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SPECIAL ARTICLE

A History of Pediatric Specialties

In the fourth article of this series, Drs. Ashwal and Rust describe the evolution of child neurology from its parent disciplines of Pediatrics and Neurology. They also document the advances that have been made in each of the many neurologic diseases of childhood. The advancement of technology and the genomic revolution have opened new pathways of research. The remarkable progress of Child Neurology in the 20th century has provided the foundation for further understanding, prevention, and treatment of the many neurologic disorders of childhood.

Alvin Zipursky
Editor-in-Chief

Child Neurology in the 20th Century

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ABSTRACT

Although considered a relatively new subspecialty, child neurology traces its origins to the Hippocratic descriptions of seizures and other neurologic conditions in children. Its true beginnings can be traced to the 1600s and 1700s with classical descriptions of chorea, hydrocephalus, spina bifida, and polio. It was, however, the remarkable clinical and scientific advances in neurology and pediatrics at the end of the 19th century that helped create its scientific foundation. Like other pediatric disciplines, child neurology evolved into a distinct clinical and scientific specialty early in the 20th century. Remarkable advances in the neurosciences, particularly in the fields of genetics, molecular biology, metabolism, immunology and nutrition, have greatly advanced our understanding of how the brain develops and responds to environmental influences. Advances in neuroimaging, electroencephalography, electromyography, muscle histology, biochemistry, and neuropharmacology have considerably improved our ability to evaluate and treat children with neurological disorders. These advances have allowed new and expanding approaches, unique to children, in the fields of epilepsy, neurodegenerative and neurometabolic disorders, nervous system infections, demyelinating diseases and tumors, neonatal neurological conditions, and neuromuscular diseases. They have also led to a better understanding of the neurobiologic basis of common problems such as global developmental delay, cerebral palsy, and autism. As remarkable as the advances have been in the past century, the accelerating pace of our understanding of the fundamental mechanisms responsible for brain development will lead to even greater achievements in the clinical care of children with neurological disorders in the 21st century **(*Pediatr Res* 53: 345–361, 2003)**

Abbreviations

ABPN, American Board of Psychiatry and Neurology
CBF, cerebral blood flow
PET, positron emission tomography
PKU, phenylketonuria
SMA, spinal muscular atrophy
HIE, hypoxic-ischemic encephalopathy
ADEM, acute disseminated encephalomyelitis
IQ, intelligence quotient
ADHD, attention-deficit/hyperactivity disorder
MRI, magnetic resonance imaging

Although formal designation as a medical subspecialty did not occur until the 1950s, child neurology traces its origins to the Hippocratic description of seizures and other neurologic conditions in children. The accumulation of a more substantial body of information and subspecialized interest in the neurologic problems of children can be traced from the 16th and 17th centuries, during which classical considerations of chorea, hydrocephalus, spina bifida, birth injuries, cerebral palsies, poliomyelitis, and other conditions were published. The rise of

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empirical clinical medicine, neuroanatomy, and of specialized-interest pediatrics, obstetrics, orthopedics, psychiatry, and neurology during the 17th and 18th centuries provided the groundwork on which child neurology would be based (1–4).

Foundations were laid for neuropsychological investigation and for the amelioration of psychomotor disorders of children, often within the setting of newly constituted residential facilities dedicated to the care of children and adolescents. Within such facilities arose the organized study and classification of mental retardation, paralyses, blindness, deafness, and epilepsy. Clinics with subspecialized and multidisciplinary interest in childhood neurologic problems followed in short order, and with this came the earliest understandings of the effects of trauma, nutrition, and inheritance on childhood neurologic diseases. Advances in diagnostic testing, such as electroencephalography, neuroimaging, electromyography, muscle histology, biochemistry and molecular biology, helped those with an interest in child neurology diagnose and treat a large array of conditions.

The notion of providing urgent neurologic consultations in hospitals and the establishment of wards devoted to the care of children with neurologic diseases arose in major hospitals before World War II. Consultations in general hospitals were generated with increasing frequency as the development of ventilators, discovery of antibiotics, improvement of fluid resuscitation, and other advances that occurred in the 1930s and 1940s permitted children to survive increasingly complicated diseases, manifesting an increasingly bewildering array of neurologic dysfunction. Neurologists interested in investigating and treating the birth-related, infectious, parainfectious, traumatic, hereditary, and other forms of neurologic illness in children acquired increasing sophistication in this emerging neurologic subspecialty and assumed increasing responsibility for the acute and long-term care of children with these problems.

The evolution of a subspecialized discipline of child neurology occurred over more than 100 years, as part of the contemporary struggle to develop the professional identities of neurology, psychiatry, and pediatrics. Many of the principal early figures in the development of modern clinical and basic neurosciences and pediatrics were profoundly interested in the neurologic diseases and normal neurologic development of children. Many of these influential neurologists, psychiatrists, and neuroscientists did not feel constrained to limit their investigations or professional practice on the basis of age. Many influential pediatricians were unconstrained by a sense that any professional boundaries prevented them from addressing neurologic issues, along with issues related to the many other organ systems of children that engaged their attention. Additional important contributions were made by general physicians, pathologists, orthopedists, obstetricians, psychologists, educational theorists, and other members of nascent medical subspecialties.

As the clinical and scientific contributions of the members of these "subspecialties in evolution" accumulated, it became increasingly clear that the study of the developing nervous system was a highly complex area, worthy of concentrated study and dedicated subspecialization. It became increasingly clear that subspecialization in this area would render medical, scientific, and social benefits. Such subspecialization was necessary for the sake of improved standards of practice and improved skill in further investigation. Subspecialization also afforded appropriate selection and preparation of individuals who possessed the traits necessary for the formation of a professional relationship with children of different ages and their parents, including the subspecialized skills necessary for obtaining a history and examining young children. Progress in the study and treatment of the developing nervous system would occur far more expeditiously if a critical mass of individuals dedicated to this family of subjects were recruited and trained, individuals who in turn could recruit successors, provide selected neurologic training for members of associated disciplines and whose zeal would encourage the devotion of time and resources to research, as well as improvement in diagnosis and management.

One of the major social and educational trends since the end of World War II was the continued shift toward a society based on information processing and sophisticated technology. Child neurologists were soon asked to evaluate many children to determine whether seizures were occurring and whether medications were indicated. The advent of CNS stimulants and other medication to treat attentional, depressive, or aggressive behavioral disorders further stimulated additional referrals. After World War II, enthusiasm for the study and treatment of childhood neurologic diseases was reflected in the clear identification of specialists in neurologic disease of children. By the mid-1970s most medical schools had pediatric neurologists on their faculty engaged in teaching, research, training, and caring for children with an ever-widening spectrum of neurologic disorders.

As the number of pediatric neurologists in many countries increased, it became obvious that separate professional societies representing their own political, medical, and academic interests were desirable. Such societies were established in Japan (1961), Scandinavia (1962), England (1971), the United States (1972), Belgium (1978), China (1985), Europe (1970), and worldwide (1973). Additional evidence for the growth of child neurology was the number of journals now devoted to this field including *Developmental Medicine and Child Neurology* (1958), *Neuropediatrics* (1969), *Brain and Development* (1979), *Pediatric Neurology* (1985), and the *Journal of Child Neurology* (1986). Many aspects of the advances in clinical and basic neurosciences pertinent to child neurology, descriptions of neurologic diseases in children, biographies of important contributors to the field, the appearance of journals and texts, and the formation of subspecialty societies and board certification have been published (4).

DEVELOPMENT OF CHILD NEUROLOGY IN NORTH AMERICA

The roots of American child neurology arose in the late 19th century in adult neurologic and pediatric soils. The neurologic origins are readily traceable. The Philadelphia Orthopaedic and Neurologic clinic of Weir Mitchell and William Osler made particularly important contributions to the process of neuro-

logic evaluation and multidisciplinary care, as well as to the understanding of cerebral palsies, childhood static encephalopathies, and movement disorders. Edouard Seguin exerted enormous influence on the awakening of interest in the intellectual development and rehabilitation of children in Boston, New York, and elsewhere. In New York, Bernard Sachs stimulated international interest in the subject of heritable metabolic and degenerative disorders of children and would continue, through the first four decades of the 20th century, as the earliest critical figure in the development of the subspecialty. He published one of the world's first textbook of child neurology in 1895 and was throughout his long career a tireless champion of the interests of children and adolescents.

From the third through sixth decades of the 20th century, neurologists Frank Ford of Baltimore and Bronson Crothers of Boston joined Sachs as fathers of child neurology. Both made contributions of great importance to the study and alleviation of birth injuries. Ford produced five editions of the most influential child neurology text of his era, although his influence as a teacher was limited by his very personal, informal, even diffident style of educational interaction as well as by his refusal to travel far or often from Baltimore. Crothers's contributions to the study of cerebral palsies provided a foundation for international study and management of that family of conditions. As did Sachs, Crothers was active and highly effective in the formulation of public policy relevant to the neurologic disabilities of children and to social and educational reform including the deinstitutionalization of handicapped children and their integration into regular public education.

In the fourth decade of the 20th century, the influence of additional fathers of American child neurology, Randolph Byers of Boston and Douglas Buchanan of Chicago, became apparent. Byers was to be the key figure in the identification and alleviation of childhood risk for lead poisoning and a figure of great importance in the study of cerebral palsies, as well as infectious and inflammatory neurologic diseases of children. Buchanan was of critical importance in the study of childhood brain tumors. Although all of the figures that have been mentioned were celebrated teachers, Buchanan was particularly effective in this role, and, although he published little, he exerted national influence. He contributed importantly to the development of the subspecialty of pediatric neurooncology.

Quite a few important North Americans contributed to the development of other areas of investigation that fueled the development of child neurology in this era, of whom only a few can be mentioned here. Clemens Benda of Boston demonstrated the importance of close specialized study of heritable causes of mental retardation and of the cerebral palsies. Although many individuals contributed to the study of the neuropathology and neurophysiology of childhood neurologic diseases, several should be singled out as particularly influential in the evolution of modern child neurology. These include Bernard Alpers of Philadelphia, Raymond Adams and Derek Denny-Brown of Boston, and Cyril Courville of Loma Linda.

Great energy was imparted to the development of child neurology by individuals who fostered the development of the study and treatment of childhood epilepsy, which continues to constitute the single largest source of referral to child neurologists. Among the most important individuals involved in the early development of this area were William Lennox and Cesare Lombroso in Boston; Edward Bridge and Samuel Livingston in Baltimore; Wilder Penfield, Theodore Erickson, and Fred and Eva Andermann in Montreal; and Fritz Dreifuss in Charlottesville. Of particular importance would be the development of a collaborative approach to comprehensive investigation, classification, and training in epilepsy in which Preston Robb, Dreifuss, and Andermann, Richard Masland, Kiffin Penry, and many others, were to play roles.

Support and developmental guidance for the concept of a separate discipline from adult neurology that just dealt with children was provided mid-century by Raymond Adams and Houston Merritt, the former designating Philip Dodge and the latter Sid Carter as leaders, respectively, of the Boston and New York "schools" of child neurology. At almost the same time, two individuals influenced by both Buchanan and Ford—David Clark and Charles Barlow—initiated careers that would prove highly influential. Clark and Dreifuss pioneered a highly successful model of "outreach clinic" circuits that would carry child neurology to rural, medically underserved areas. All of these individuals would make noteworthy contributions to various subjects of clinical or basic science relevant to the neurologic care of children and provide the additional personal inspiration that attracted promising young physicians to the study of child neurology and related issues.

By the mid-1950s, it was clear that further progress required the establishment of a systematic program of training and certification for subspecialists in child neurology. Very close and important alliances with both adult neurology and pediatrics made it clear that both forms of training were essential to the new discipline. It was also clear that the professional "personality" and method of the parent subspecialties differed from one another in small but important ways. Deliberations held by a handful of leading figures in the child neurology movement (Byers, Dodge, Carter, and others), with a small number of highly prominent pediatricians determined that although child neurologists should be pediatricians, that training in adult neurology was of critical importance. Therefore, the subspecialty was placed under the aegis of the American Board of Psychiatry and Neurology (ABPN) that had been established in 1934. The 1950s was a decade wherein formal training programs in neurology enjoyed considerable expansion in scope and number, a process that was considerably aided by the establishment of the American Academy of Neurology in 1948 and by guidance and investment of training and research funds by the National Institutes of Health during and after the Korean War. The work that was involved in convincing the federal government to fund research and training was greatly indebted to the contributions of another neurologist, William Caviness, of the National Institutes of Health.

Dodge (Boston), Carter (New York), and Charles Kennedy (Philadelphia) established the first training programs in the 1950s. Training and certification for individuals interested in specialization in either neurology or psychiatry was separated in 1946, retaining only abbreviated elements of psychiatric training for those interested in the practice of neurology. In 1959, the ABPN formally incor-

porated examination concerning child neurology as a portion of the board examination process, then consisting exclusively of an oral examination.

In 1959, Sidney Carter was the first child neurologist to be appointed as a director of the ABPN. His assistant director and co-developer of all child neurologic aspects of these examinations was David Clark. Child neurology initially constituted 25% of an 8-hour examination. During the ensuing 8 years, a written neurologic examination was established with appropriate representation of child neurologic diseases among the questions, whereas the oral examination was scaled back to 4 hours with 25% of the time devoted to child neurology in 1967. In 1969, "Special Qualification in Child Neurology" was developed as an added board qualification. In that year, 106 certificates based on the record of achievement were granted to those already engaged in this subspecialty in the United States. On average, certification has been granted by examination to ~30–40 individuals each year since that time. Negotiations between the ABPN and the American Board of Pediatrics, initiated in 1956, established that individuals who successfully completed 2 years of pediatric training and 3 years in neurology were eligible for certification in pediatrics as well as neurology with special qualification in child neurology. That child neurology is the only pediatric subspecialty that is enabled to become board certified in pediatrics with just 2 years of formal pediatric training constituted recognition that formal training in child neurology represented an important aspect of pediatrics. In 1969, guidelines for future certification of child neurology training programs were first formally considered by the ABPN, launching an ongoing process of revision that continues to the present day. As a result of all of these forces, the number of formal child neurology training programs in the United States expanded from six in the 1950s to a peak of greater than 80.

The 1960s marked a tremendous flowering of interest in child neurology and the launching of many important child neurology careers. Although continued development occurred on the East Coast, the location of events of particular importance to the development of identity of child neurology in the decade of the 1970s shifted to the Midwest. The formation of the Upper Midwest Child Neurology Society and in short order the Child Neurology Society (CNS), under the particular guidance and leadership of Ken Swaiman, recapitulated midwestern leadership in the establishment of the American Academy of Neurology several decades earlier. This movement entailed association of the CNS with the American Neurologic Association in sponsorship of what would become the most prestigious North American neurologic journal, the *Annals of Neurology*. Two American journals devoted exclusively to child neurology were also founded in the 1970s.

The following sections review some of the major scientific contributions and discoveries in child neurology in the 20th century related to advances in the neurosciences and in the clinical understanding and treatment of childhood neurologic disorders.

ADVANCES IN THE UNDERSTANDING OF CHILDHOOD NEUROLOGIC DISEASES

Pediatric Epilepsy

The field of pediatric epilepsy owes much to advances in the scientific principles and instrumentation that led to the development of electroencephalography as well as to the elucidation of many fundamental principles of the neurophysiology of the developing nervous system.

Electroencephalography. Development of electroencephalography can be traced to the studies of Gustav Fritsch and Eduard Hitzig (1870), who showed that the cerebral cortex could be electrically excited and produce focal or generalized seizures, as well as the studies of Richard Caton, who observed that the brain intrinsically produced electrical activity that could be recorded (5, 6). By 1912, the first experimental records of EEG were preserved photographically, and shortly thereafter the first photographs of paroxysmal EEG were published. The 1929 report of Hans Berger of the first recordings of spontaneous brain activity in humans and 2 years later of interictal EEG discharges marked the beginning of the modern era of the clinical and laboratory study of epilepsy. The first EEG studies in children were done by Hans Berger in 1932, when he reported on 17 children ranging in age from 8 days to 15 years (5). In a landmark 1935 study of 12 children with petit mal epilepsy, Frederic Gibbs and colleagues reported finding three per second spike-wave complexes during seizures as well as interictally. In the following year, several groups recorded focal spike discharges in patients with focal epilepsy. In the 1930s, Herbert Jaspar while at Brown University conducted a series of EEG studies in children with behavioral disorders, and D.B. Lindsley at the University of California in Los Angeles (as did other groups) began pioneering studies on maturational changes of the EEG, particularly the alpha rhythm. The first studies of EEG in the neonatal period were published in 1949, but it was the studies of Dreyfus-Brisac and Monod in France (1964) and of Parmelee (1968) in the United States that delineated the complex changes in electrocortical maturation that are now widely recognized (5). Petersén and Eeg-Olofsson carried out investigations on large populations of normal older children and adolescents in Scandinavia in the 1970s.

Advances in technology led the way for future epilepsy research. Simultaneous display of clinical seizures with electrical recordings were carried out in the late 1930s using movies and later, in the 1960s, closed-circuit television. These techniques have been replaced by computerized digital video-EEG telemetry systems that are universally available and facilitate long-term recording. The use of depth electrodes and subdural strips or grids for intraoperative recordings has also been important in the intraoperative management of epilepsy surgery patients. The contribution that these techniques made to the understanding of the semiology and treatment of epilepsy cannot be overstated. Important contributions were made by the epilepsy programs that developed in Montreal, Boston, Philadelphia, and Baltimore. The approaches developed in these centers were further refined and particularly effectively applied in the development of the comprehensive epilepsy

program model by Fritz Dreifuss in Charlottesville. Dreifuss was especially influential in developing approaches to the "missions" of classification; development and evaluation of drug therapies, training of epileptologists, education of the public and government; and funding. Much effort in the 1960s and later went into development of computerized automated EEG interpretation and spike detection programs, but in large part these have been unsuccessful (5). Other efforts using the EEG for computerized brain mapping have also been developed and used to study many forms of behavioral and learning disorders.

Basic mechanisms of epilepsy. The 20th century saw dramatic advances in understanding the basic mechanisms of epilepsy. Pathologic studies provided abundant evidence before 1969 that brain abnormalities gave rise to most epilepsy, due in most instances to abnormal development, hypoxic-ischemic or traumatic injury, or tumor. A landmark of particular importance was the identification of the importance of mesial temporal sclerosis as an epileptogenic lesion and its association with prolonged childhood convulsions, the work of Ounsted and others from 1966 to 1970. The relation of cerebral blood flow (CBF) to epilepsy was studied as early as 1934 by Gibbs, and studies of the metabolic disturbances that seizures produced were undertaken as early as the 1940s. The earliest studies concentrated on the effects of glucose and brain acidity, studies that were enlarged to include measurement of other aspects of energy metabolism in the 1960s and 1970s, with particular interest in the changes peculiar to the developing brain.

A fundamental advance was achieved with the development of the brain slice technique, wherein biochemistry and blood flow could be ascertained in relation to progressive pathologic changes that resulted from seizures. The development of extra- and intracellular microelectrodes represented an additional fundamental advance that allowed for recording from single neurons *in vivo*, in slice preparations, and in tissue culture; development of animal models of epilepsies (alumina gel, strychnine, penicillin, maximal electroshock, pentylenetetrazol, etc.); use of ion-sensitive microelectrodes; biochemical and metabolic studies of brain tissue; and the application of electron, fluorescent, and other microscopy techniques. More recently, molecular biology has allowed identification of genes responsible for certain epilepsy syndromes, the study of receptors (*e.g.* glutamate, gamma amino butyric acid), and the identification of channelopathies. The results have been a considerable increase in basic knowledge about the roles of calcium, potassium, glutamate, GABA, pH, and other factors in the development of brain function and epilepsy, the concept of the paroxysmal depolarizing shift, inhibitory and excitatory postsynaptic potentials, modulation of neuronal circuitry, and the development of neuronal loss or gliosis that contribute to epileptogenesis. The work of Dominic Purpura and many others also examined these phenomena from a developmental perspective in an attempt to understand why the immature brain is more vulnerable to seizures (6). Neuroimaging and neuropathology over the past two decades has confirmed and enlarged observations that Paul Yakovlev and others made during the first half of the 20th century concerning the relationship of malformations, heterotopias, and other neuronal migrational disorders to epilepsy.

Syndrome classification of childhood epilepsy. Nineteenth-century authorities inherited only a modest body of knowledge concerning seizures and epilepsy (7, 8). Hughlings Jackson first clearly advocated the importance of distinguishing focal (unilateral or uncinate) from generalized (absence or generalized tonic clonic) seizures. It was recognized that some seizures and epilepsies pursued a limited course, whereas others persisted for longer intervals, sometimes lifelong. By the turn of the 20th century, there was realization that the classification of epilepsy should take into consideration anatomical lesions and pathophysiological disturbances of brain function. It was acknowledged that focality or generality of brain involvement and the likelihood that seizures were idiopathic or symptomatic could be adduced from clinical observations and history and that childhood focal seizures could arise from heritable disorders, perinatal difficulties, nervous system infections, trauma, and other causes.

The clinicopathological investigation of epilepsy in the first decades of the 20th century led to the sweeping conception of epileptic seizures as a symptomatic manifestation of an enormous collection of neurologic or systemic diseases that could be transient or permanent. It was understood that inherited tendencies to "cerebral dysrhythmia" were important but that the threshold for seizures was exceeded by the additional contributions of other factors. Among the first important demonstrations of the clinical value of the EEG were the specific patterns corresponding to particular types of epilepsy as identified by the Cobb group in 1935 to 1936. More extensive subclassification occurred in the ensuing decade. These achievements marked the beginning of the distinction between epilepsies that impaired consciousness on the basis of being generalized *versus* those focal epilepsies that would come to be called psychomotor or partial complex epilepsies (5).

As has been noted, the development of comprehensive epilepsy programs (Montreal, Boston, Baltimore, and Philadelphia) and in particular the development of comprehensive "centers of excellence in epilepsy" (initially Charlottesville, Minneapolis, Los Angeles, and Portland) greatly advanced the work of classifying epilepsy, a task in which Dreifuss played a key role. The split-screen prolonged monitoring methods that he pioneered generated real-time EEG and video data that were essential for the promulgation of the epoch-making classification of epileptic seizures of 1981. Additional international collaborative work generated in 1989, a revised system that incorporated cause, anatomic substrate, age of onset, and other features, supported the important conceptual advance of epileptic syndromes. Proper classification of epilepsy served as an important basis for the characterization of the epidemiology of the epilepsies of childhood and adolescence. W. Allen Hauser, J.F. Annegers, Jonas Ellenberg, Karin Nelson, and others played particularly important North American roles in this effort. These studies confirmed the suspected enhanced propensity of the developing brain for manifestation of seizures and the large number of factors capable of their provocation. They also disclosed the intriguing resistance of developing brain to the development of injury as a result of some types of

seizures, corresponding to longitudinal studies that have confirmed the relatively favorable outlook of children for recovery from certain types of epilepsy as compared with adults. Although many individuals figured in these studies, the pioneering role of Jean Hollowach-Thurston in demonstrating the metabolic effects of seizures on brain at various developmental ages and her confirmation that withdrawal of antiseizure medications could safely be undertaken after well-defined periods of freedom from seizures deserve to be mentioned. Longitudinal studies of well-defined populations continue to refine expected treatment intervals and outcome of childhood epilepsies.

However, studies have also confirmed that the developing brain is in some ways more susceptible to the development of epilepsy than the mature brain. In some individuals, this susceptibility has been shown to be genetic, a conclusion of the twins-with-epilepsy studies of the Lennoxes that was first effectively confirmed in a population-based study by Annegers and colleagues in 1992. The subsequent course of investigations has involved many hands, including linkage studies demonstrating chromosomal localization of "susceptibility genes" for nearly 20 childhood epilepsies. This area of investigation continues to be complicated. Etiologic and genetic heterogeneity of childhood epilepsies suggest the importance of such potential modifying factors as maternal transmission, pleiotropy, and gene–environment interactions,

Pathophysiological studies of epilepsy flourished during the last three decades of the 20th century and demonstrated intriguing developmentally related variation in the function of cells, synapses, and brain circuitry that are pertinent to seizures, epilepsy, and other paroxysmal brain processes. This highly successful research endeavor has involved so many individuals and their insights have proved so extensively interdependent as to render any attempt within the limited confines of this review to assign particular significance to individuals a perilous undertaking. The important observations have included the following. Predominance of excitatory processes in the neurotransmission of developing brain, a burgeoning area in neuroscience to which the early work of Olney and Rothman proved an exceptionally important stimulus, has prompted close investigation of the role of excitatory and inhibitory influences in childhood epileptogenesis. Morphologic aspects of the developing brain with the assignment of excitatory and inhibitory functions to specific synapses, subunit composition of excitatory receptors, the ionic microenvironment of synapses, ion channels coupled to receptors, metabotropic receptors, various classes of neuromodulators, glial cells, and the development and subsequent modification of brain circuits are among the important areas of ongoing and fertile investigation. These studies are demonstrating with increasing clarity the mechanisms whereby developmentally determined changes regulate onset, propagation, inhibition, and kindling of potentially epileptic foci.

Febrile seizures. The concept of febrile seizures also evolved in the 20th century, although the relation between fever and convulsions in children had been recognized for centuries (9). Patrick and Levy (1924) initiated studies that were among the first to demonstrate the clinical relation of prolonged febrile seizures to brain injury and to provide estimates for the risk of epilepsy after febrile convulsions. Wegman initiated experimental studies of the vulnerability of the developing brain to fever-evoked convulsions in 1939. By the mid-1940s, M.G. Peterman at the Mayo Clinic, the first investigator to use movies in combination with EEG to study infantile convulsions in depth, had collected more than 2500 cases of pediatric seizures. Among these patients were ones with "sporadic convulsions," which he defined as "only one or two seizures and often only after the body temperature reaches a certain point." William and Margaret Lennox carried out important studies concerning the epidemiology of fever-related seizures in children and the circumstances that were associated with brain injury or subsequent epilepsy between 1949 and 1953.

It was, however, the work of Samuel Livingston (1954), whose studies of febrile seizures that suggested a benign outcome; J. Gordon Millichap, who demonstrated that febrile seizures were the most common cause of convulsions in infants; and van den Berg and Yerushalmy, who reported that the highest incidence was from 9 to 30 months of age that provided the impetus for continued investigations. Karin Nelson and Jonas Ellenberg in their studies from the National Collaborative Perinatal Project, a large prospective cohort study, proposed a strict definition of febrile seizures and provided further evidence that febrile seizures usually had a favorable outcome. This was followed by a National Institutes of Health consensus conference in 1980 that addressed the definition, prognosis, treatment, and future research needs for the entity of febrile seizures.

Medical and surgical treatment of epilepsy in children. Medical treatment of seizures began in 1857 with bromides. A group under the leadership of Putnam and Merritt undertook the screening of antiseizure medications that yielded, in 1938, diphenylhydantoin. This introduced not only the second great antiseizure medication of the 20th century, the first being phenobarbital (1912); it proved that seizures were controllable on some basis other than sedation. The 20th century saw the introduction of other new drugs in the United States, including trimethadione (1946), ethosuximide (1960), diazepam (1968), carbamazepine (1974), clonazepam (1975), valproic acid (1978), felbamate (1992), gabapentin (1993), lamotrigine (1995), topiramate (1997), levetiracetam (1999), and zonisamide (2000)

ACTH was introduced for treatment of intractable seizures in mid-childhood and adolescence in the 1950s, and a particularly dramatic response to ACTH therapy by patients with infantile spasms was demonstrated in 1956. The drug remains a mainstay of treatment in that particular disorder and finds occasional use in the treatment of intractable mixed childhood epilepsies.

The origins of the ketogenic diet can be traced to the early 1920s, when it was ascertained that fasting and then specialized diets could control seizures (10). Wilder at the Mayo Clinic (1921) suggested that a diet high in fat and low in carbohydrates could maintain ketosis and termed this the ketogenic diet. Over ensuing decades and up until the 1970s, investigators at various institutions treated several thousand

children with good success, notably Samuel Livingston at Johns Hopkins and H.M. Keith at the Mayo Clinic. By the 1970s, with the advent of new antiepileptic drugs (carbamazepine and valproic acid), the diet fell out of favor. It was almost single-handedly resurrected by the efforts of the Charlie Foundation and John Freeman and his colleagues at Johns Hopkins University in the early 1990s and once again enjoys widespread use.

Although initial surgical treatment of epilepsy is credited to Victor Horsley (1886), trephination was performed as early as 1828 for posttraumatic epilepsy (11). In the early 20th century, Krause and Förster recognized the importance of cerebral localization and devised separate surgical procedures for treating generalized and focal epilepsies. Of critical importance to the development of this approach to the management of epilepsy was the work of Wilder Penfield at the Montreal Neurologic Institute. More than 169 individuals, including children, had undergone operations for management of epilepsy by Penfield and his colleague Erickson by 1939. The EEG became a critical part of the presurgical evaluation, based largely on the seminal contributions of Herbert Jasper. Successful use of frontal lobectomy for epilepsy (Jason Mixter in 1938), hemispherectomy (Krynauw in 1950), selective corticectomy (Ransohoff in the 1940s), and corticography with selective focal resections (Matson, Penfield, Baldwin, and others in the 1950s) are important landmarks. Falconer and his colleagues were the first to report large-scale success in performing temporal lobectomies in children (1974). This work and those of others, such as Goldring (focal extratemporal cortical resections, 1978), Van Wagen and Herren in 1940 and later Geoffroy in 1983 (corpus callosotomy), and Rasmussen (functional hemispherectomy, 1983), paved the way over the next several decades for pediatric epilepsy surgery centers to evaluate and treat children with intractable seizures.

Contributing to the success of epilepsy surgery has been the role of positron emission tomography (PET) scanning. PET studies have shown that metabolic activity is increased in the epileptic brain region during partial seizures, a finding that has proven helpful in identifying epileptogenic foci that could be surgically resected. Even in patients with infantile spasms, it was shown that some patients had areas of regional hypometabolism and that surgical resection of such regions was associated with clinical improvement.

A relatively new treatment for epilepsy is vagal nerve stimulation. Irving Cooper championed interest in chronic cerebellar stimulation for the treatment of various neurologic conditions, including epilepsy, in the 1970s. However, this did not meet with much success. Interest shifted to vagal nerve rather than cerebellar stimulation in the 1980s, when it was appreciated that vagal nerve stimulation might cause retrograde firing at the level of the vagus nerve nucleus in the brainstem with secondary activation of cortical and subcortical regions. This technique has now been added to the armentarium of treatments of otherwise intractable epilepsy.

What has made much of the evaluation and treatment of children with epilepsy possible in the past several decades is the establishment by the National Institutes of Health of comprehensive centers for the management of epilepsy. These had been preceded by the opening of the first Seizure Unit dedicated to the study of childhood epilepsy at the Boston Children's Hospital in the 1940s. Establishment of epilepsy centers allowed for continued clinical and basic research in many directions and led to the development of the multispecialty team approach to the evaluation of patients so that the neuropsychological, educational, social, and quality-of-life issues could be evaluated and treated.

NEUROGENETIC AND NEUROMETABOLIC DISORDERS

Identification of genetic loci for heritable metabolic disturbances and other conditions. The field of heritable biochemical diseases that affect the nervous system was established by Garrod's recognition, in 1892, of alkaptonuria. His theory that such disorders represented "inborn errors of metabolism" was among the earliest important medical applications of the laws of Mendel. The one gene–one enzyme concept was advanced by Johannsen in 1911. Electrophoresis (1930) permitted phenylketonuria (PKU) to be defined as the first neurologically pertinent aminoaciduria in 1934. Paper chromatography (1944, 1948) and the subsequent development of much more sophisticated liquid and gas chromatographic methods permitted more than a thousand variations in human amino acid metabolism to be recognized in this century and the associated abnormalities of function, if any, to be characterized. The enzymatic defects producing almost all of the clinically important amino acid disturbances have been characterized, starting with phenylalanine hydroxylase (1947), the enzyme associated with the most common form of PKU. An excellent working knowledge of the clinical phenotypes of most of the classical amino acid disorders had been achieved by the mid-1970s; subsequent work has enlarged the understanding of "variant" presentations. Investigations of the pathophysiological mechanisms of these disorders were reported from the mid-1960s through the mid-1980s. The specific gene defects responsible for these disorders have rapidly been characterized, starting with PKU in 1984. The one gene–one enzyme concept has expanded to include genetically determined defects in nonenzymatic proteins. Efforts to establish effective methods for gene therapy for these various disorders were initiated early in the 1990s.

Among the most important achievements of the second half of the 20th century was prevention of the clinical consequences of amino acid disturbances by early diagnosis and provision of therapy. Development of the Guthrie inhibition test in 1963 and the subsequent establishment of universal newborn screening programs throughout North America have permitted early diagnosis of PKU and a number of other treatable diseases that produce neurologic injury to the developing brain. The type and degree of protein restriction (for mothers and infants) necessary to minimize nervous system injury and maximize normal growth and development for various treatable disorders was largely worked out between 1960 and 1980. In some instances, improved understanding of biochemical mechanisms has permitted vitamin cofactors to be provided as effective treatment for certain aminoacidurias.

Genetic reclassification of heritable ataxias of childhood. The earliest important landmark in the understanding of childhood ataxic conditions was the description of Friedreich's "hereditary ataxy" in 1861. The latter half of the 19th century marked the beginning of the study of clinical aspects of infantile and early-onset ataxic conditions, including the initial distinction of cerebellar ataxia from chorea and athetosis. Much of the progress in this area of child neurology during the first seven decades of the 20th century entailed setting apart from other ataxic syndromes those caused by various structural or biochemical causes of ataxia. The description of ataxia telangiectasia in 1941 marked a particularly important point, the initiation of studies that in time would designate a family of conditions wherein disordered mechanisms of DNA repair affect various organ systems.

The last two decades of the 20th century saw the characterization of genetic aspects of ataxic conditions. Demonstration that Friedreich ataxia is the result of variable degrees of unstable trinucleotide expansion in DNA and with failure of adequate expression of a mitochondrial protein has been followed by demonstration that other forms of polymorphic trinucleotide expansion are the basis of most dominantly inherited ataxias. It has also been demonstrated that at least some of the hereditary periodic ataxias of childhood are in fact genetically determined channelopathies.

MITOCHONDRIAL DISORDERS

During the last half of the 19th century, the presence of particular subcellular organelles was recognized and the term *mitochondria* was proposed by Benda in 1898 (10, 12). The metabolic roles of mitochondria were defined in the early 20th century. Mitochondrial diseases were shown to result in three categories of metabolic dysfunction: defects of the respiratory chain, fatty-acid oxidation, or pyruvate and Krebs cycle metabolism (12).

In 1963, the presence of DNA within mitochondria (mtDNA) was recognized, as was the description of ragged-red fibers in skeletal muscle of some patients with mitochondrial disease. In 1988, the first disorder associated with a mtDNA deletion, chronic progressive external ophthalmoplegia, was reported, as was Leber hereditary optic neuropathy. Within several years, other major forms of mitochondrial diseases that more typically present in childhood were recognized, including myoclonic epilepsy with ragged-red fibers and mitochondrial encephalopathy with lactic acidosis and stroke. It was also recognized that nuclear encoded defects could affect mitochondrial function and that mitochondrial disorders contributed to the pathogenesis of many clinical and metabolic diseases and play a role in apoptosis, cell injury, and cell death.

The first well-documented disorders of mitochondrial fatty acid oxidation were described in the early 1970s in patients with skeletal muscle weakness and exercise-induced rhabdomyolysis with decreased carnitine or carnitine palmitoyltransferase (12). Characterization of another group of mitochondrial disorders began in 1982–1983 with the description of medium-chain Acyl-CoA dehydrogenase deficiency. Since then, more than 15 disorders of mitochondrial fatty-acid oxidation have been described.

PEROXISOMAL DISEASES

Conventional thinking in the mid-20th century that separated metabolic disorders from those with congenital anomalies was altered when peroxisomal disorders were recognized in 1971 (12, 13). Virtually all of the peroxisomal diseases had previously been described in the literature before it was realized that they were due to dysfunction of this organelle. X-linked adrenoleukodystrophy was described in 1923 and the name *adrenoleukodystrophy* was introduced in 1970, Refsum disease in 1946, Zellweger syndrome in 1964, and rhizomelic chondrodysplasia punctata in 1971. Peroxisomal disorders are categorized according to whether they are due to defects in peroxisomal biogenesis or to defects in either single or multiple peroxisomal enzymes with intact peroxisomal structure. Genetic studies have enhanced understanding of peroxisome synthesis and their complex metabolic roles (10).

LYSOSOMAL STORAGE DISEASES

Lysosomal storage diseases are disorders in which abnormal amounts of normal substrate and their catabolites accumulate within lysosomes. They encompass several major metabolic disease groups, including the sphingolipidoses, mucopolysaccharidoses, mucolipidoses, glycogen storage diseases, and glycoproteinoses. The history of these disorders can be traced to the work of Thudichum and the year 1884. Over the next half century, many of the classical lysosomal diseases were reported as isolated case histories, and by the mid-20th century, their pathology and the fact that they were storage diseases was established. Disease-specific enzyme defects leading to the accumulation of stored biochemical intermediates were recognized, beginning with Tay-Sachs disease in 1940. The seminal observations of Hers and colleagues (1963) in infants with Pompe's disease followed as did the subsequent recognition of more than 30 lysosomal diseases. Hers and colleagues also showed that excessive mucopolysaccharide accumulation was due to deficiencies of lysosomal hydrolases involved in the breakdown of mucopolysaccharides and that storage of this material occurred in the lysosome. By the mid-1970s, Neufeld and colleagues as well as other investigators identified the metabolic pathways involved in the degradation of mucopolysaccharides and also reclassified some clinical syndromes on the basis of the specific enzyme deficiency. By the 1980s, a new group of disorders and a distinct condition, carbohydrate deficient glycoprotein syndrome, was suggested and well defined in 1989 (12). It was soon realized that some of these diseases were not due to disruption of a specific metabolic pathway but to alternative mechanisms (*e.g.* sphingolipid activator proteins, 1964). Enzyme replacement treatment (*e.g.* α-glucerase for Gaucher disease) has also become available for certain of these disorders.

NEURONAL CEROID LIPOFUSCINOSES

The original description of a form of the neuronal ceroid lipofuscinoses is credited to Stengel, who identified four chil-

dren with progressive visual and speech loss, dementia, seizures, progression to a vegetative state, and death (14). The eponym Batten disease, now associated with the juvenile form, was named for Frederick Batten, who in 1903 described the cerebral and macular changes. Speilmeyer (1908) reported on the autofluorescent lipopigments in the neurons, and Vogt (1905) added to the clinical description of these conditions. A late infantile form was described by Jansky in 1909 and Bielschowsky in 1914. Kuf recognized the adult form in 1925, and Santavuori and colleagues described an infantile form in 1973. In the early 1990s, the gene for Batten disease was mapped to chromosome 16. It is believed that the defect in the neuronal ceroid lipofuscinoses involves abnormalities of lysosomal function and at least 25 mutations and two polymorphisms have been associated with the CLN3 gene.

NEUROCUTANEOUS DISORDERS

Although the clinical features of many neurocutaneous disorders were recognized in the latter 19th and early 20th centuries, it was only recently that their structural and molecular basis began to unfold. Bielschowsky (1914) recognized the dysplastic nature and tendency to form tumors in neurofibromatosis and tuberous sclerosis, and Van der Hoeve (1923) called particular attention to these conditions, giving them the name *phakomatoses* (10). Later, Van der Hoeve included Von-Hippel Lindau disease (1932) and Sturge-Weber syndrome (1933), although it became apparent that neither had phakomata. Louis-Bar (1941) identified the condition that is now called ataxia telangiectasia.

Several important observations stand out about the neurocutaneous disorders. First was the importance of genetics in differentiating the various subtypes. From the time of von Recklinghausen's report in 1882 until recently, neurofibromatosis type 1 (NF1) and type 2 (NF2) were classified as the same disease (14). The landmark study of Crowe and colleagues in 1956 brought together the salient clinical features of NF1, including its high incidence and spontaneous mutation rate, usefulness of the café au lait spot as a diagnostic feature, and recognition of the wide range of complications (12, 14). The first recognized case of NF2 was probably that reported by Henneberg and Koch (1902). In 1930, Gardiner and Frazier reported a large kindred with NF and suggested that the bilateral acoustic neuromas represented a separate form of NF (14). By 1987, diagnostic criteria were agreed on for the clinical diagnosis of NF1 and NF2, and later, mapping and molecular cloning of the gene for NF1 to chromosome 17 (1987) and NF2 to chromosome 22 (1987) confirmed that they were separate entities. In the late 1980s, the two TSC genes for tuberous sclerosis were found: the TSC1 gene mapped to chromosome 9q34.3 (1987) and the TSC2 gene mapped to 16p13.3 (1992) (14).

A second important achievement was the recognition of genetic mechanisms of cell proliferation and suppression. The last decade has seen identification of neurofibromin in NF1 patients, a modulator of ras-mediated cell proliferation and of merlin (NF2), which has tumor-suppressor functions. Likewise, the product of the TSC1 gene (hamartin) and the TSC2 gene (tuberin) both show tumor suppressor functions. Less recognized is that the gene defect on the short arm of chromosome 3 in patients with Von Hippel-Lindau disease also behaves as a tumor suppressor gene (14). Studies of ataxia telangiectasia from the 1950s onward demonstrated the higher incidence of chromosomal breakage, increased risk of radiation sensitivity, and elevated serum alpha-fetoprotein levels. With discovery of the ataxia telangiectasia gene on chromosome 11 (1988) came an explosion of findings regarding genes coding for protein kinases involved in cell growth and cell cycle control and in oncogenesis, knowledge that has contributed greatly to the general understanding of toxic injury to cells, aging, and tumor biology.

A third finding relates to the patterns of genetic inheritance of these disorders. In a family of diseases that has expanded to include more than 150 conditions, it is now clear that neurocutaneous conditions may arise on the basis of a wide variety of mechanisms, including autosomal dominant, autosomal recessive, and x-linked conditions that may or may not be lethal to male embryos, and most recently conditions with mosaic inheritance, some of which involve genetic traits that are otherwise autosomally lethal. This last category has begun to address the puzzle concerning the unilaterality of some neurocutaneous conditions that seem to be sporadic and their involvement of tissues arising from any of the embryonic tissue layers. The genetics of a large group of neurocutaneous conditions remains uncertain.

A fourth major finding is the multisystem involvement seen in these disorders. As important was that neurologic symptoms vary dramatically. As noted, there is increasing understanding of the manner and means whereby these conditions involve not only nervous system tissues (including striated and smooth muscle) and cutaneous elements but also subcutaneous tissues, blood vessels, bone, fat, and a wide variety of other organs. It has also become apparent that seizures, learning disabilities, behavioral disorders, and mental retardation are more common and characteristic problems of many of the neurocutaneous disorders that leave a severe imprint on affected children. The progressive nature of some of these illnesses is yielding to increasing understanding and providing treatments that seem to attenuate the progression of some of these conditions.

NEUROMUSCULAR DISORDERS

Many of the most important pediatric neuromuscular disorders were reported by the end of the 19th century. The first half of the 20th century was replete with clinical descriptions and pathology of the more common disorders, which at times created more confusion than illumination. This was best exemplified when Oppenheim introduced the term *amyotonia* in 1900. Although some of his patients had spinal muscular atrophy, others did not as they showed improvement. For a long time, the term *amyotonia congenita* was used to describe all floppy infants. Once adequate myopathology developed in the 1960s, it became possible to reclassify these conditions.

Ebashi and colleagues (1959) found that serum creatine kinase determinations were a sensitive and specific indicator of some muscle diseases (15). Another advance was the develop-

ment of neurophysiology and its clinical counterpart, electromyography (3, 16). In children, these techniques were applied to the study of poliomyelitis in the 1940s, spinal muscular atrophies and other genetic myopathies and neuropathies in the 1950s and 1960s, early diagnosis of infant botulism in the 1970s, and differentiating forms of congenital myasthenic syndromes in the 1980s. Muscle histochemistry benefited from the addition of electron microscopy and enzyme histochemistry in the 1960s and 1970s.

Clearly, the greatest advances in pediatric neuromuscular diseases have been genetic. Beginning with identification of the gene for Duchenne muscular dystrophy in the late 1980s, the molecular biology of most disorders has been accomplished. Duchenne muscular dystrophy in most patients was shown to be caused by loss-of-function mutations of an extremely large gene on the X-chromosome (Xp21) and the cytoskeletal protein product of the gene, dystrophin, was found to be absent or markedly deficient (12, 14). Another major series of breakthroughs followed the discovery of the dystrophin-associated glycoproteins (*i.e.* sarcoglycans), associated with the severe childhood autosomal recessive muscular dystrophy and forms of limb-girdle muscular dystrophy (15). Also of importance was the discovery of alpha-2 laminin (*i.e.* merosin) deficiency in patients with congenital muscular dystrophy and the discovery of utrophin (1992), a protein that shared 80% homology with dystrophin. Attempts to up-regulate utrophin synthesis are being investigated as a treatment for Duchenne muscular dystrophy.

The clinical parallels between myotonic dystrophy and fragile X mental retardation had been recognized and with the finding of an expanded CGG repeat sequence in the FraX gene, the search for a trinucleotide repeat in myotonic dystrophy was soon rewarded with the discovery of a causative CTG expansion. Several studies confirmed the correlation between the size of the CTG expansion and age at onset, severity of disease, and the phenomenon of anticipation that had been described in 1918 (12).

The hereditary motor and sensory neuropathies offer another example of how genetic classifications are superseding those based on clinical description. In the 1960s and again in the 1970s, Dyck and Lambert modified earlier classifications of peripheral nerve disease on the basis of clinical findings, neuropathology, and results of nerve conduction studies. Gene abnormalities of dominant, recessive, and X-linked subtypes of the demyelinating and axonal forms of Charcot-Marie-Tooth disease have been described.

Discordance between clinical and genetic findings in children with spinal muscular atrophy (SMA) remains puzzling. The three clinical subtypes, SMA1 (onset before 6 mo), SMA2 (onset 6 to 18 mo), and SMA3 (onset after 18 mo), have been established for decades. The presence of two gene abnormalities at the 5q locus were reported in SMA patients in the early 1990s with deletion of the survival motor neuron gene at 5q13 in greater than 95% of SMA patients and deletion of the neuronal apoptosis inhibitory protein gene in approximately two thirds. However, no clear-cut relation between the SMA type and the genetic abnormalities has been established.

Several of the myotonic disorders were shown to be due to impaired ion channel function. Periodic paralysis (Westphal in 1885) and the related disorders paramyotonia congenita (Eulenberg in 1886) and myotonia congenita (Thomsen in 1876) were described more than 100 years ago (14). By the 1930s, it was evident that, in some families, episodic weakness was associated with low levels of serum potassium (1934) or with hyperkalemia (1956). During the past 30 years, the physiologic basis of these diseases has been studied, and in the past decade, the molecular pathology has been delineated. For example, autosomal dominant and recessive myotonia congenita are due to a gene defect on chromosome 7 that decreases conductance through the chloride ion channel.

Recognition that certain forms of myasthenia are due to genetic rather than acquired autoimmune disorders is another achievement of the scientific revolution of the past three decades. The earliest report of genetic forms of myasthenia was that of Rothbart (1937) and in 1948 the term *congenital myasthenia* was suggested (10). By 1972, 97 familial cases of early-onset myasthenia gravis had been collected. Using microelectrode recording techniques, Andrew Engel and colleagues at the Mayo Clinic in the 1970s and 1980s described three forms of congenital myasthenic syndromes. Since then, several additional forms have been described, and in 1996, an international workshop classified the congenital myasthenia syndromes on the basis of their genetic and clinical features (14).

FETAL AND NEONATAL NEUROLOGY

Brain development: cytogenesis and migration. The basic mechanisms and control of the processes of normal brain development were recognized in the 20th century by the cumulative efforts of a legion of developmental neurobiologists. What has emerged from these studies is the surprising degree of homology across species for regulatory genes, the overlap and interaction between different gene families, the reduction during embryogenesis in the number of neurons as a result of programmed cell death, and the finding that genetic abnormalities can result in widely known brain malformations. Also of importance is the identification of the role of cell-cell communication *via* calcium and other ionic pathways in mediating brain development and the role of neurogenic proteins, growth factors, and neurotransmitters in modifying neuronal synthesis, migration, and programmed cell death (17, 18).

Neurochemistry and energy metabolism. The pioneering studies of Dobbing and others in the 1960s showed how brain protein, lipid, cholesterol, and carbohydrate content increased regionally in association with brain maturation, myelination, and synaptic activity. Later, the deleterious effects of undernutrition on these normal developmental patterns were determined. Also elaborated were the complex metabolic pathways of amino, organic, and fatty acids; mucopolysaccharides; and glycoproteins and their roles in the development of brain function and structure. Delineation of central and peripheral neurotransmitters and their role in autonomic function, control of movement, pain, and neuropsychiatric conditions has clari-

fied the mechanisms underlying many of the subtle ways the nervous system is integrated (19).

The brain consumes disproportionate amounts of oxygen and glucose. Our understanding of the biochemistry of metabolic fuel uptake, storage, synthesis, degradation, and utilization has evolved during the past 80 years, as have the descriptions of cell organelles that serve as the factories and engines to maintain brain activity and growth.

Central blood flow (CBF). Observations at the end of the 19th and early 20th centuries that preterm and term infants could experience intracranial hemorrhage or asphyxia prompted interest in studying CBF regulation during development and in various acute disorders. Pioneering animal work in the 1970s demonstrated that CBF was much lower in the fetus and newborn compared with adults, that regional changes in blood flow were present, and that intrauterine asphyxia was associated with dramatic alterations in CBF. With the use of PET scanning, CBF was shown to increase with development reaching adult levels by 3 years of age and that regional flow differences correlated with differences in brain glucose and oxygen metabolic activity. It was later established that blood pressure autoregulation was present in the fetal and newborn cerebral circulation, although less effective than in adults, and that asphyxiated newborns could have impaired autoregulatory control.

Fetal and neonatal behavior. Systematic observations of fetal neurologic responses and behaviors began with the work of Minkowski (1921) and were later advanced by the studies of Hooker (1952), Peiper (1963), and Humphrey (1964) (4, 20, 21). Beginning in the 1930s, attempts were made to correlate these observations with neuropathology, particularly showing a relation between function and myelination. With the advent of ultrasonography (1980s), numerous studies examined the development of fetal motor activity, eye movements, heart rate, and respiration and correlated these variables with brain structure and development.

The principles of the neonatal neurologic examination were developed by André-Thomas and colleagues beginning in the 1940s (4). Changes in active and passive tone, primary or "automatic" reactions, and evaluation of numerous developmental reflexes formed the basis of standardized examinations that during the next four decades were studied intensely. The neurologic examination could be used to estimate gestational age, which allowed one to separate the appropriate- from the small-for-gestational age infant, an ability that carried important therapeutic and prognostic implications (21).

Hypoxic-ischemic encephalopathy. Scientific investigations of the contributions of the birth process to traumatic or hypoxic ischemic brain injury can be traced from the 1830s. William Little, an orthopedist, provided the most influential and elaborate consideration of these ideas (1862), including the important observation that birth-related injuries might become apparent only after a latency of several months. Various ideas concerning the cause of prenatal- and perinatal-onset brain injury, particularly as related to trauma, infection, or otherwise-determined abnormal development, were entertained during the second half of the 19th and early 20th centuries. Concern about traumatic perinatal brain injury was supported in the minds of some by the frequency with which pathologic investigation discovered extra-axial blood collections in infants who died after difficult deliveries. This concept diverted attention away from the role that Little had suggested for asphyxia as a cause of cerebral palsy and other neurologic problems (22). Windle and colleagues created a model of neonatal asphyxia in guinea pigs and Myers and coinvestigators demonstrated significant brain injury in primates. Since then, a vast amount of research has been devoted to unraveling the pathophysiology of hypoxic-ischemic encephalopathy (HIE) (17). Important strides were made to characterize the clinical syndrome of neonatal HIE. The classification scheme developed by Joseph Volpe in the 1980s combined the clinical features of neonatal HIE with neuropathology and long-term outcome (17). Apgar scores (1953) came into use as a means to diagnose HIE. Epidemiological studies as part of the National Perinatal Collaborative Study, however, demonstrated that only a small percentage of children ultimately diagnosed with cerebral palsy or mental retardation had perinatal asphyxia.

Intraventricular hemorrhage in the preterm neonate. For the first half of the 20th century, most newborns who developed intracranial hemorrhage were likely to have subdural hematomas; with the advent of modern obstetrical care, the incidence decreased dramatically. As early as 1914, Kowitz reported on 128 newborns with intraventricular hemorrhage and later Ruckensteiner and Zollner (1929) observed that intraventricular hemorrhage was commonly due to hemorrhage into subependymal germinal matrix regions. With the use of ultrasound in the 1980s, it became possible to diagnose intraventricular hemorrhage noninvasively (21). In addition to the structural immaturity of blood vessels and capillaries, alterations in CBF was a major contributing factor to rupture of the microvascular network (10).

Mechanisms of periventricular leukomalacia. Periventricular leukomalacia was first described by Virchow (1867), but it was Parrot (1873) who noted that this condition was more common in preterm infants and that immature white matter might be more susceptible to injury (21). Banker and Larroche (1962) reported on the neuropathology in 51 infants, introduced the term *periventricular leukomalacia*, and suggested a vascular cause. During the next two decades, it was suggested that hypoperfusion of certain vascular border zone regions contributed to the insult. Loss of autoregulation and the effects of endotoxins and cytokines were also believed to contribute to injury. In the 1990s, investigations by Volpe and colleagues showed a relation between periventricular leukomalacia and maturation-related injury to oligodendroglial cells.

Antenatal diagnosis of neural tube defects. Antenatal diagnosis of neural tube defects was made possible in the 1970s by the discovery that amniotic fluid levels of alpha-fetoprotein were elevated. Likewise, the value of maternal serum alpha-fetoprotein screening for neural tube defects was demonstrated (1977), as was the value of amniotic fluid measurement of acetylcholinesterase as a more sensitive indicator of the presence of neural tube defects (1989) (21).

ACQUIRED NERVOUS SYSTEM INJURIES

Cerebral palsies and their causes. Characterization of the clinical and pathologic aspects of the cerebral palsies played a major role in the development of neurology and neuroscience in the 19th century. Neuropathological studies of individuals with congenital hemiparetic cerebral palsies proved fundamental to the understanding of cerebral localization and formed a foundation on which experimental studies of cerebral anatomy and localization were designed. By the turn of the 20th century, the general classification of cerebral palsies had been filled out with the exception of ataxic varieties. This was a category that would convincingly be described in the first decades of the 20th century by individuals such as Frederick Batten and James Ramsay Hunt.

The 19th century theories of the pathology of cerebral palsies had included atrophic sclerosis, porencephaly, hypertrophic sclerosis, meningoencephalitis, encephalitis, and cortical agenesis (Freud 1897, Sachs 1887, 1892). It had become clear that cerebral palsies could be the result of pre-, peri-, or postnatal processes. The 19th century authorities had recognized the role of birth trauma in the production of neonatal brain injuries. In the early 20th century, emphasis on hemorrhagic compression of the hemispheres was reduced and appreciation of the consequences of hypoxic-ischemic injury to brain was increased (22). Traumatic cervical injury to infants produced by difficult deliveries, especially breech, had been appreciated by some observers for more than a century. The work of Ehrenfest (1922), Capon (1922), and Ford and Crothers (1926) in particular resulted in changes in obstetrical technique that rendered such injuries rare.

Pathologic investigations in the first decades of the 20th century concentrated on recognition of nerve cell injury, glial response, and sclerotic induction of developmental arrest and white matter injury, especially of prematurely born children (22). Attention was focused on the characterization of the hypoxic-ischemic aspects of parturitional encephalopathy. It was recognized that the mechanical aspects of birth injury might have, as a final common pathway, circulatory disturbances, whether through recognized methods of vascular tears and compressive hemorrhage or through much more subtle disturbances without hemorrhage.

Excitotoxic mechanisms of brain injury. The concept of excitotoxicity, that increased amounts of glutamate were injurious to the brain, originated in the 1970s. Since then, the role of glutamate toxicity has been established in a variety of acute and degenerative CNS diseases and blockade of glutamate-mediated activity has been shown to reduce hypoxic neuronal death in cell culture and in animal models of ischemic brain injury. These findings were later extended to the newborn. Effective treatments using glutamate antagonists in humans have not yet been realized.

Deleterious effects of external agents on early brain development. Many critical observations made in the 20th century showed the vulnerability of the developing nervous system to external injury. Well known since the studies of Little, Osler, Gowers, and Freud at the end of the 19th century was the injurious role of intrapartum asphyxia and birth trauma. Additionally, the harmful effects of prenatal irradiation (1928), maternal rubella (1945) and other intrauterine infections, mercury poisoning (1953), folate deficiency (1965), fetal alcohol exposure (1968), maternal smoking (1973), maternal diabetes (1979), and maternal substance abuse (1983) bear mention. In the newborn period, the deleterious effects of kernicterus were recognized as early as 1875, and in 1941, Levine proved that one could prevent kernicterus by Rh antibody testing and use of immunoglobulins. Also of importance were the effects of neonatal hypoglycemia on brain development (1967). Nutritional deprivation and lead poisoning received much attention as they affected large numbers of infants and had serious effects on brain development.

Treatment of congenital, rheumatic, and other forms of heart disease has been one of the great medical and surgical achievements of the 20th century but with recognition that neurologic injury could occur. Osler was among the great pioneers of understanding the neurologic dysfunction associated with various forms of cardiac disease of childhood onset. Before the era of corrective surgery (1950s), the effects of right-to-left shunting, cyanosis, polycythemia, and hyperviscosity led to an increased risk of stroke and brain abscess (10). The advent of cardiopulmonary bypass (1953) allowed for complete surgical repair with good outcomes in children with simple defects. In the 1970s, development of deep hypothermic circulatory arrest and low-flow bypass improved the ability to surgically repair complex lesions in younger infants with much greater safety margins.

A major public health problem, nonaccidental brain injury, became prominent in the latter half of the 20th century. Recognized by Tardieu as early as 1860, it was the report of Caffey (1946) of six infants with subdural hematomas and long bone fractures that ultimately led to the more complete description of the battered child syndrome by Kempe in 1962 (10, 23). The advent of neuroimaging in the past two decades has made diagnosis of this condition easier and allowed characterization of the multiple types of brain injuries

Inflammatory demyelinating diseases of the central nervous system (CNS) and peripheral nervous system (PNS). The first evidence that immune responses could play a role in human neurologic disease emerged more than a century ago, when some patients receiving injections of Pasteur's new rabies vaccine were observed to develop paralytic encephalomyelitis. These observations gave rise in the 1930s to careful experimental pathologic investigations with particular relevance to transverse myelitis (24). The postinfectious vulnerability of central and peripheral nervous tissues to demyelination was recognized by pathologists in the 1880s. Tremendous advances in the pathologic characterization of inflammatory demyelinating brain diseases of children and adolescents were achieved in the second and especially the third decade of the 20th Century. Excepting diphteritic polyneuropathy, similar advances in the pathologic consideration of inflammatory demyelinating conditions of the peripheral nerve did not occur until after World War II. This was followed early in this century by attempts to determine specific brain antigens and later by development of autoimmune animal models of disease including experimental allergic encephalomyelitis (1932), neu-

ritis (1955), myositis (1965), myasthenia gravis (1973), and motor neuron disease (1986).

Although numerous reports of children and adolescents with postinfectious encephalopathies and paralyses are to be found in the medical literature from the late 19th century, it was not until the 1920s that it was noted that a subset of these conditions bore a strong pathologic resemblance to multiple sclerosis. The term in most common usage is acute disseminated encephalomyelitis (ADEM); the characteristic pathologic change is perivenular inflammatory demyelination. Acute perivenular demyelination in association with hemorrhage described in 1943 and designated acute hemorrhagic leukoencephalitis, has on the basis of experimental pathologic studies been regarded as a hyperacute form of ADEM. Several additional acute demyelinating illnesses, described early in the late 19th and early 20th centuries, occupy positions that are in many ways intermediate between multiple sclerosis and ADEM. The borders between multiple sclerosis, ADEM, and these conditions constituted an area of careful investigation in the mid-20th century.

Other notable advances have been made in several pediatric neuroimmunologic disorders. Since the 1950s, the relation between group A beta-hemolytic streptococcal infection, rheumatic fever, Sydenham chorea, and antibodies against the caudate and subthalamic nuclei has been appreciated. Over time, this led to the suggestion that some children who had other neuropsychiatric problems, obsessive-compulsive behavior, and tics with laboratory confirmation of antecedent streptococcal infection might have a neuroimmunologic disorder termed *PANDAS* (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection).

NEUROCOGNITIVE AND BEHAVIORAL DISORDERS

The 20th century saw explosive growth in the study of the mind with contributions from many medical and social science disciplines. A natural byproduct of this new science was an interest in how cognition and behavior developed in children under normal as well as abnormal circumstances. It also was influenced by other trends in pediatrics and neurology at the end of the 19th century in which there was an interest in the so-called "functional" rather than "organic" diseases of the nervous system (4). A century later, the organic bases of many of these functional disorders are now being elucidated.

Mental retardation. Although mental retardation has been recognized since biblical times, the 20th century saw important advances (25). Development of psychological testing and the discipline of psychology, and scientific investigation into developing definitions of mental retardation and determining its cause were critical (25). Introduction of the Binet-Simon test for children (1905), introduction of the term *intelligence quotient* (IQ) by Terman (1916), and the work of Thurston describing factors of intelligence (1938) all led to an explosion of developmental and psychological test instruments that examined virtually all aspects of infant and childhood development. The first edition of the Diagnostic and Statistical Manual (1952) statistically defined categories of mental retardation delineated by IQ level. In 1992, The American Association on Mental Deficiency published a definition that included not only subaverage intellect but also related limitations in two or more adaptive skill areas (10). By the end of the 20th century, the ability of a physician to diagnose the cause of mental retardation in an individual had increased dramatically. Currently, a specific cause can be determined in up to 60% of children with developmental delay.

Attention-deficit/hyperactivity disorder. The concept of attention-deficit disorder can be traced to the early 20th century to what Still (1902) termed *morbid defects in moral control* (10, 14). In the 1930s and 1940s, Strauss and associates described hyperactivity, distractibility, emotional lability, and perseveration in a group of survivors of the 1918–1919 epidemic of encephalitis lethargica. It was suggested that children who demonstrated these behaviors were brain damaged even when there was no visible injury (1955). This concept of minimal brain damage persisted until the 1960s, when it gave way to the concept, developed by Clements, of minimal brain dysfunction (14, 26). During the 1970s, criteria for attention-deficit/hyperactivity disorder (ADHD) were established and centered on the specific core symptoms of inattention, impulsivity, and hyperactivity. This was followed by the recognition of several coexisting features seen in children with ADHD, including learning disabilities, comorbid neuropsychiatric disorders, and tics. Advances have been made in understanding the possible role of neurotransmitters, particularly the central monoamines, specific gene abnormalities in certain patients with ADHD, and recently the use of PET scanning and functional magnetic resonance imaging (MRI) to examine brain metabolic activity. Molecular biologic clues in the past decade have also suggested that the dopamine transporter gene on chromosome 5 and the dopamine D2 receptor gene on chromosome 11 might be implicated in ADHD (26). All of this has occurred in an era since the mid-part of the century, of somewhat controversial pharmacologic treatments of ADHD, beginning with the use of d-amphetamine (1937), methylphenidate (1960s), pemoline (1960s), and mixed amphetamines (1996) in conjunction with educational and psychological therapies (27).

Learning disabilities. The term *word blindness* was used by Kussmaul in 1877 to describe the acquired loss of reading skills in adults who developed aphasia and who at autopsy had left hemispheric brain lesions (26). In 1896, Morgan described congenital word blindness, and in 1917, the ophthalmologist James Hinshelwood published a monograph on the same subject (4). Samuel Orton's *Reading, Writing and Speech Problems in Children* was a major medically oriented contribution to the topic of learning disabilities (4). At the same time, psychological studies by Burt (1937) and Schonell (1942) began to categorize children's abilities and their achievement based on IQ testing (26). What followed during the remainder of the 20th century were thousands of studies from many disciplines to develop a definition and criteria for the diagnosis of learning disabilities; to differentiate children with learning disabilities from other neurodevelopmental and psychiatric conditions; to determine the biologic basis of learning disabilities; and to examine the effects of educational, behavioral, and pharmacologic therapies. New technologies such as functional

MRI are beginning to help localize areas of brain dysfunction associated with dyslexia and other learning disabilities. A recent review by Whitmore and Bax (26) provides an in-depth discussion of the fascinating and complex evolution of ideas related to this subject.

Language disorders. The first account of a developmental language disorder or "developmental dysphasia" was published in 1853 by William Wilde, an otologist who commented on children who were "dumb but not deaf" (28). Until the 1940s, developmental language disorders were considered to be due only to emotional disorders. This changed with the work of Orton, who hypothesized a neurologic basis for many of the cognitive developmental disorders, including those of language development (4). Much work was done in the 1950s and 1960s that provided a theoretical framework for future studies, including the cause and pathogenesis of developmental language disorders. This included studies on the normal development of language across many cultures, influence of the family and the environment on early language development, and attempts to determine whether language hemispheric organization changed with development. Attempts were also made to compare the classical motor (Broca) and sensory (Wernicke) aphasias of adults with their childhood counterparts. As neuroimaging became available in the 1970s, investigations of brain-injured neonates and children were carried out to examine issues of developmental plasticity and language functional reorganization. Attempts were also made to reclassify these developmental language disorders (*e.g.* mixed expressive/receptive, predominantly expressive, higher-order processing disorders) (10).

Tourette syndrome. Gilles de la Tourette's 1885 paper first described this disorder (4). Early in the 20th century, it was hypothesized that Tourette syndrome likely was due to psychiatric causes (29). Once striatal lesions were tenatively identified (1954), and first chlorpromazine (1957) and then haloperidol was successfully introduced to treat tics (1961), emphasis gradually shifted toward the search for an organic cause and other forms of psychopharmacologic treatment. Other advances in the past several decades have included the development of specific criteria for Tourette syndrome (1993), differentiating Tourette syndrome from other tic and nervous system disorders, recognition of the role of dopaminergic pathways in producing tics, defining common coexisting features, developing models of genetic inheritance, and more recently demonstrating a potential immunologic basis with basal ganglia involvement.

Autism and related disorders. In 1943, Kanner first described a syndrome of "autistic disturbances" with case histories of 11 children who shared previously unreported patterns of behavior, including social remoteness, obsessiveness, stereotypy, and echolalia (10). Autism was first considered a form of psychosis, but by the 1970s, several research groups had formulated diagnostic criteria for this disorder and the term *pervasive developmental disorders* was used. Under pervasive developmental disorders, diagnoses included infantile autism (with onset before age 30 mo) and childhood-onset pervasive developmental disorder (with onset after age 30 mo). Autism was also differentiated from childhood schizophrenia and other psychoses.

The past three decades have seen intensive research concerning the biologic basis of autism with evidence of increased blood serotonin levels (1961), abnormalities in dopamine metabolism (1978) and in the endogenous opioid system (1978). Identical twin studies (1977) showed higher concordance risks for autism, and family studies demonstrated greater risks for behavioral and cognitive symptoms in first-degree relatives. Autistic features have been shown to occur more frequently in inherited disorders such as the tuberous sclerosis complex, fragile-X syndrome (1985), Down syndrome, untreated phenylketonuria (1967), and several chromosomal abnormalities (*e.g.* duplication of the proximal arm of chromosome 15). Despite several early reports of smaller cerebellar vermian lobules using volumetric MRI and different regional cortical abnormalities, no consistent or reproducible changes have been found.

Brain death and the vegetative state. Since the mid-20th century, descriptions of several entities encompassing severely altered states of consciousness have proved to be clinically useful. The concept of brain death was first proposed by Mollaret and Goulon (1959), but it was not until the publication of clinical guidelines (Harvard criteria, 1968) that this alternative to cardiac death was accepted (10). Two decades later, consensus pediatric brain death guidelines were published (1987). The concept of the vegetative state was introduced in 1972 to describe patients with "eyes open" coma who had lost all awareness of self and the environment. By 1994, specific criteria were developed to diagnose this condition, and much has been learned about its epidemiology and prognosis (10).

Psychopharmacologic treatment of neuropsychiatric disorders. The "modern" era of pediatric psychopharmacology, by most accounts, began in 1937, when Bradley reported on the effects of administering amphetamine sulfate to children with various behavioral disturbances (30, 31). Since then, there has been significant growth in the field of pediatric psychopharmacology. Research in the field has been hampered by ethical constraints in performing studies in children. What has emerged from these studies is that reactions to medications are different in children and there is a need to do careful pharmacological studies in neonates, infants, and older children. Excellent historical overviews have been provided by Weiner and Jaffe in 1985 (32) and by Weinberg and colleagues in 1998 (27).

NEUROONCOLOGY

The remarkable advances in the study of childhood brain tumors can be traced to the studies of Bailey and Cushing (1926), who based their classification of brain tumors on the embryological origin of tumor cell type (4, 33) and to the pioneering monograph on infantile and childhood brain tumors by Bailey. Buchanan and Bucy (1939). Kernohan and colleagues (1949) modified the Bailey schema and also introduced tumor grading for estimating prognosis. The advent of computed tomography in the 1970s, MRI in the 1980s, and single-

photon emission computed tomography, magnetic resonance spectroscopy, and functional MRI in the 1990s allowed exquisite preoperative localization and determination of the extent of disease (34). The importance of new immunohistochemical stains, monoclonal antibodies, and flow cytometry to determine DNA content, and genetic marker techniques combined with conventional neuropathology have allowed reclassification and better delineation of tumor cell subtypes as well as recognition of new childhood tumors. Also appreciated is that childhood tumors differ from those of adults in many respects.

Recognition that certain hereditary diseases (*e.g.* neurofibromatosis, tuberous sclerosis) have an increased risk for tumors has led to the discovery of disease-specific tumor suppressor genes. Likewise, the genetic basis for tumor risk in patients with certain inherited immunosuppressive diseases (*e.g.* Wiskott-Aldrich syndrome, ataxia telangiectasia) is now established. It has recently been recognized that abnormalities of the p53 tumor suppressor gene on chromosome 17 (medulloblastoma) and chromosome 13 (retinoblastoma) increase tumor risk.

For many childhood brain tumors, the outlook for long-term survival has improved dramatically. Approximately 85% of children with medulloblastomas survive, as do up to 70% of children with low-grade gliomas. Treatment in the 20th century followed three sequential and ultimately integrated approaches: surgery, radiation, and chemotherapy (10).

Although earlier reports of surgical excision of brain tumors exist, MacEwen (1879) is believed to have removed the first dural tumor from a teenage girl (35). The first brain tumor was removed by Godlee in 1884, and the first spinal cord tumor was removed by Horsley in 1888. In large case studies, Cushing demonstrated that children with medulloblastomas (1930) and cerebellar astrocytomas (1931) were amenable to surgical treatment. Publication in 1926 of his report on 154 patients demonstrated the high incidence of gliomas in children as well as their more common location in the posterior fossa. With better surgical techniques, use of stereotactic surgery (1953), and tumor reconstructive approaches with three-dimensional CT and MRI technologies, results from surgery continue to improve.

As early as 1928, it was shown that radiation could improve survival in children with medulloblastoma, and by 1953, there was good evidence that radiotherapy could result in complete cure. In 1969, the value of prophylactic craniospinal radiation was demonstrated. Whereas the 1960s and 1970s emphasized improved survival, direction shifted in the 1980s and 1990s to balance between improved survival *versus* reducing neurotoxicity. Watchful waiting and serial neuroimaging replaced early treatment in patients with low-grade tumors. Reduction in radiation volume and dosing and, in younger patients, use of chemotherapy rather than radiation protocols were implemented.

Chemotherapy developed in the 1940s when drugs such as nitrogen mustard, the folic acid antagonists, and cortisone were discovered to have specific tumoricidal effects. In the following decade more than 20,000 agents were studied for their potential use. Although it is recognized that surgery and radiation for children with medulloblastoma have greatly improved survival, use of intrathecal methotrexate and intravenous vincristine (1960s) and alkylating agents (1970s) has suggested the potential additive benefit of chemotherapy.

CNS INFECTIONS

The transmissible and epidemic features of some febrile illnesses with neurologic consequences have been recognized since ancient times. Sydenham chorea was described in the 17th century. At the end of the 18th century, poliomyelitis was recognized to be a discrete illness. Febrile seizures were described shortly thereafter, although the clinical significance of prolonged seizures in the setting of meningoencephalitic illnesses would not be worked out until the end of the 19th century. Pasteur established the efficacy of postexposure vaccination in the treatment of rabies. The complicating postvaccinial myelitis and encephalomyelitis that the vaccine occasionally provoked formed one important foundation stone for the understanding of inflammatory demyelinating illnesses of the CNS.

By the end of the 19th century, many exanthematous illnesses with neurologic manifestations had been distinguished on the basis of clinical observations. The association between Sydenham chorea and cardiac disease was appreciated in the early 20th century. Guillain-Barré syndrome was convincingly set apart from poliomyelitis, providing a critical example of the importance of the newly developed lumbar puncture for the diagnosis of inflammatory or infectious diseases of the nervous system. The virus and vector of a particularly widespread and devastating encephalitis endemic in Asia (Japanese encephalitis) was identified between the world wars. The viruses causing the major arboviral encephalitides were found during the 20th century, the last great group of which were the California viruses in 1943.

Studies recognizing the importance of acute meningoencephalitic and severe acute (ADEM) and long-term (subacute sclerosing encephalitis) as postinfectious neurologic complications of measles were initiated in the 1930s. Gregg's astute observations in 1941 led to the appreciation of the devastating consequences that maternal rubella has on the fetus. Development of a vaccine against this agent in 1969 has prevented as many as 30,000 stillbirths and the birth of as many as 20,000 neurologically impaired children each year throughout the world.

Based particularly on the work of Enders, vaccines were developed for many of the most important of these devastating viral neurologic illnesses. Polio vaccine was the first of these, developed at the very height of the epidemic evolution of this illness, with as many as 55 000 cases of paralytic poliomyelitis each year in the United States, a number that was very promptly reduced to less than 100 per year in the 1960s and less than 10 per year, mostly induced by attenuated vaccine strains, in the 1990s. Continued progress in the development of vaccines has provided the industrialized parts of the world with an effective vaccine for *Haemophilus influenza*, which has led to a 70–90% reduction in meningitis caused by this organism.

Herpes simplex encephalitis was first recognized in 1926. Increasingly effective therapy has been provided for nonneonatal cases, and preventive strategies such as cesarean delivery have

been applied to prevention of the severe neonatal variety. Despite this, the outlook for the neonatal form remains dismal. Additional forms of herpesvirus would be identified through the 1990s, including herpes hominis virus and its role in febrile seizures and pseudotumor of infants. The potential role of viruses such as cytomegalovirus in intrauterine brain injury was first entertained in 1904. The association of cytomegalovirus and the devastating neurotropism of this virus for the developing brain have been the subject of considerable study since the 1950s. The neurologic consequences of infection with Ebstein-Barr virus were characterized between the 1940s and 1980s as were the encephalitogenic properties of mycoplasma.

Guillain-Barré syndrome was first characterized between 1892 and 1916. Increasingly varied antecedents have been recognized, other epidemiologic aspects have been clarified, and between 1986 and 1993 the axonal and chronic varieties that had generated confusion in treatment trials were set apart. The advent of intravenous immunoglobulin therapy has evidently improved the rate of recovery and replaced other less efficacious or less convenient forms of therapy.

At the close of the 20th century, mortality remained high for tuberculosis; malaria; meningitis caused by meningococcus, pneumococcus, cryptococcus, and Gram-negative organisms; tetanus; rabies; AIDS; and many viral, fungal, and parasitic illnesses that manifest themselves so readily in immunosuppressed individuals. Together with the advent of AIDS has occurred an increasing prevalence of cytomegalovirus infection of the developing brain. Arboviral encephalitides are on the increase in wide areas of the world as a result of the evolution of mosquito resistance to chemicals developed for their eradication as well as to agricultural and industrial practices favorable to the mosquito.

NUTRITIONAL DISORDERS, VITAMIN DEFICIENCY, AND HORMONAL AND METABOLIC DISEASES

Realization that the developing brain required adequate nutrition for proper growth received much attention in the 20th century. Studies in the 1920s established the normal fluid and electrolyte needs of infants and proved that the major complications of infantile gastroenteritis were due to acidosis and dehydration. This stimulated fluid replacement therapies that saved countless lives and prevented brain injury from dehydration and electrolyte imbalance. By the 1960s, the effects of specific electrolyte abnormalities on the nervous system were better understood, and remedies to minimize long-term brain injury were advocated. A better understanding was achieved of dietary protein, carbohydrate, and fat requirements to ensure appropriate body and brain growth. The advent of newborn screening programs and the early diagnosis of inborn errors of metabolism led to development of specifically designed formulas to treat affected children.

The importance of vitamins as cofactors for many enzymatic reactions in the developing nervous system were described in the first half of the 20th century, as were the benefits of vitamin replacement. Pyridoxine dependence, an autosomal recessive disorder presenting with neonatal seizures that could be treated with pharmacologic amounts of pyridoxine (1954) as well as pyridoxine deficiency states in infants fed formulas deficient in pyridoxine (1954), were recognized and treated. Likewise, supplementation with thiamine (certain forms of lactic acidosis, maple syrup urine disease), folate (reduction of neural tube defects), riboflavin (forms of glutaric acidemia), cobalamin (methylmalonic acidemia, deficiency states, etc.), vitamins A and E (neuropathy, ataxia syndromes), and biotin (propionic acidemia, biotinidase deficiency, multiple carboxylase deficiency) were among many vitamin deficiency or dependency conditions in which vitamin supplementation had a significant positive impact.

Thyroxin was isolated in 1913 and desiccated thyroxin was used soon after to treat cretinism. During the next several decades, many of the remaining hormones were described, as were their effects on somatic and brain growth. The syndrome of inappropriate antidiuretic hormone secretion was recognized (1967), as were specific treatment paradigms. Likewise when diabetes insipidus occurred in conjunction with trauma, surgery, or CNS tumor, replacement therapy was available. Of importance was the recognition that certain neurologic syndromes could be associated with endocrine abnormalities and would require hormone supplementation. Likewise, the central and peripheral nervous system complications of many of the endocrine disorders were established. With some conditions, neurologic concerns were the initial symptom. There also has been evidence to suggest that susceptibility to certain forms of epilepsy (*i.e.* infantile spasms) may be related to specific hypothalamic hormones such as corticotrophin releasing hormone.

A variety of dietary and enzyme replacement therapies have been used to treat many of the neurometabolic disorders. These range from dietary therapy of phenylketonuria, enzyme replacement for storage disease (*e.g.* α-glucerase for Gaucher disease), and bone marrow transplantation for neuronopathic (type III) Gaucher disease and other lipid storage diseases. The compendium by Scriver *et al.* (12) should be consulted for in-depth discussion.

Advances in molecular genetics have had a profound impact on neurology, particularly child neurology, so it is to be expected that research in molecular biology will lead to effective treatment strategies that emerged at the end of the 20th century (14). Attempts at using various retroviral vectors "carriers" for missing genetic constituents have been used experimentally in the past decade in animal models and in some affected children and young adults with the following severe nervous system diseases: tetrahydrobiopterin deficiency, adrenoleukodystrophy, many of the lysosomal storage disorders, ornithine transcarbamylase deficiency, Lesch-Nyhan syndrome, and Canavan disease. It is possibly only a question of time before genetic strategies will be implemented to treat Rett syndrome or the trinucleotide repeats disorders, which cause some of the most debilitating forms of childhood neurologic disorders. Likewise, the use of multipotent neural progenitor stem cells to express specific genes whose products would supply deficient cells may be on the horizon for treatment of some of these disorders.

CONCLUSIONS

The 20th century concluded with the "Decade of the Brain," and as this brief survey suggests, it is remarkable to reflect on the advances in pediatrics, neurology, and child neurology. One hundred years ago, pediatrics was in its infancy, neurology was just beginning to declare its separateness from psychiatry and medicine, and child neurology was a gleam in the eyes of a few physicians. Today all three disciplines have grown and matured, and the scientific advances have been extraordinary with new discoveries announced at an ever-accelerating pace. Through all of these changes, child neurology has remained as a unique merger of its two parent disciplines.

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