescence and early adulthood (Rapin, Lindenbaum, Dickson, Kraemer, & Robbins, 2000). Cockayne syndrome (type II) is a less common and more severe form of the syndrome. These children exhibit intrauterine growth retardation, poor postnatal growth, cataracts or early structural eye abnormalities, and more rapidly progressive neurological impairment. In type II, the symptoms are present at birth, and death usually occurs by age 6 or 7 years. A third, milder form of Cockayne syndrome is typified by late onset and slow progression of signs and symptoms (Nance & Berry, 1992). A related disorder, xeroderma pigmentosa–Cockayne syndrome, combines the features of both these disorders. Since Cockayne first described Cockayne syndrome (Cockayne, 1936) more than 150 cases have been reported in the literature (Bender, Potocki, & Metry, 2003). The syndrome has been described in children from almost every ethnic background (Nance & Berry, 1992; Ozdirim, Topcu, Ozon, & Cila, 1996).

Mulvihill–Smith Syndrome

Mulvihill–Smith syndrome is often referred to as "progeroid short stature with pigmented nevi." The features of this syndrome include (1) a bird-like appearance, with decreased subcutaneous facial fat, hypoplasia of the lower half of the face, microcephaly, short stature, light body weight, stocky trunk, dental abnormalities, and a high-pitched voice; (2) multiple pigmented nevi of the skin, which increase in prevalence over time; (3) sensory–neural hearing loss; (4) endocrine–metabolic disorders, including diabetes, hypogonadism and infertility; and (5) a progressive immune deficiency of varying degree. Mild to moderate mental retardation is common in individuals with Mulvihill–Smith syndrome (Bartsch, Tympner, Schwinger, & Gorlin, 1994; de Silva et al., 1997; Ohashi et al., 1993). The first reported case of Mulvihill–Smith syndrome was found in a 17-year-old male (Mulvihill & Smith, 1975). Baraitser, Insley, and Winter (1988) recognized another child with similar features and made the condition more widely known.

Acrogeria (Gottron Syndrome)

Acrogeria is also commonly referred to as "Gottron syndrome." Cases of acrogeria present with (1) small stature, a thin pinched nose, wrinkling at the angles of the mouth, small ears without lobes, protruding eyes, and micrognathia (abnormal smallness of the jaw); (2) recession of the hairline (present in some, but not all, individuals); (3) prominent atrophy of the skin of the hands and feet, easy bruising, poorly healed scars, atrophic nails, and clearly visible vasculature, particularly over the trunk; and (4) musculoskeletal abnormalities, including congenital dislocation of the hips, clubfoot, and spina bifida (Pesce & Rothe, 1996). Central nervous system abnormalities are not indicated (Ahmad & Majeed, 2003; Blaszczyk, Depaepe, Nuytinck, Glinska-Ferenz, & Jablonska, 2000). Acrogeria has been reported mainly in females (de Groot et al., 1980). Gottron's (1941) report of two siblings whose hands and feet appeared old since infancy was the first reported case of acrogeria in the literature. Since that time, approximately 40 cases have been identified. Metageria is regarded as a more severe variant of acrogeria (Blaszczyk et al., 2000).

Hallerman–Streiff Syndrome

Hallerman–Streiff syndrome may be called "oculo-mandibulodyscephaly with hypotrichosis syndrome." According to Pivnick, Burstein, Wilroy, Kaufman, and Ward (1991), Hallerman, Streiff, and Francois researched this syndrome during the years of 1948–1958. This syndrome is characterized by (1) dyscephaly (malformation of the head and face) with a characteristic facial appearance, including a beaked nose, small mouth and jaw, and a hypoplastic mandible; (2) proportional dwarfism; (3) congenital cataracts; (4) microphthalmia (abnormal smallness of the eyes); (5) thin and sparse hair; (6) dental abnormalities; and (7) cutaneous atrophy (Pivnick et al., 1991). Other common characteristics include frontal and parietal bossing, open sutures and fontanelles, high arched palate, nystagmus, strabismus, scoliosis, hyperextensive joints, hypogenitalism, cardiac abnormalities, wormian bones, and obstructive upper airway disease (de Fonseca & Mueller, 1994, Pivnick et al., 1991). Intelligence is within normal limits for most affected individuals with Hallerman–Streiff syndrome (Fryns, Borghgraef, Lemmens, & Van den Berghe, 1993). Mental retardation is reported in between 15% (Gorlin, Cohen, & Levin, 1990) and 30% (Francois, 1982) of those with this syndrome.

Rothmund–Thomson Syndrome

Rothmund–Thomson syndrome may be called "hereditary poikiloderma congenitale," "poikiloderma atrophicans and cataract," or "poikiloderma congenitale." In 1868, the German ophthalmologist August Rothmund reported on a progressive skin condition called "poikiloderma," associated with a high incidence of juvenile cataracts, in 10 young related patients from an isolated Bavarian village (Rothmund, 1868). Several decades later, the British dermatologist Sidney Thomson reported similar patients with hyperpigmentation of the skin and bone abnormalities (Thomson, 1936). The overlapping clinical features seen in cases are known as Rothmund–Thomson syndrome. Individuals with this syndrome generally exhibit (1) small stature, with unusually small hands and feet; (2) skeletal dysplasias, including underdeveloped or absent thumbs, underdeveloped or missing forearm bones, delayed bone formation, and/or osteoporosis; (3) poikiloderma, which is characterized by the abnormal dilation of groups of small blood vessels (telangiectasia), skin tissue atrophy, and hyper- or hypopigmentation; (4) gray hair, baldness, cataracts, dystrophic teeth and nails, and an increased risk of bone and skin cancer; and (5) delayed sexual development and infertility (Balraj et al., 2002; Piquero-Casals, Okubo, & Nico, 2002; Wang et al., 2001). Intelligence in affected individuals appears normal (Piquero-Casals et al., 2002; Vennos & James, 1995). Since Rothmund's initial description in 1868, a total of approximately 300 cases of this syndrome have been reported in the literature. Rothmund–Thomson syndrome has been described in all races and many nationalities (Wang & Plon, 2004).

Bloom Syndrome

Bloom syndrome has several synonyms, including "Bloom–Torre–Mackacek syndrome," "dwarfism—Levi type," "short stature and facial telangiectasis," and "short stature with telangiectatic erythema of the face." David Bloom, a dermatologist in New York City, made the first clinical report of Bloom syndrome (Bloom, 1954). This syndrome is often included

among the Jewish genetic diseases. The frequency of the abnormal Bloom syndrome gene is approximately 1 per 110 in the Ashkenazi Jewish population, but it is rare in other groups (German et al., 1977; Li, Eng, Desnick, German, & Ellis, 1998). It appears to be characterized physically by the following features: (1) proportional dwarfism; (2) photosensitivity and erythematous skin lesions on the nose and cheeks, lower lip, and dorsa of the forearms and hands; (3) *café au lait* spots; (4) primary immunodeficiency; and (5) an early development of a wide variety of cancers that may include leukemia and lymphoma (Barranger, 2004; German, 1997). Individuals with Bloom syndrome typically have normal intelligence; however, learning difficulties are common (Chisholm, Bray, & Karns, 2001; Murphy, 2001). As of 2001, there were 168 reported cases in the Bloom Syndrome Registry, which was initiated in 1960 to study this population (Chisholm et al., 2001).

Louis-Bar Syndrome

Louis-Bar syndrome may be called "ataxia–telangiecasia." The disease was first reported by Syllaba and Henner in 1926 (see Berg, 1994), and later described by Louis-Bar (1941). Louis-Bar syndrome is characterized by (1) progressive cerebellar dysfunction and ataxia; (2) premature aging of hair and skin; (3) oculocutaneous telangiecasia (tiny red "spider" veins that appear in the corners of the eyes); (4) immunodeficiency; and (5) an increased incidence of cancer and radiosensitivity. Normal higher mental functions are indicated initially (Rohatgi, Pardasani, Sharma, Gupta, & Gurtoo, 2003); however, intelligence becomes impaired as the illness progresses (Datta, Datta, & Panja, 2001).

DEVELOPMENTAL COURSE

Features of the progeroid disorders usually become apparent in early childhood, though the first symptoms of Werner syndrome do not become apparent until adolescence. Although there may be individual variations, each of the syndromes has a typical developmental course that includes the age of onset of symptoms and the progression of impairment.

Werner Syndrome

Individuals with Werner syndrome usually develop normally until they reach the second decade of life. Generally, the first sign is a lack of pubertal growth spurt during the adolescent years. According to Chen and Oshima (2002), individuals with Werner syndrome frequently recall that they were of average height when they entered grade school, but were the shortest ones in their class by they time they graduated from high school. During their 20s and 30s, individuals with Werner syndrome typically have a short stature, light body weight, and a bird-like appearance. These individuals begin to manifest skin atrophy, regional atrophy of subcutaneous tissue, voice changes (the voice becomes weak and high-pitched), and graying/loss of hair. The patients also have slender extremities and a stocky trunk. Osteoporosis, hyaluronuria, and bilateral cataracts are evident; the eventual prevalence of cataracts in individuals with Werner syndrome is close to 100%. Diminished fertility is evident by the second to third decade of life; premature testicular atrophy has been well documented in middle-aged males with Werner syndrome, and there is probably an accelerated loss of primordial ovarian follicles in females (Martin & Oshima, 2000). Flat

feet may be present after the third decade of life, possibly as a result of the heavy load of the stocky trunk weighing on the slim extremities, and/or the underdevelopment of foot connective tissue (Murata & Nakashima, 1982). By the beginning of the fourth decade, atherosclerotic disorders manifest themselves. Atherosclerotic lesions are more extensive in arterioles, whereas members of the general population exhibit such lesions primarily in major arteries. Calcification of cardiac valves is also sometimes observed in Werner syndrome (Chen & Oshima, 2002). Various benign and malignant neoplasms may occur (Martin & Oshima, 2000); the high rate of malignancy in Werner syndrome could be partly explained by chromosomal instability (Goto, 1997).

Other features of Werner syndrome are more variable. Most individuals have severe ulcerations around the Achilles tendons and around the ankles. Type 2 diabetes mellitus is a common complication. The most common causes of death are myocardial infarction (the consequence of coronary artery atherosclerosis) and cancer. Cancer is the most common cause of death among Japanese patients with Werner syndrome, whose overall cancer risk is increased 30- to 50-fold over that of the general population (Oshima, Huang, Pae, Campisi, & Schiestl, 2002). The median age of death in individuals with Werner syndrome is 46–48 years.

Cockayne Syndrome (Type I)

The majority of children with Cockayne syndrome (type I) are of normal weight and appearance at birth. The syndrome begins to be apparent at 6–24 months of age. The seemingly normal initial development is followed by photosensitivity, which manifests itself as a scaly erythematous dermatitis, especially on the cheeks and sun-exposed skin. Cockayne syndrome is often associated with skin disorders such as xeroderma pigmentosum and trichothiodystrophy that exhibit sensitivity to light; however, there is no increased risk of skin cancer among individuals with the syndrome (Lindenbaum et al., 2001). Individuals with Cockayne syndrome exhibit significant postnatal growth failure of the soma and brain, and all individuals with the syndrome are affected with developmental delay and mental retardation (Nance & Berry, 1992). "Cachectic dwarfism" has been used to describe these children, because weight is usually more affected than height. The faces of patients with Cockayne syndrome begin to appear prematurely aged, with a progressive loss of fat, deep-set eyes, a thin nose, shrinkage of the vermilion border of the lips, and severe early dental caries (Rapin et al., 2000). Many individuals with the syndrome also exhibit a "stooped" appearance, with kyphoscoliosis (backward and lateral curvature of the spine) and flexion deformities of the hip, knees, and ankles (Moyer, Marquis, Shertzer, & Burton, 1982).

In addition to growth failure, individuals with Cockayne syndrome undergo a deteriorating process that includes advancing cachexia (increasing weight loss, wasting of muscle, and loss of appetite). Continuing problems with cutaneous sun sensitivity; a progressive loss of hearing; cataracts, optic atrophy, and pigmentary retinopathy; microcephaly, hydrocephalus, dementia, ataxia, and weakness; and a demyelinating neuropathy are evident. Despite the presence of dementia, most individuals with Cockayne syndrome continue to exhibit a remarkably preserved sociability (Lindenbaum et al., 2001). Approximately one-third of boys with the syndrome have undescended testes, and girls frequently exhibit menstrual irregularities (Nance & Berry, 1992). Patients with classic Cockayne syndrome (type I) generally live into adolescence and early adulthood (Rapin et al., 2000).

Mulvihill–Smith Syndrome

Mulvihill–Smith syndrome is characterized by low birth weight. Available reports indicate that pigmented nevi of the skin are present at birth or within the first few years of life (Bartsch et al., 1994; de Silva et al., 1997; Mulvihill & Smith, 1975). Growth delays in childhood lead to short stature (dwarfism) and a prematurely aged facial appearance. Over the course of the first and second decades of life, other physical findings develop, including hearing impairment, diabetes, and primary immunodeficiency. Hypogonadism and infertility are common features. The life expectancy of individuals with Mulvihill–Smith syndrome is variable; although many die in the first two decades of life, a few reports of individuals living into their 20s and 30s are available (Bartsch et al., 1994; Ohashi et al., 1993).

Acrogeria (Gottron Syndrome)

Acrogeria, or Gottron syndrome, is characterized by cutaneous atrophy and loss of subcutaneous fat beginning at birth or shortly thereafter. The skin atrophy is most prominent in the distal limbs, including the hands and feet, but changes may occur on the face and trunk too. A brown discoloration of the skin and bruising often become evident sometime during childhood. Whereas some individuals exhibit short stature, others are of normal height but have thin limbs (Ahmad & Majeed, 2003; Blaszczyk et al., 2000). No other progressive symptoms are consistently reported in the literature. Life expectancy is normal.

Hallerman–Streiff Syndrome

The gestation and birth weight of individuals with Hallerman–Streiff syndrome are usually normal; however, prematurity and low birth weight have been reported in one-third of all cases (Fryns et al., 1993). During early infancy, severe microstomia (abnormal smallness of the mouth), hypoplastic mandible, small nares, and small jaws cause feeding and respiratory problems. There is variability in symptom severity. Failure to thrive in infancy is not uncommon and has sometimes been attributed to poor suckling (Steele & Bass, 1970; Suzuki, Fujii, & Fukuyama, 1970). The feeding difficulties lead to malnutrition and an inability to manage oral secretions (Hou, 2003). Severe ocular defects occur, and these usually culminate in blindness despite surgery. Microphthalmia is common, and cataracts are always bilateral and complete. Spontaneous lens absorption sometimes occurs in older individuals with Hallerman–Streiff syndrome (Sato, Terasaki, Amano, Okamoto, & Miyake, 2002). Reproduction is possible for some but not all individuals with Hallerman–Streiff syndrome; however, few case reports exist (Spaepen et al., 1991). Severe complications resulting in death may include early pulmonary infections, chronic respiratory insufficiency, and obstructive sleep apnea. The use of anesthesia poses a dangerous risk, due to the small mouth and relatively large tongue in these individuals (Hou, 2003). There is insufficient follow-up of patients with Hallerman–Streiff syndrome to permit an analysis of life expectancy trends (Jones, 1988).

Rothmund–Thomson Syndrome

Most individuals with Rothmund–Thomson syndrome are the products of full-term pregnancies, but tend to be small for their gestational age. The first indication of

Rothmund–Thomson syndrome is the presence of a rash that develops during infancy, usually between 3 and 6 months of age. In some cases, however, the rash does not develop in children until they are 2 years of age. The rash starts as red inflamed plaques (erythema) with edema on the cheeks and face. These plaques usually first appear on the cheeks; however, the ears, forehead, chin, hands, forearms, lower legs, and buttocks may be affected to a lesser degree. Gradually over a period of months to years, the rash enters a more chronic phase: with patchy areas of reticular hyper- or hypopigmentation, abnormal dilation of groups of small blood vessels (telangiectases), and skin tissue atrophy. These skin changes constitute the poikiloderma originally identified by Rothmund (1868), and persist throughout life. Most individuals with Rothmund–Thomson syndrome exhibit photosensitivity. Skeletal abnormalities include dysplasia, absent or malformed bones (such as absent radii), osteopenia (decreased calcification, density, and mass of bone), and delayed bone formation. Individuals with Rothmund–Thomson syndrome are short in stature, have small hands and feet, and may have gray and/or sparse hair, eyelashes, and eyebrows.

The rate of juvenile cataracts in this syndrome has been reported to be as high as 50% (Starr, McClure, & Connor, 1985; Vennos, Collins, & James, 1992), with onset between 3 and 7 years of age. Many individuals with Rothmund–Thomson syndrome also have dental abnormalities, including microdontia, missing teeth, delayed eruption, and increased incidence of caries (Kraus, Gottlieb, & Meliton, 1970). Osteosarcoma of the bone is the most commonly reported malignancy (Green & Rickett, 1998). The median age of osteosarcoma diagnosis is 11 years. Skin cancer can occur at any age, although it often occurs earlier than in the general population. The prevalence of skin cancers is estimated at 5% (Wang et al., 201). Individuals with Rothmund–Thomson syndrome exhibit delayed sexual development. In adulthood, infertility has been described in males and females; however, some affected females have had normal pregnancies. There are no reports of cognitive decline in individuals with Rothmund–Thomson syndrome. Death from metastatic osteosarcoma has been reported in a number of children and adults. Lifespan, in the absence of malignancy, is probably normal, although follow-up data are limited (Wang et al., 2001).

Bloom Syndrome

In Bloom syndrome, telangiectactic erythema on the face, and sometimes on the dorsa of the hands and forearms, becomes apparent at age 2 weeks to 3 years. In addition to the redness of the face, blistering and bleeding are evident (Murphy, 2001). On the body, *café au lait* spots are found, and depigmented areas occur. Individuals with Bloom syndrome frequently exhibit small stature but a normal growth rate. Frequent infections in childhood are often noted, including sinusitis, tonsillitis, and urinary tract infections. Individuals with Bloom syndrome have reduced fertility. Male infertility is typical; females have normal menses but a high rate of premature ovarian failure (German, 1993). Bloom syndrome is associated with a 300-fold increase in malignancy (Murphy, 2001). The mean age for a diagnosis of cancer is 24 years (German, 1995). Individuals are susceptible to the full range of cancers seen in the normal population. As of January 1996, there had been 100 cancers among 71 of the 168 individuals in the Bloom Syndrome Registry, resulting in 50 deaths (German, 1997). In addition to leukemia and lymphosarcoma, cancers of the gastrointestinal tract, breast, and skin are common (Norris & Lehmann, 1999).

Louis-Bar Syndrome

In Louis-Bar syndrome, early motor development appears typical until the onset of ataxia; the ataxia usually becomes apparent during the early years of life and progresses until the individual is 10–12 years old. There is a progressive difficulty in standing and walking, accompanied by problems with coordination. Hypotonia, diminished reflexes, and generalized muscular weakness occur later and often lead to a bedridden state. Impassive facies, drooling, and slow slurred speech are also evident. Conjunctive telengiectasia appears between 3 and 10 years of age, but occasionally remains inconspicuous into adult life. Other characteristic telangiectatic lesions are prominent over the ears, the exposed parts of the neck, the bridge of the nose, the cheeks, and in the flexor creases of the forearm (Rohatgi et al., 2003). Recurrent bacterial sinopulmonary infections occur in roughly 80% of these individuals (Nelson, 1996).

There are reports of an increased incidence of cancer in patients with Louis-Bar syndrome. Of all patients with this syndrome, 10% develop cancer and lymphomas, 80% of these before they turn 15 years old (Taylor, 1992). In the literature, lymphomas (41%), leukemias (23%), and solid tumors (26%) of the stomach, central nervous system, ovaries, and uterus have been reported (Hecht & Hecht, 1990). Ten percent of patients with Louis-Bar syndrome who develop a malignancy present with Hodgkin disease. Patients with Louis-Bar syndrome are of normal intelligence, but by the third or fourth decade of life, there may be short-term memory loss (Gatti, Boder, & Vinters, 1991). Most individuals affected with Louis-Bar syndrome die within the second decade of life from pulmonary disease or cancer (Datta et al., 2001; Hecht & Hecht, 1990).

MEDICAL, PSYCHOLOGICAL, AND SOCIAL COMPLICATIONS

Medical Complications

For individuals with progeroid syndromes, medical complications occur in many organ systems. Because these individuals are indeed prematurely aging, many of the medical complications associated with the progeroid syndromes are similar to the complications associated with old age. Typically, individuals diagnosed with any of the progeroid syndromes may be susceptible to dental problems (i.e., dental defects, dental caries), dermatological conditions (i.e., photosensitivity, thin or dry skin, skin tissue atrophy, baldness, premature graying), ophthalmological conditions (i.e., cataracts, oculocutaneous telangiectasia, microphthalmia), audiological conditions (i.e., hearing loss), certain cancers, a loss of body fat, muscular skeletal abnormalities, atherosclerosis, joint stiffness, and other cardiovascular problems. Endocrine–metabolic disorders, including diabetes and thyroid dysfunction, are common. Respiratory infections, obstructive airway disease, and immunodeficiency are additional medical complications for many individuals. Delayed sexual maturation and infertility frequently occur. Premature mortality is often due to cardiovascular abnormalities (i.e., myocardial infarction or congestive heart failure), but mortality often varies, depending on the specific progeroid syndrome diagnosed (Brown et al., 2003; Satre, 2003).

Neurological and Neuropsychological Complications

In several of the progeroid syndromes, including acrogeria, Hallerman–Streiff syndrome, and Rothmund–Thomson syndrome, central nervous system abnormalities are not usually

evident. In Bloom syndrome, normal intelligence is indicated; however, learning disabilities are common. In Mulvihill–Smith syndrome, mild to moderate mental retardation is reported. More significant neurological complications have been documented in individuals with Cockayne syndrome, Louis-Bar syndrome, and Werner syndrome. Care should be taken in neuropsychological assessments of patients with progeroid syndromes, because individuals with visual and auditory deficits may appear to be lower-functioning than is actually the case.

Neurological involvement is invariably at the forefront in Cockayne syndrome. All patients with Cockayne syndrome are affected with growth failure, developmental delay, and mental retardation. Most patients have microcephaly and hydrocephalus that become apparent in early childhood. Sensory–neural hearing impairment is also a prominent feature. Neurodegeneration and dementia (with preserved sociability) occur. Abnormalities in myelinization and the excessive proliferation of neuroglia (the delicate network of branched cells and fibers supporting the tissues of the central nervous system) in the brains of individuals with Cockayne syndrome, as well as the dementia reported in the longer-term survivors with the syndrome, are consistent with the ongoing degeneration (Lindenbaum et al., 2001). The gliosis and neuronal loss, although widespread, are particularly marked in the cerebellum, cortex, and basal ganglia. This pathology explains the loss of motor milestones, with increasing ataxia, peripheral neuropathy, and muscle weakness (Rapin et al., 2000).

In Louis-Bar syndrome, intelligence reportedly becomes impaired as the illness progresses (Datta et al., 2001). Progressive, disabling neurological findings include cerebellar ataxia, ocular motor apraxia, impassive facies, dystonia, and peripheral neuropathy (Woods & Taylor, 1992). The selective degeneration of Purkinje cells (Gatti et al., 1991) may account for the short-term memory loss that is often evident in the third or fourth decade in individuals with Louis-Bar syndrome.

The relationship between cognitive decline and Werner syndrome is uncertain. In general, it has been reported that the nervous system in patients with Werner syndrome is spared significant age-associated disorders such as Alzheimer disease (Postiglione et al., 1996; Sumi, 1985). However, dementia has been reported in a few patients (Fleischmajer & Nedwich, 1973; Murata & Nakashima, 1982). Furthermore, cerebral atrophy and multiple cerebral infarcts have been found in some cases (De Stefano et al., 2003; Epstein, Martin, Schultz, & Motulsky, 1966; Haustein, Pawlas, & Cervos-Navarro, 1989; Ishii et al., 1985; Perloft & Phelps, 1958; Sumi, 1985; Tokunaga, Mori, Sato, Nakamura, & Wakamatsu, 1976), and amyloid plaques and neurofibrillary tangles have been detected in other cases (Leverenz, Yu, & Schellenberg, 1998), but these abnormalities were not sufficient to permit a diagnosis of Alzheimer disease. Generally, symptoms involving the central nervous system are late and inconstant. Significant brain abnormalities were found in postmortem brains of patients with Werner syndrome but without a history of cognitive decline or other neurological symptoms (Haustein et al., 1989; Leverenz et al., 1998); these findings suggest that central nervous involvement in such patients may be more pervasive than was originally thought.

In a review of cases of Werner syndrome, one-third of patients in whom neurological findings were reported had loss of distal tendon reflexes (Epstein et al., 1966). Peripheral neuropathy has been reported in association with Werner syndrome, although this is usually mild, and it mainly affects sensory nerves (Haustein et al., 1989; Malandrini, Dotti, Villanova, Battisti, & Federico, 2000; Umehara et al., 1993). The pathogenesis of the peripheral neuropathology is unknown; however, peripheral neuropathy could be caused by diabetes.

Social Complications

Social stress often occurs because of the multiple demands placed on individuals with progeroid syndromes. Due to their unusual physical appearance and their frequent medical concerns, individuals affected with these disorders feel different from others and may exhibit social withdrawal (Bartsch, 1999). Dating and forming intimate relationships in adulthood may be challenging for individuals who are affected. There are increased pressures for individuals and their families caused by repeated medical procedures and the financial demands of hospital care. Family members often feel uncomfortable leaving an individual with a progeroid syndrome, sometimes because of the fear that their loved one may die. Relatively few family members receive any type of assistance from a mental health care provider. For those cases with childhood and adolescent onset, negative attention from peers is often a problem. Individuals with a form of progeria are visibly different from others and may be subjected to stares, teasing, and intrusive questioning. They are often socially isolated during crucial periods of identity development and have less peer interaction with age-mates than the typical child or adolescent has during these important developmental years.

IDENTIFICATION, TREATMENT, AND INTERVENTION

Because the progeroid disorders are extremely rare, local health care providers are likely to have little or no personal experience with affected individuals. Early identification is important, to allow for early treatment and intervention. Multiple interventions are commonly required. No research has addressed interventions for the specific medical and psychosocial problems posed by the progeroid disorders. Several different medical and mental health specialists are required for optimal care.

Diagnosis

Diagnosis of the various progeroid syndromes is typically based on the presenting clinical features in early childhood. For many of the syndromes, distinct numbers of predetermined symptoms are used for a positive diagnosis. Skin biopsies often confirm diagnoses in acrogeria, Rothmund–Thomson syndrome, and Cockayne syndrome. For those syndromes with a known gene mutation, including Bloom syndrome and Werner syndrome, diagnosis can be confirmed by genetic analysis; however, molecular testing is often available on a research basis only (Yu, Oshima, & Fu, 1996). Sister chromatid exchange analysis and chromosome breakage studies confirm a clinical diagnosis in Bloom syndrome (Chisholm et al., 2001). Individuals are usually diagnosed with Werner syndrome when they are over the age of 30. Urinary hyaluronic acid is usually elevated in patients with this syndrome (Kieras, Brown, Houck, & Zebrower, 1986). A diagnosis of Louis-Bar syndrome is based on clinical findings and changes noted in the immune system at cellular and humoral levels, including elevated alpha-fetoprotein; decreased immunoglobulin levels (IgG, IgG1, IgG2, and IgG3); defective T-cell function; and failure to respond to mitogens *in vitro* (Tomanin et al., 1990).

Medical Treatment and Interventions

There is currently no cure for progeroid syndromes, and supportive treatment has been the most commonly provided intervention. Supportive treatment focuses on alleviating the

symptoms and complications of these disorders. It has been recommended that clinical management focus on the more life-threatening and developmental issues at earlier stages of life, and on reconstructive procedures after the adolescent growth period is complete (Hou, 2003).

There is typically a high prevalence of eye complications in individuals with progeroid syndromes. Lifelong annual eye exams by an ophthalmologist to screen for cataracts and other ocular complications are recommended. Since screening is noninvasive and cataracts are surgically treatable, screening seems warranted (Wang et al., 2001). In those with Hallerman–Streiff syndrome, spontaneous lens absorption sometimes occurs in older patients, and early surgical removal of the lens is recommended to prevent secondary glaucoma (Sato et al., 2002). Despite surgical treatment, blindness is an eventual outcome for some individuals with progeroid syndromes.

Interventions for hearing loss are frequently necessary. Individuals with progeroid syndromes should have regular evaluations for sensory and conductive hearing loss. Auditory training, including lip reading and making use of residual hearing, may be useful for some individuals. Hearing aids can be helpful for many individuals with progeroid syndromes who have hearing loss. Alternative communications skills, including the use of sign language, may be necessary for those who have total hearing loss.

Respiratory infections need prompt and aggressive treatment. Some of the more severe respiratory problems may require reconstructive surgery or acute tracheostomy. The narrow upper airway associated with the craniofacial configuration may lead to obstructive sleep apnea in individuals with Hallerman–Streiff syndrome (Hou, 2003). Problems with nutrition are often by-products of respiratory infections and should be monitored carefully.

Skeletal dysplasias and ataxia are common in some individuals with progeroid syndromes. Skeletal radiographs should be conducted when the suspicion of osteosarcoma is present. Due to a high risk of skeletal dysplasias, it is recommended that all individuals with Rothmund–Thomson syndrome have baseline radiographs by the time they are 5 years old. Individuals should seek prompt evaluation if they exhibit any signs suggestive of osteosarcoma, including bone pain, swelling, or an enlarged lesion on an arm or leg (Wang & Plon, 2004). Ataxia and mobility difficulties are common problems for some patients with progeroid syndromes. Physical and occupational therapy may help maintain flexibility. Speech therapy may also be needed.

Problems with endocrine–metabolic disorders often exist, as noted earlier. An endocrinologist should regularly evaluate individuals who develop diabetes. Those affected need to learn how to monitor their blood glucose with daily testing, to help determine whether medication, diet, and activity are keeping blood glucose levels within a normal range. Hypogonadism and short stature may be related to pituitary dysfunction. Such individuals should be evaluated for hypopituitarism, as this is a condition that is easily treated with growth hormone therapy (Hou, 2003).

Regular dental examinations are important in dealing with potential dental problems. A strong dental prevention program should be implemented as early as possible. Because of the agenesis of permanent teeth, healthy primary dentition is of paramount importance (de Fonseca & Mueller, 1994).

A higher rate of cancers is reported in affected individuals with progeroid syndromes than in the general population. For those syndromes with impaired DNA repair mechanisms, the treatment of cancers should not include radiotherapy, because several severe reactions to ionizing radiation have been reported. Reports in the literature indicate that the use of low doses of chemotherapy is the preferred treatment for those with chromosomal instability (Abadir & Hakami, 1983).

Due to the increased risk of skin cancers in individuals with progeroid syndromes, an annual monitoring for precancerous skin lesions is recommended. Sun avoidance is important when photosensitivity is of concern. Although sunscreens should be extremely useful in the management of photosensitivity, there remain practical problems related to the type of sunscreen used and the correct application technique (Azurdia, Pagliaro, Diffey, & Rhodes, 1999). If sunscreens are applied too little and the skin is not well covered, photodermatosis can occur. It is important that individuals who experience photosensitivity seek the medical advice of their physician regarding the optimal types of sunscreen and the appropriate application regimens. A pulse dye laser has reportedly been used to lighten or remove poikilodermatous and telangiectatic skin lesions. A series of treatments is usually required to maintain the maximum benefit (Silverberg, Biro, & Laude, 1999). Skin grafting can be performed on areas where ulcerations have occurred from scleroderma.

At this time, gene therapy is not an option for individuals affected with progeroid syndromes. Significant research strides have been made in the last decade, however, and the genes responsible for several of the progeroid syndromes have been identified. In 1996 the WRN gene was located in adults with Werner syndrome, and in 2003 the LMNA encoding nuclear lamin A/C was located in children with Hutchinson–Gilford progeria. Although gene therapy is not feasible at present, future therapies may depend on having a precise molecular classification (Hegele, 2003).

Psychosocial Issues and Interventions

Several psychosocial issues may be addressed through counseling. Individuals diagnosed with progeroid syndromes and their families will need help coping with their diagnosis and its implications. Family education and support are recommended, as families may not be well informed about progeroid syndromes. Affected individuals and families may also benefit from counseling and realistic planning for the individuals' future.

Because most individuals with progeroid syndromes have normal intellectual functioning, teachers and family members should not assume from the outward manifestations of the disorder that there is significant mental impairment. Appropriately high expectations of academic achievement in high school and college will foster realistic self-appraisal and enhanced academic achievement. Socialization and independence should be encouraged. Additional support may be necessary during adolescence, when physical appearance becomes especially important. Lifestyle counseling to encourage smoking avoidance, weight control, and regular exercise (to reduce the risk of atherosclerosis) also may be beneficial. Depending upon the particular form of progeria evident, psychotherapeutic work surrounding the high probability of premature death may be necessary as an adjunct to other psychosocial interventions.

Reproductive counseling regarding the rapid rate of fertility decline for both genders is recommended. A specialist in genetics should explain the risk of having a child with a genetic disorder. The routine health care of women with progeroid syndromes should include contraceptive counseling to help them avoid unintended pregnancies. Women should undergo a thorough physical examination to ascertain optimal health before becoming pregnant (Schieve et al., 2000). The issues surrounding premature death and physical ability to provide care for offspring should also be discussed with adults with a form of progeria, as part of their process of deciding whether to bear or father children.

SUMMARY

The progeroid syndromes are a group of rare genetic disorders characterized by the appearance of premature aging. Many of the syndromes are inherited in an autosomal recessive manner, and there is an increased prevalence of these syndromes in individuals who are the products of consanguineous marriages. Varying degrees of physical and cognitive complications are evident across syndromes. Historically, there has been no successful direct treatment for progeroid syndromes, and supportive treatment has been provided. Such treatment focuses on alleviating the manifestations and complications of these disorders. A multidisciplinary approach to assessment and intervention is necessary for individuals with progeroid syndromes. Medical treatment is usually aimed at treating physical symptoms and conditions associated with old age. Counseling and education for affected individuals and their families is essential. Local care providers are unlikely to have experience with these disorders, and information and evaluation from regional or national specialists may be required. In the past decade, several of the genes responsible for the progeroid syndromes have been identified. As medical science progresses, gene therapy offers the greatest hope for more effective interventions in the future.

Once a family knows of the progeroid disorder, it is helpful for the family to contact the National Organization for Rare Disorders (NORD), which provides descriptions of numerous progeroid disorders as well as contact information for patient organizations, foundations, registries, and networking programs that offer support for affected families. Families may contact NORD at P.O. Box 1968, Danbury, CT 06813-1968; phone (203) 744-0100; website www.rarediseases.org; or email orphan@rarediseases.org. NORD also provides educational information in papers, books, and conferences for families and professionals.

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