Volpe's Neurology of the Newborn

Sixth Edition

JOSEPH J. VOLPE

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To my wife,
Sara,
for her love and understanding,
without which this book would not be possible

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Preface to the Sixth Edition

In the preface to the first edition of this book, published more than 35 years ago, I expressed the view that the neurology of the newborn "should be viewed as a discipline in its own right." Over the decades, through four subsequent editions, the evolution of this discipline has been extraordinary. Work relevant to neonatal neurology now is abundant in clinical journals in the fields of pediatrics, neurology, neonatology, perinatology, and obstetrics, among others, and in multiple scientific journals of the many neurobiological disciplines. The explosion of information in the field led me to conclude several years ago that single authorship is no longer feasible, especially if the quality of the book is to be at the highest level. With the prompting of Kate Dimock and others of the Elsevier team, I decided to embark on a multiauthored effort. Thus this edition has been updated and revised with remarkable efforts from 5 editors and 12 additional authors. The editors and authors are particularly meaningful to me because they are former trainees, current colleagues, or both. They are truly experts and in this edition have tolerated my compulsive editing and sometimes incessant suggestions for each chapter. In addition to their great skills as scholars, they have proven to be markedly resilient and tolerant of my often intrusive role in each chapter.

The organization of the sixth edition is identical to that of previous editions. However, in addition to extensive updating, revising, and rewriting, many original chapters have been split into multiple chapters. The first eight chapters constitute the unit on human brain development, which were previously contained in two chapters. Particular expansion of this unit reflects new insights into the neurobiology of brain development, fetal diagnosis, intrauterine interventions, and molecular genetics. A major expansion of the discussion of brain organizational events of the third trimester of gestation was undertaken to accommodate the explosion of brain information from advanced neuroimaging of normal cerebral cortical and white matter development and derangements thereof in the human premature infant. Unit II, concerning the neurological evaluation, was expanded to describe new methodologies, especially advanced MRI techniques, to study the newborn brain. A new chapter on neurodevelopmental follow-up was added to this unit. My longstanding devotion to the neurological examination and the importance thereof is reflected in its own dedicated chapter. Unit III, which focuses on neonatal seizures, serves as an effective bridge between the initial chapters and the later, diseased-focused chapters because neonatal seizure is a key manifestation of many of the neurological disorders dealt with later in the book. The discussion of neonatal seizures reflects the impact of new neurobiological insights (e.g., chloride channels, GABA excitation) and their importance for understanding the newborn's propensity to seizures, the impact on subsequent brain development, and the effects of anticonvulsant medications. Unit IV, concerned with hypoxic-ischemic and related disorders, the largest unit of the book, was increased from four to nine chapters. The principal changes involved separation of the discussions of the preterm and term infant because the etiologies, neuropathology, pathophysiology, and clinical features exhibit many differences and unique aspects. The chapters on neuropathology, especially, reflect new insights gained by application of advanced neuropathological techniques, those on pathophysiology, the impact of many relevant neurobiological and clinical research studies, and those on clinical features, the knowledge gained from advanced neuroimaging and the remarkable advances in therapeutic interventions. Unit V, concerned with intracranial hemorrhage, includes a separate chapter on cerebellar hemorrhage and the impact thereof on cognitive and related outcomes. The chapter on intraventricular hemorrhage and posthemorrhagic hydrocephalus in the preterm infant expands on previous discussions, especially of management, that are based on recent clinical investigations. Unit VI, concerned with metabolic encephalopathies, includes insights from clinical and basic research into hypoglycemia and hyperbilirubinemia, particularly management thereof, as well as important updates on neonatal amino acid and organic acid disorders. Unit VII is a single chapter on degenerative disorders, specifically those that present clinically in the newborn period. Insights obtained from recent studies of molecular genetics, clinical features, and novel interventions are emphasized. Unit VIII, which covers neuromuscular disorders, has been expanded to four chapters, with a new chapter on arthrogryposis. These chapters reflect the enormous advances in this field in delineation of phenotypes, diagnosis, and interventions. The roles of molecular genetics in disease characterization and gene manipulation therapies in interventions are among the new areas of emphasis in neuromuscular disorders. Unit IX, which covers intracranial infections, remains as two chapters, but they have been expanded considerably. Important insights provided by modern neuroimaging and the advent of new therapies are emphasized. Unit X, which is on perinatal trauma, remains a single chapter about injuries of extracranial, cranial, intracranial, spinal cord, and peripheral nervous system structures, expanded by insights obtained from modern neuroimaging. Unit XI, which is about intracranial mass lesions, includes a chapter on brain tumors and vein of Galen malformations that provides new insights into molecular characterization of tumors, clinical features, and advances in management. Unit XII, which covers drugs and the developing nervous system, remains a single chapter, with particularly new insights into clinical features and treatment. The impact of recent surges in opioid abuse and the effects on the newborn are among the areas of special emphasis.

Concerning the specific editors and authors who contributed to the sixth edition of *Volpe's Neurology of the Newborn,* the critical first unit, as noted earlier, was expanded from two to eight chapters. The first four of these chapters were updated and revised by one of my first neonatal neurology fellows at

Washington University in St. Louis and later a faculty member in neonatal neurology with me in Boston, Dr. Adré du Plessis, who has developed especial expertise in disorders of neural tube formation, prosencephalic development, fetal ventriculomegaly, and cerebellar development and the clinical impact of defects thereof. Dr. Annapurna Poduri, a child neurology resident and later member of the faculty in the Department of Neurology that I led at Boston Children's Hospital, is an accomplished expert in cerebral cortical development, especially proliferative and migrational defects, and genetic disorders thereof. Dr. Hannah Kinney, a distinguished neuropathologist and my longtime colleague at Boston Children's Hospital, is a pioneer in the application of advanced neuropathological techniques to the study of organizational events and myelination of the brain, especially premature and early infant brain.

Particularly involved in the update/revision of Unit II was Dr. Jeffrey Neil, a former child neurology resident and fellow during my years at Washington University in St. Louis. Dr. Neil, who is now a colleague in Neurology at Boston Children's Hospital, is internationally recognized for his expertise and innovation in advanced MR methodologies, especially as applied to premature infants. The only new chapter in the book, which is on neurodevelopmental follow-up, was prepared by Dr. Petra Huppi, a neonatal neurology fellow with me in Boston at the turn of the century when she carried out pioneering research on the application of MR methodologies to the study of the premature brain and who is currently a leading figure in neurodevelopment, and by Dr. Lianne Woodward, an esteemed colleague in the Department of Pediatric Newborn Medicine at Harvard Medical School.

Especially involved in the update/revision of Unit III was a former colleague in my Department of Neurology at Boston Children's Hospital, Dr. Frances Jensen (currently Chair of Neurology at the University of Pennsylvania). Her work on the pathophysiology of neonatal seizures has been seminal. Her colleague, also formerly with us in Boston, Dr. Nicholas Abend, contributed importantly to the update. Dr. Terrie Inder (see later) my former trainee and current colleague, also contributed in a major way to this chapter.

Unit IV, the largest unit of the book, now includes nine chapters. The update/revisions were led by Dr. Inder (see later), Dr. Kinney, Dr. Neil, and Dr. Back. The first three are current colleagues in Boston, and Dr. Stephen Back, currently at Oregon Health Sciences University, was a former child neurology resident and postdoctoral fellow with us at Boston Children's Hospital. He is now recognized as a world leader in the pathophysiology of brain injury in the premature infant. Exceptional expertise also is apparent in relation to clinical features (Dr. Inder), neuroimaging (Dr. Neil), and neuropathology (Dr. Kinney).

Unit V includes major efforts by Dr. Terrie Inder (see later), Dr. Catherine Limperopoulos, and Dr. Jeff Perlman (see later). Dr. Limperopoulos was a fellow in neonatal neurology in my Department of Neurology at Boston Children's Hospital, when I had the privilege of working with her during her initial work on the developing cerebellum. She has established her own program at George Washington University and has developed greatly her widely recognized research in the study of the cerebellum.

The four-chapter Unit VI was updated by Dr. Jeffrey Perlman. Dr. Perlman was my first fellow in neonatal neurology (then at Washington University in St. Louis) and as a brilliant clinician and clinical investigator taught me a great deal about the critical nonneurological aspects of the sick newborn and the importance thereof in the genesis of neurological illness. Over the years he has been an admired colleague who now leads a major neonatology program at Cornell University in New York.

Unit VII was updated with the help of Dr. Christopher Elitt, a fellow in neonatal neurology with me at Boston Children's Hospital and now a junior faculty member here. The final product in this important area reflects his strong background in neuroscience and molecular genetics and his ability to tolerate my incessant critiquing of his generally fine work in updating this chapter.

Unit VIII was updated and revised by Dr. Basil Darras, my closest colleague at Boston Children's Hospital during my tenure as Chair of Neurology from 1990–2005. I am especially proud that he holds a Neurology Chair in my name. He remains an esteemed colleague and a trusted friend. His stature in the neuromuscular field is recognized internationally and is reflected in part by his leading role in the outstanding book *Neuromuscular Disorders of Infancy, Childhood and Adolescence*.

Unit IX on intracranial infections, constituting two chapters, was updated by Dr. Linda de Vries. She is an admired leader in our field, with whom I have had the privilege of previously coauthoring. Her great expertise in neuroimaging and all aspects of clinical research in neonatal neurology is reflected in the two chapters.

Unit XI is a single chapter that was greatly enriched by the work of my former colleague at Boston Children's Hospital, Dr. Shenandoah (Dody) Robinson. As a leading pediatric neurosurgeon, she enhanced the chapter with new insights into surgical approaches and results, as well as molecular aspects of tumor classification and clinical characteristics.

The final unit consists of a single chapter updated by Dr. Lianne Woodward and Dr. Christopher McPherson. The latter, a particular expert on the pharmacology of drugs in the developing fetus and newborn, was a colleague during his recent period on the faculty in Pediatric Newborn Medicine at the Brigham and Women's Hospital.

Particular recognition should be accorded to Dr. Terrie Inder who has authored/coauthored multiple chapters and, importantly, has interacted copiously with Elsevier concerning myriad details involved in generating a finished product. After completing her training in neonatology in New Zealand, Terrie trained with me in Boston in the late 1990s as a resident in child neurology and then as a fellow in neonatal neurology. During that period she spearheaded seminal studies of preterm brain by advanced MR techniques, which she used also in subsequent years with distinguished academic positions in New Zealand, Australia, and St. Louis and finally as Chair of Pediatric Newborn Medicine here (Brigham and Women's Hospital and Harvard Medical School).

My colleagues in this undertaking have been aided immeasurably by many people. My assistant for the past 25 years, Irene Miller, typed manuscripts, prepared tables, manipulated thousands of references, checked and double-checked table and figure numbering, and tolerated my obsessive pursuit of perfection, as she has over three previous editions of this book. Shaye Moore, leader of the Medical Writing Team of

the Department of Neurology, dealt with such complex issues of digital manuscript preparation (multiplied by 38 chapters), that I cannot begin to understand or explain. No challenge was too great for her to confront and overcome. The Elsevier team, particularly Kate Dimock and Janice Gaillard, struck a remarkable balance of guidance, patience, efficiency, and implementation in bringing this project to fruition. All the editors and authors agree that we could not have had a better publishing group.

Joseph J. Volpe, MD
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Preface to the First Edition

The neurology of the newborn is a topic of major importance because of the preeminence of neurological disorders in neonatology today. The advent of modern perinatal medicine, accompanied by striking improvements in obstetrical and neonatal care, has changed the spectrum of neonatal disease drastically. Many previously dreaded disorders such as respiratory disease have been controlled to a major degree. At the same time, certain beneficial results of improved care, for example, markedly decreased mortality rates for premature infants, have been accompanied by neurological disorders that would not have had time to evolve in past years.

This major importance of neonatal neurological disease has stimulated efforts by workers in many disciplines to recognize, understand, treat, and ultimately prevent such disease. This book is an attempt to bring together the knowledge gained from these efforts and to present my current understanding of the neurology of the newborn. Because of the diversity of knowledge that I have attempted to bring to bear upon the problems discussed in this book, I may have oversimplified in certain areas and displayed my own ignorance in others. Nevertheless, I have written the material in the hope that it will be of value to all health professionals involved in the care and follow-up of the newborn infant with neurological disease.

The prime focus of the discussions of neonatal neurological disease throughout this book is the clinical evaluation of the infant, that is, what we can learn from observation of the setting and mode of presentation of the disease and the disturbances of neurological function apparent on careful examination. The theme that recurs most often is that careful clinical assessment, in the traditional sense, is the prerequisite and the essential foundation for understanding the neurological disorders of the newborn. The infant does not advertise his or her neurological disorder with the drama that older children and adults exhibit, but with patience and diligence we can discover a treasure of important clinical clues when we elicit a complete history and perform a careful physical examination. It is this quality of discovery with simple techniques that has made the neurology of the newborn so stimulating for me, and I hope that this book can lead the reader to similar discoveries.

With accomplishment of the essential first step of definition of the clinical problem, we can turn in a rational way to the increasingly sophisticated means of studying the infant's deranged neural structure and function. Although my emphasis is, first, on the simplest and least invasive techniques for providing us with the necessary information, we are in an era when sophisticated and informative procedures such as imaging the brain itself can be done in a safe and effective way.

The final process in our understanding the infant with a neurological disorder requires an awareness of a burgeoning corpus of information derived from studies in human and experimental pathology, physiology, biochemistry, and related fields. Of necessity, often we must extrapolate to our newborn patient data obtained from animals. Such extrapolation must always be made cautiously, and yet we cannot ignore the many lessons learned from the laboratory that have proved invaluable in our understanding of neonatal neurological disease. In this book, on the one hand, I attempt to synthesize in a comprehensible manner relevant material from a diversity of disciplines and, on the other hand, try very hard not to oversimplify what are clearly very complex issues.

I believe that the neurology of the newborn has come of age and, indeed, should be viewed as a discipline in its own right. I hope that in some way this book will contribute to establishing that status. My most fervent hope is that this discipline excites the interests and efforts of others concerned with the neonatal patient and that, through concerted actions, the greatest possible benefits accrue to the infant with neurological disease.

Joseph J. Volpe, MD

Acknowledgments

It is with pleasure and eagerness that I acknowledge with gratitude the help of so many over the years. I am grateful to Dr. Raymond Adams, who introduced me to neurology and neuropathology and provided a model of scholarship in medicine that I have since striven to achieve; to Dr. C. Miller Fisher, who taught me the inestimable value of looking carefully at the patient and never denying observations that did not fit preconceived notions; and Dr. E. P. Richardson, Jr., who taught me neuropathology and provided a framework for study on which I remain dependent.

I owe enormous gratitude to Dr. Philip Dodge, who stimulated me to study pediatric neurology and, after my training, guided me to the neurology of the newborn. To this day he has been a continual source of support and inspiration.

I gratefully acknowledge the help and contributions of many investigators with an interest in the newborn. Their work is included on many of the pages of this book, and although acknowledgment is made in those places, I take this particular opportunity to thank them again for their generosity. Many other physicians involved in the care of newborns have shared their unusual and interesting cases with me; I thank them for their stimulation and education. Many faculty, fellows, and house officers at St. Louis Children's Hospital and Boston Children's Hospital have helped me immeasurably in the study of neonatal patients. My collaborators in clinical and basic research have been wonderful partners in our pursuit of discovery and creativity in the study of the newborn brain.

For this edition I acknowledge with great pride and gratitude the work of my former trainees and current esteemed colleagues who served as editors and authors. They are distinguished and dedicated scholars in their own right, and their efforts in bringing to fruition this sixth edition were prodigious indeed.

Joseph J. Volpe, MD

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UNIT I

HUMAN BRAIN DEVELOPMENT

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Chapter 1

Neural Tube Development

André J. du Plessis • Joseph J. Volpe

An understanding of the development of the nervous system is essential for an understanding of fetal and neonatal neurology. An obvious reason for this contention is the wide variety of disturbances of neural development that are flagrantly apparent in the neonatal period and increasingly diagnosed in the fetal period. In addition, all the insults that affect the fetus and newborn, and that are the subject matter of most of this book, exert their characteristic effects in part because the brain is developing in many distinctive ways and at a very rapid rate. As discussed further in Chapter 14, a strong likelihood exists that many of these common insults exert deleterious and far-reaching effects on certain aspects of neural development—effects that until now have escaped detection by available techniques.

In Chapters 1, 2, and 4 we emphasize the aspect of normal development that has been deranged, the structural characteristics of the abnormality, and the neurological consequences. It is least profitable to attempt to characterize exhaustively all the presumed *causes* of these abnormalities of the developmental program. Although a few examples of environmental agents that insult the developing human nervous system at specific time periods and produce a defect are recognized, few of these agents leave an identifying stamp. This obtains particularly because, in the first two trimesters of gestation, the developing brain is not capable of generating the glial and other reactions to injury that serve as useful clues to environmental insults that occur at later time periods. The occasional example of a virus, chemical, drug, or other environmental agent that has been shown to produce a disorder of brain development is mentioned only in passing. However, we emphasize genetic considerations whenever possible because of their importance in parental counseling. Therefore the organizational framework is the chronology of normal development of the human nervous system. A brief review of the major developmental events that occur most prominently during each time period is presented, followed by a discussion of the disorders that result when such development is deranged.

This chapter is devoted to the first major process in human brain development: the formation of the neural tube. These early events culminate in formation of the fundamental central neuroaxis. Development of the neural tube and the subsequent development of the prosencephalon (discussed in the next chapter) can be considered the neural components of *embryogenesis.* In subsequent chapters we discuss later *fetal* developmental events that lead to the intrinsic structural development of the central nervous system (CNS).

NORMAL DEVELOPMENT OF THE FUNDAMENTAL CENTRAL NEUROAXIS

Developments in recent years have required a reevaluation of conventional paradigms for developmental disorders of the central neuroaxis. A variety of traditional classification systems have been unsatisfactory, and the persistent inconsistent use of terminology has compromised the diagnostic and prognostic accuracy in clinical practice. New insights from animal models, advanced fetal imaging, and fetal intervention trials for neural tube disorders have led to the notion of primary and secondary consequences of these conditions. For example, the *unifying hypothesis* for open neural tube defects proposes that the primary failure of spinal closure leads to cerebrospinal fluid (CSF) leakage, which in turn leads to the secondary consequences of posterior fossa underdevelopment, hindbrain herniation, and the development of hydrocephalus.[1] More precise diagnostic paradigms consider the germ cell layers involved (i.e., ectodermal, neuroectodermal, or mesodermal) in the primary dysgenetic lesion, as well as the secondary effects of trauma, *toxicity*, and mechanical disruption of subsequent development. For example, it is now proposed that the primary defect in anencephaly is likely not failure of neurulation but rather failure of normal cutaneous and mesenchymal development (skin, bone and dural coverings), with a secondary degeneration of the exposed neural tissue. Similarly, lesions such as meningoceles with no neural involvement are often still classified as "closed neural tube defects," although their etiology is unrelated to neurulation.

Milestones of Major Events

The major developmental events and their peak times of occurrence are shown in Table 1.1. The time periods are those during which the *most rapid progression* of the developmental event occurs. Although some overlap exists among these time periods, it is valid and convenient to consider the overall maturational process in terms of a sequence of individual events. In a discussion of the timing of the disorders, the time periods shown in Table 1.1 are obviously of major importance. Nonetheless, it is necessary to recognize that an aberration of a developmental event need not be caused by an insult impinging *at the time of the event.* Thus a given malformation may not have its onset after the developmental event is completed, but the developmental program may be disturbed *at any time before* the event is under way. The concept of a *termination stage* refers to the time in the development of an organ after which a specific

TABLE 1.1 Major Events in Human Brain Development and Peak Times of Occurrence

MAJOR DEVELOPMENTAL EVENT	PEAK TIME OF OCCURRENCE
Primary neurulation	3–4 weeks of gestation
Prosencephalic development	2–3 months of gestation
Neuronal proliferation	3–4 months of gestation
Neuronal migration	3–5 months of gestation
Organization	5 months of gestation to years postnatally
Myelination	Birth to years postnatally

TABLE 1.2 Development of the Fundamental Craniospinal Axis—Major Phases and Peak Times of Occurrence

MAJOR DEVELOPMENTAL PHASE	PEAK TIME OF OCCURRENCE
1. Gastrulation	16–18 days p/c
2. Primary neurulation	18–26 days p/c
Neural plate formed	18 days p/c
First fusion of neural folds	22 days p/c
Anterior neuropore closes	24 days p/c
Posterior neuropore closes	26 days p/c
3. Secondary neurulation	26 days p/c—postnatal
Vacuolation-canalization	26 days—7 weeks p/c
Retrogressive differentiation	7 weeks p/c—postnatal
4. Disjunction and fusion of mesodermal-cutaneous structures	Tracks regional neural tube closure

malformation cannot occur by any teratogenic mechanism.[2] Thus, in the discussion of timing of malformations, we state that the onset of a given defect could occur *no later than* a given time. Note that in this text the timing of events is based on the postconceptional (p/c) age, rather than the postmenstrual or gestational age.

Formation of the Neural Tube

Formation of the neural tube and its coverings proceeds through four phases (Table 1.2)—namely gastrulation, primary neurulation, secondary neurulation, and dorsal midline closure of the mesodermal-cutaneous ectodermal layers. *Gastrulation* is the fundamental formation of the trilaminar plate between days 16 and 18 p/c during which the endodermal, mesodermal, and ectodermal layers of the embryo become distinct. The ectodermal layer differentiates into cutaneous and neural ectoderm. The neural ectoderm develops in the longitudinal plane along the dorsal surface of the embryo as the neural plate. *Neurulation* refers to the inductive events that occur in the neural plate that result in formation of the neural tube, which ultimately gives rise to the entire CNS. Neurulation can be divided into *primary neurulation* (i.e., formation of brain and spinal cord down to the sacral level) and *secondary neurulation* (i.e., events related to the later formation of the sacrococcygeal segments of the spinal cord). With fusion of the neural folds, there is separation of the cutaneous and neural ectoderm, with the ingrowth of the mesodermal layers between them; the timing of these events closely follows the progressive closure of the neural tube. Primary neurulation and secondary neurulation are discussed separately.

BOX 1.1 Primary Neurulation

Peak Time Period
3–4 weeks of gestation

Major Events
Notochord, chordal mesoderm → neural plate → neural tube, neural crest cells
Neural tube → brain and spinal cord → dura, axial skeleton (cranium, vertebrae), dermal covering
Neural crest → dorsal root ganglia, sensory ganglia of cranial nerves, autonomic ganglia, and so forth

Primary Neurulation

By the end of gastrulation, the most anterior part of the axial mesoderm is the prechordal plate, a critical ventral patterning center for the developing forebrain, while the more posterior parts of the axial mesoderm are made up of the notochord. Primary neurulation is a series of events in the dorsal neural ectoderm of the embryo culminating in formation of the neural tube—rostral to the upper sacral level—and its separation from the other germ cell layers.[3,4] The critical events are summarized in Box 1.1. By 18 days p/c the neural plate has been formed by differentiation of the dorsal neural ectoderm from the original ectodermal layer. Next the lateral edges of the neural plate become elevated into neural folds, and the midline of the neural plate invaginates (Fig. 1.1). The neural folds continue to elevate in a dorsomedial direction, until the edges meet in the midline to begin closure of the neural tube. In the human embryo, the first fusion of the neural folds is at the level of the future hindbrain-cervical junction (foramen magnum), which occurs at 22 p/c days. Closure generally proceeds rostrally to form the anterior neural tube (and then the brain) and caudally to form the posterior neural tube (and then the spinal cord), although it is not a simple, zipper-like process.[5-10] The anterior neuropore of the neural tube closes at approximately 24 days, and the posterior neuropore closes at approximately 26 days, at which point primary neurulation is complete. During closure of the neural tube, cells from the dorsal-most region become separated from the neural tube to form the neural crest, which in turn gives rise to the future craniofacial bony structures, dorsal root ganglia, sensory ganglia of the cranial nerves, autonomic ganglia, Schwann cells, and cells of the pia and arachnoid (as well as melanocytes, cells of the adrenal medulla, and certain skeletal elements of the head and face).[11] Finally, the neural tube becomes physically separated from the meso-endoderm and cutaneous ectoderm, a process called disjunction (see Table 1.2). Ongoing interaction between the neural tube and surrounding mesoderm gives rise to the dura and axial skeleton (i.e., the skull and the vertebrae). Understanding this sequence of normal differentiation of the different germ cell layers is critical to an understanding of the different features of cranial and spinal dysraphism.

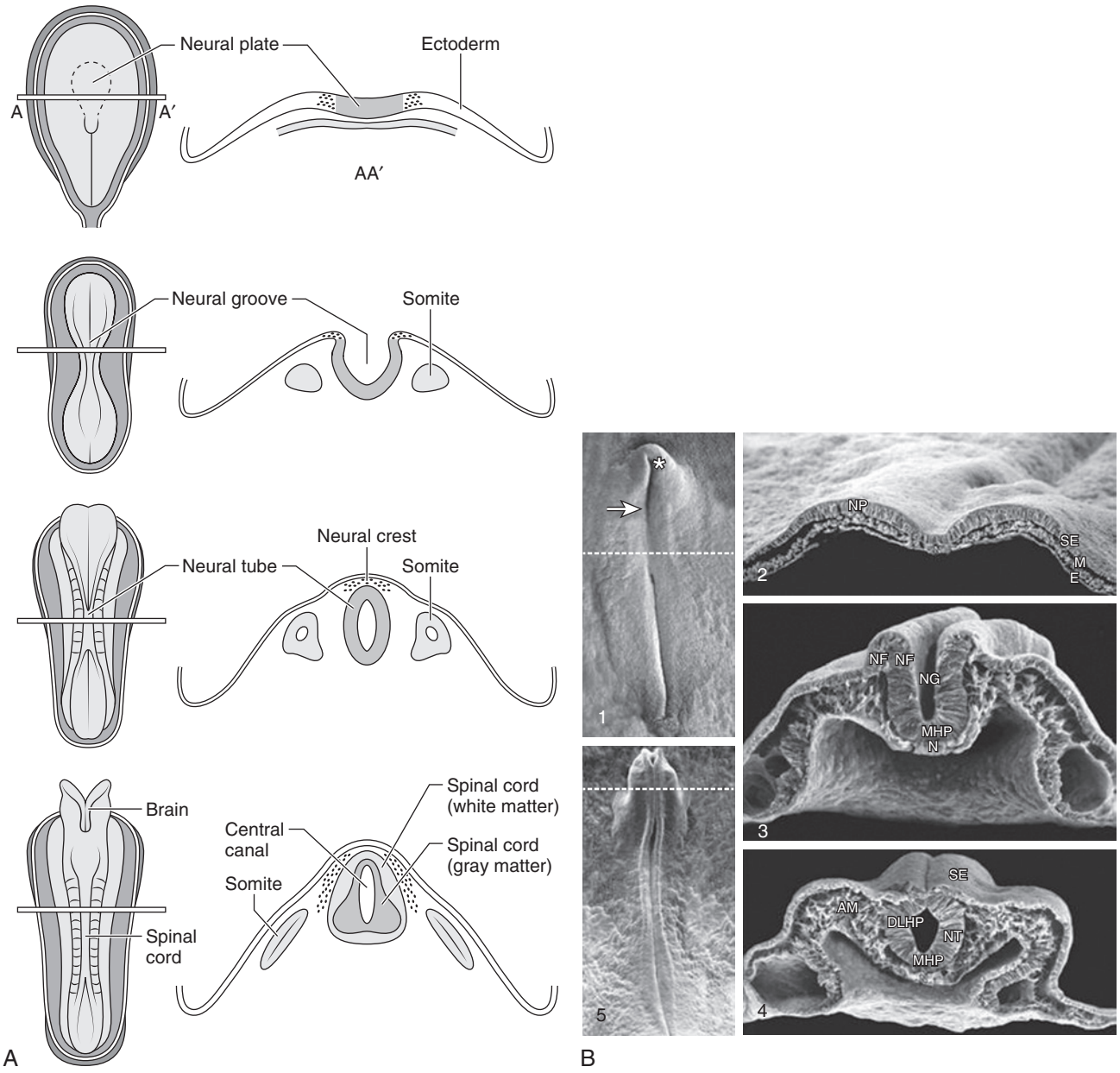


Figure 1.1 Primary neurulation. *Schematic depiction* (A) *of the developing embryo*: external view *(left)* and corresponding cross-sectional view[407] at about the middle of the future spinal cord. Note the formation of the neural plate, neural tube, and neural crest cells. (B) *Neurulation in the chick embryo*. Dorsal view showing cranial-to-caudal neural plate formation at the level of the line in *panel 1*. More cranially *(arrow)*, the neural plate is shaping, and still more cranially, the neural plate is bending *(asterisk)*, and a neural groove and paired neural folds have formed. *Panel 2:* Transverse section through the neural plate. *Panel 3:* Transverse section through neural groove at the future midbrain level. *Panel 4:* Dorsal view during closure of the neural groove. groove. *Panel 5:* Transverse section through the incipient neural tube. *DLHP*, Dorsolateral hinge point; *E*, endoderm; *M*, mesoderm; *MHP*, median hinge point; *N*, notochord; *NF*, neural fold; *NG*, neural groove; *NP*, neural plate; *NT*, neural tube; *SE*, surface ectoderm. (A, From Cowan WM. The development of the brain. *Sci Am*. 1979;241:113–133. B, From Schoenwolf GC, PhD, *Larsen's Human Embryology*, Chapter 4, 82–107. Copyright © 2015, 2009 by Churchill Livingstone, an imprint of Elsevier Inc.)

Cellular and Molecular Mechanisms of Primary Neurulation. Primary neurulation occurs under the induction of the underlying notochord and chordal mesoderm during the third and fourth weeks p/c (see Box 1.1 and Fig. 1.1).[11] The neural plate deformations required for development of the neural folds, and subsequently the neural tube, are mediated by a variety of cellular and molecular mechanisms,[5,6,9,12-33] the most important of which involve the cytoskeletal network of microtubules and microfilaments. Under the influence of vertically oriented microtubules, cells of the developing neural plate elongate, while contraction of actin microfilaments arranged circumferentially around the apical portions of the cells results in cells with a

BOX 1.2 Secondary Neurulation (Caudal Neural Tube Formation)

Peak Time Period
Canalization: 4–7 weeks of gestation
Retrogressive differentiation: 7 weeks of gestation to after birth
Major Events
Canalization: undifferentiated cells (caudal cell mass) → vacuoles → coalescence → contact central canal of rostral neural tube
Retrogressive differentiation: regression of caudal cell mass → ventriculus terminalis, filum terminale

broad base and narrow apex. These forces on the neural plate result in invagination of its midline, dorsomedial folding of its edges, and closure to form the neural tube (see Fig. 1.1). The process of neural fold bending in a dorsomedial direction also appears to involve differential proliferation and translocation of the neuroepithelial cells.[34] Surface glycoproteins, especially cell adhesion molecules important for cell-cell recognition, as well as adhesive interactions with extracellular matrix, mediate fusion of the opposing neural folds. Other critical molecular events include action of the products of certain regional patterning genes (especially bone morphogenetic proteins and sonic hedgehog), homeobox genes, surface receptors, and transcription factors.

Secondary Neurulation (Caudal Neural Tube Formation)

Secondary neurulation is the process of caudal neural tube formation, which commences at completion of primary neurulation (i.e., on closure of the posterior neuropore around the S2 spinal level, on day 26 p/c; Box 1.2).[35,36] Secondary neurulation occurs in the caudal cell mass and, by forming the remaining sacrococcygeal neural tube, completes neural tube formation. Secondary neurulation gives rise to the conus medullaris, cauda equina, as well as components of the genitourinary tract and hindgut. Starting between 28 and 32 days p/c, the caudal cell mass undergoes vacuolation, coalescence, and canalization, processes that culminate by 7 weeks p/c.[18,37,38] At this point the vacuoles connect to the central canal of the neural tube previously formed by primary neurulation.[3] Not infrequently, accessory lumens remain and may be important in the genesis of certain anomalies of neural tube formation (discussed later). Following canalization, the caudal cell mass undergoes retrogressive differentiation between 7 weeks p/c and into postnatal life (see Box 1.2). At 8 weeks p/c the spinal cord tissue extends the entire length of the spinal column. Subsequent disproportionate growth of the spinal column results in relative ascent of the conus medullaris (which contains the ventriculus terminalis), leaving the filum terminale in its wake. As a result the conus ascends to the level of L3 by 40 weeks,[39] reaching its final level of L1–L2 by 3 months postnatal.

DISORDERS OF CRANIOSPINAL DEVELOPMENT

The terminology used to describe embryonic anomalies of craniospinal development is inconsistent and often imprecise, which in turn has compromised diagnosis and counseling. To remedy this situation, we first review the definitions and categorization to be used in this text.[40,41] The term *dysraphism* is best understood by considering its root (i.e., raphe), which is defined as a line of union between two contiguous bilaterally symmetric structures. Dysraphism is therefore a failure of this process, and in its broadest sense includes any incomplete midline closure of the developing head and spine, and may involve the mesenchymal and ectodermal structures individually or in combination. Embryologically, dysraphic states of the central neuroaxis can be divided into those that occur (1) pre-neurulation (during gastrulation) and involve the neurenteric canal; (2) during primary neurulation, forming the vast majority of open neural tube defects; (3) during secondary neurulation with disturbed development of the caudal cell mass, which is responsible for most closed neural tube defects; or (4) during midline closure of the mesoderm and cutaneous ectoderm. *Spina bifida* refers only to defects of vertebral arch formation (described later); subtyping of spina bifida is based on the presence and nature of associated neuroectodermal malformations. Isolated vertebral arch dysraphism without underlying neural defects or cystic evagination of the meninges or cord results in true *spina bifida occulta*.

Neural tube defects refer to a disturbance in neuroectodermal development, defined embryologically as defects of primary or secondary neurulation. Anatomically, neural tube defects can be further categorized by their location relative to the first fusion point of the neural tube, at the level of the future foramen magnum. Lesions of the anterior neural tube (rostral to the foramen magnum) lead to cranial dysraphism, while those of the posterior neural tube (caudal to the foramen magnum) lead to spinal dysraphism. The distinction between open or closed dysraphic lesions is important for understanding the primary lesion and its secondary complications. *Open* neural tube defects have at least some continuity between the external surface of the fetus and the underlying neural tissue and at least intermittent CSF leakage. In addition, open neural tube defects are usually associated with other CNS anomalies, including hindbrain, callosal, and cerebral cortical malformations. *Closed* neural tube defects are skin covered, with no exposed neural tissue and no CSF leak; the defect is confined to the spine, and other associated CNS anomalies are rare.[42] As a general rule, most open neural tube defects result from disturbed primary neurulation, while most closed neural tube defects result from disturbed secondary neurulation. However, there are exceptions to this rule. For example, higher (thoracic and cervical) myelomeningoceles may be skin covered (see the discussion of cervical myelocystoceles later on in this chapter), and sacral lesions are occasionally open.[43]

Disorders of primary neurulation are discussed in order of decreasing severity, starting with complete failure of neural tube formation (craniorachischisis totalis), followed by disorders of anterior neural tube formation (cranial dysraphism) and disorders of posterior neural tube formation (spinal dysraphism).

Craniocerebral Dysraphism (Box 1.3)

Craniorachischisis Totalis

Anatomical Abnormality. Craniorachischisis totalis (see Box 1.3) results from essentially total failure of neurulation at a very early stage, leaving an exposed neural plate–like structure (with no overlying axial skeleton or dermal covering) running down the entire dorsal extent of the central neuroaxis (Fig. 1.2).[44,45] Because the neural plate is formed by 18 days p/c,

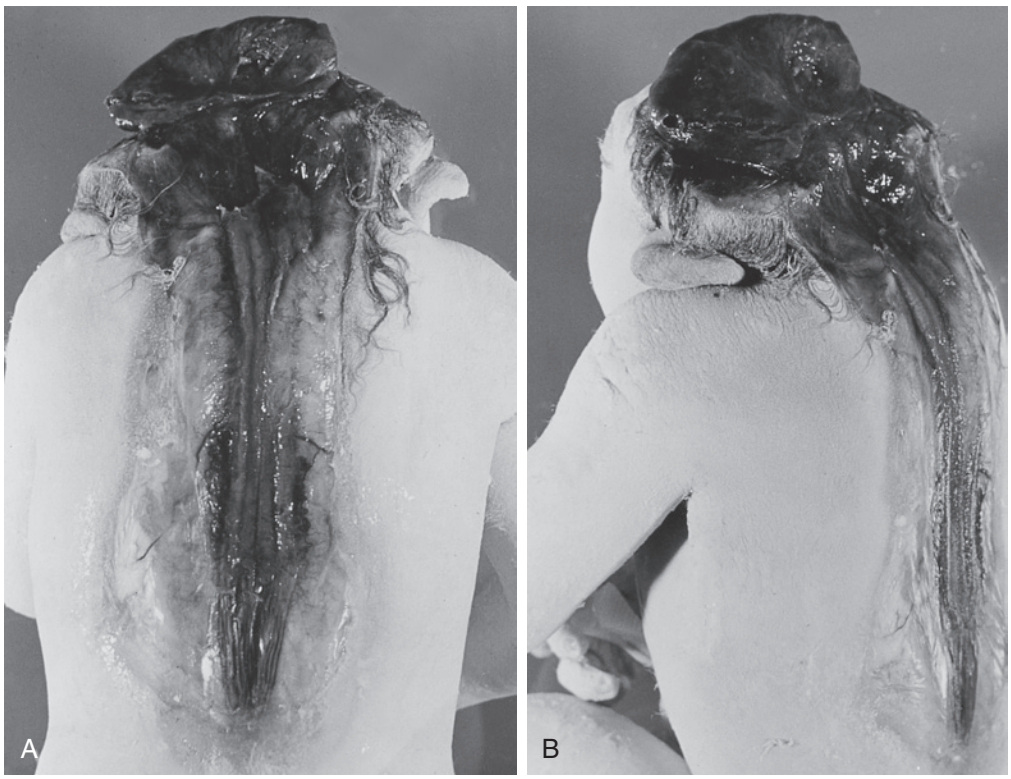


Figure 1.2 Craniorachischisis. Dorsal (A) and dorsolateral (B) views of a human fetus. (Courtesy Dr. Ronald Lemire.)

BOX 1.3 Cranial and Spinal Dysraphism

Order of Decreasing Severity
Craniorachischisis totalis
Anencephaly
Encephalocele
Myelomeningocele, Chiari type II malformation
Myeloschisis

and first point of closure of the neural tube occurs at 22 days p/c, the onset of craniorachischisis totalis is estimated to be no later than 20 to 22 days of gestation.[3] The precise incidence of this lesion is unknown because most cases are aborted spontaneously in early pregnancy, and only a few have survived to early fetal stages.

Anencephaly

Anatomical Abnormality. Anencephaly (see Box 1.3 and Fig. 1.3) has traditionally been classified as an anterior neural tube defect. However, based on human and animal observations,[46] some consider this lesion to be a primary defect in the formation of the cranial vault and its coverings, with secondary degeneration of the cranial neural contents. Specifically, it is proposed that anencephaly results primarily from (partial) absence of the cranial vault (acrania), with initial protrusion of the early fetal brain above the remaining skull bones (exencephaly), and subsequent degeneration of the underlying telencephalic mantle due to direct exposure to the amniotic fluid.[46] According to this viewpoint, anencephaly is not a true neural tube defect, because the primary lesion results from a skeletal (mesodermal) defect. Instead the underlying pathogenetic mechanism of anencephaly invokes a *two-hit* hypothesis similar to that discussed for myelomeningoceles later in this chapter. This notion that anencephaly is not a true neural tube defect is not universally held.[47] The cranial defect usually involves the frontal bones above the supraciliary ridge, the parietal bones, and the squamous part of the occipital bone, and in the most severe cases, the cranial vault abnormality extends back to or through (holoacrania or holoanencephaly) the foramen magnum.[3,45] Defects stopping short of the foramen magnum are known as meroacrania or meroanencephaly. The underlying neural tissue defect in anencephaly most commonly involves the forebrain and variable amounts of upper brain stem (Fig. 1.4; see also Fig. 1.3), leaving a residual degenerated mass of hemorrhagic, fibrotic, and neuroglial tissue with little definable structure. Onset of anencephaly is estimated to be no later than 24 days of gestation.[3] Polyhydramnios is a frequent feature.[48]

Timing and Clinical Aspects. Approximately 75% of anencephalic infants are stillborn, and the remainder die in the neonatal period. The disorder is not rare, and epidemiological studies reveal striking variations in prevalence as a function of geographical location, sex, ethnic group, race, season of the year, maternal age, social class, and history of affected siblings.[45,49-53] The risk increases with decreasing social class and with a history of affected siblings in the family. Since the late 1970s, the incidence of anencephaly in the United States, like that of myelomeningocele (discussed later), declined to approximately 0.2 per 1000 live births in 1989, remaining relatively stable since then,[53,54] with the most recent estimates (2009–2011) being 0.28/1000 live births.[55] Both genetic and

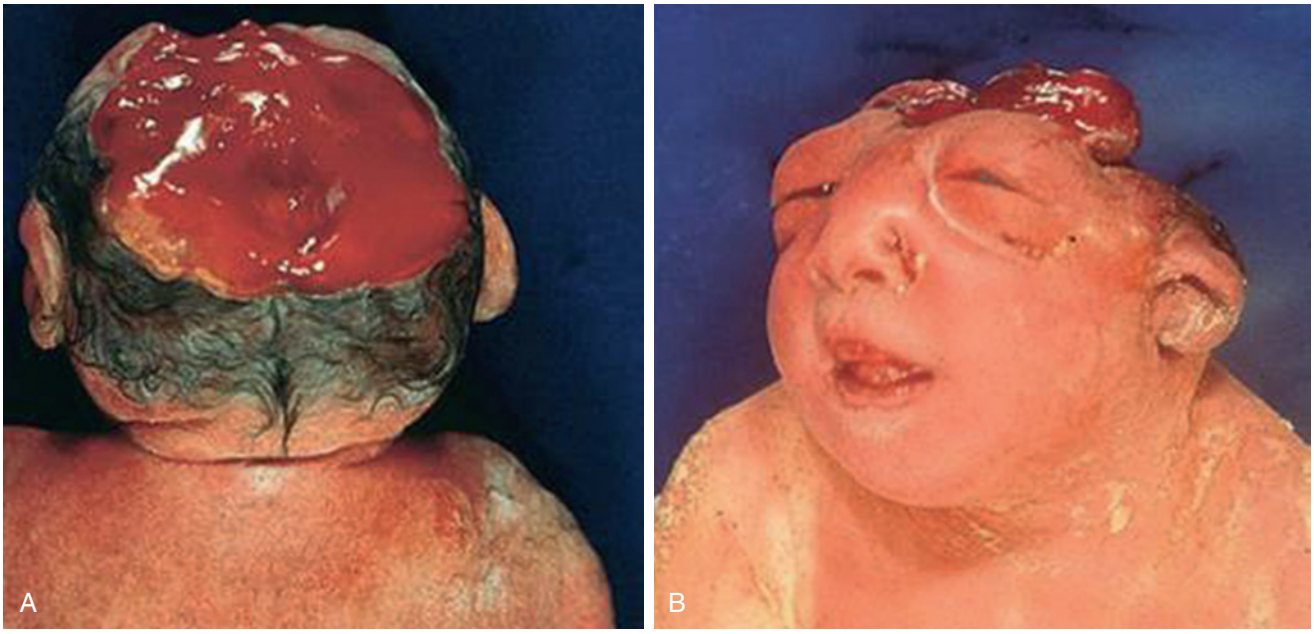


Figure 1.3 Anencephaly. Dorsal (A) and frontal (B) views. Note the absence of scalp, calvarium, and almost the entire brain, with the characteristic facies, including absent forehead giving the eyes an appearance of bulging. The lack of cranial bones causes the cranial cavity to be completely open. There is no discernible brain grossly; however, there is sometimes a small mass of neurovascular tissue (area cerebrovasculosa) in the base of the cranium. Rarely, there can be acrania without anencephaly in which the calvarium is absent, but with significant development of brain.

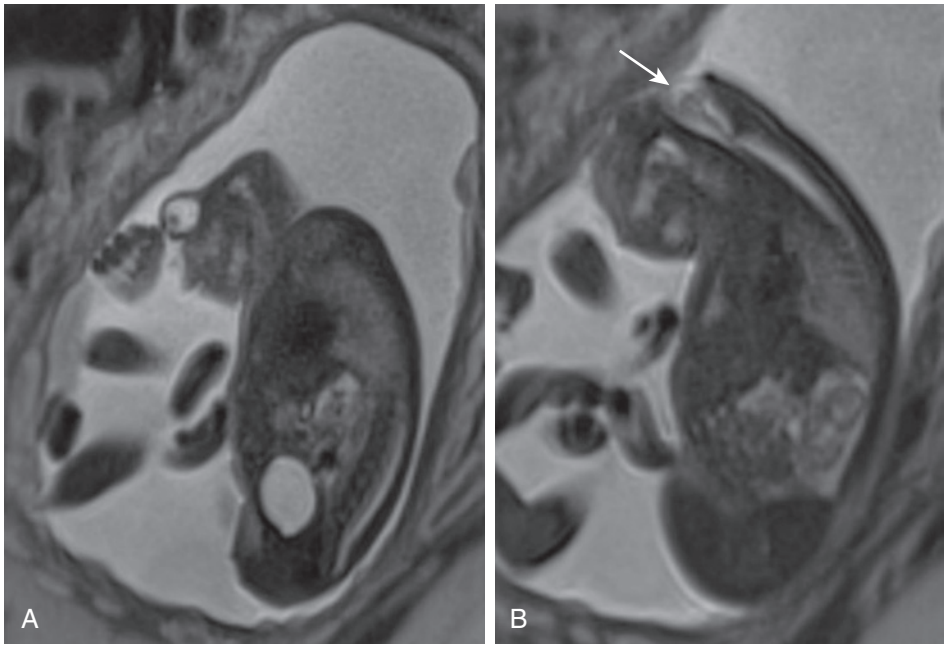


Figure 1.4 Fetal magnetic resonance imaging showing anencephaly. Note abrupt ending of brain parenchyma at the rostral end of the rudimentary brain stem *(arrow)*.

environmental influences appear to operate in the genesis of anencephaly (see later discussion of myelomeningocele). Recently, maternal use during pregnancy of the selective serotonin reuptake inhibitor paroxetine has been implicated in the development of anencephaly.[56]

Diagnosis. The skull bones begin to ossify around 11 weeks p/c, making the cranial defect readily identifiable by second trimester fetal ultrasound.[57] In fact, the proportion of anencephaly detected prenatally has been reported to be as high as 96% to 100%.[58,59] Systematic prenatal detection and elective termination

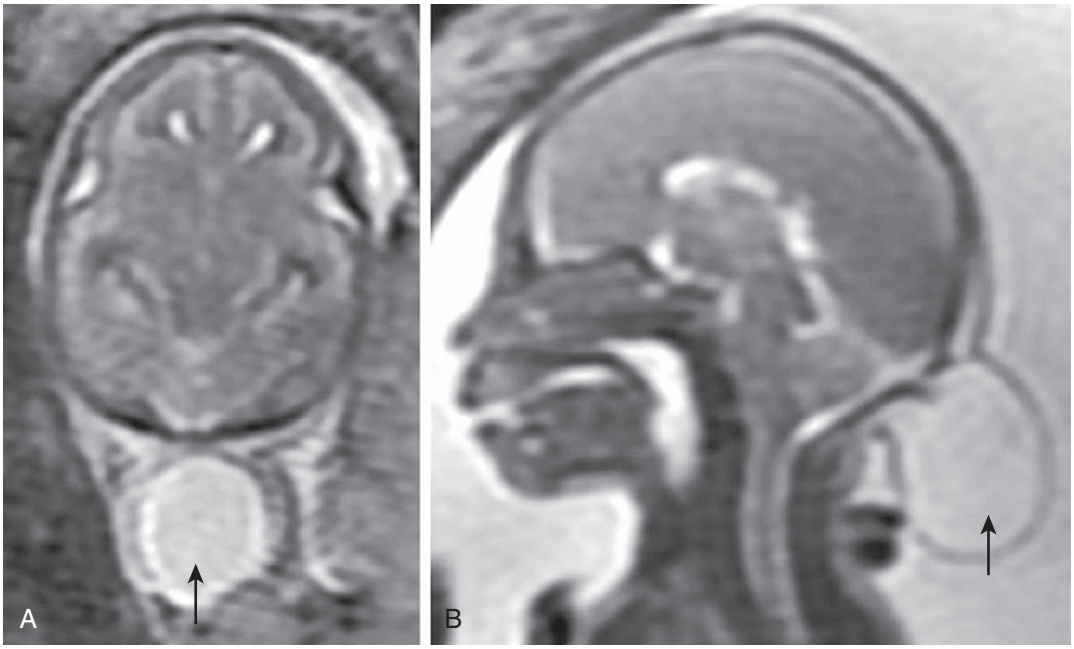


Figure 1.5 Fetal magnetic resonance imaging (MRI) showing occipital meningocele. T2-weighted fetal MRI axial (A) and sagittal (B) views showing cerebrospinal fluid-filled cystic lesion *(arrows)* apparently devoid of brain parenchymal tissue.

of pregnancy complicated by anencephaly have resulted in a sharp decline in the number of live-born cases.[60,61]

Encephaloceles

Anatomical Abnormality. Encephaloceles (see Box 1.3) were previously considered a restricted disorder of neurulation involving anterior neural tube closure, although the precise pathogenesis of these lesions remains unknown. It may be better to consider these lesions as developmental disorders of cranial mesoderm in which the cranial defect is associated with a cystic extracranial extension of meninges, neural tissue, and CSF. The notion that encephaloceles are not disorders of primary neurulation is supported by the fact that the herniated brain parenchyma is relatively normal and shows no evidence of defective neurulation.[47] Many encephaloceles are skin-covered (i.e., *closed*) lesions. When the cystic lesion includes parts of the ventricular system, the term meningoencephalocystocele is used. Lesions that involve primarily or only the overlying meninges or skull,[45] without obvious inclusion of neural elements, are called cranial meningoceles (Fig. 1.5); these are thought to be later in onset and account for up to 20% of cystic occipital lesions. Encephaloceles occur most commonly (70%–80%) in the occipital region (Fig. 1.6),[62-66] less commonly in the frontal region (Fig. 1.7), and least commonly in the temporal and parietal regions.[67] Frontal encephaloceles may protrude into the nasal cavity (frontoethmoidal encephaloceles). In the typical occipital encephalocele, the protruding brain is usually derived from the occipital lobe and may be accompanied by dysraphic disturbances involving cerebellum and superior mesencephalon. The neural tissue in an encephalocele usually connects to the underlying CNS through a narrow neck of tissue. The protruding mass is usually represented by a closed neural tube with cerebral cortex, exhibiting a normal gyral pattern, and subcortical white matter. As many as 50% of cases are complicated by hydrocephalus.[68] Encephaloceles located in the low occipital (below the inion) or high cervical regions and combined with deformities of lower brain stem and of base of skull and upper cervical vertebrae characteristic of the Chiari type II malformation (associated with myelomeningocele [discussed later]) comprise the Chiari type III malformation.[69] This type of encephalocele contains cerebellum in virtually all cases and occipital lobes in approximately one-half of cases (Fig. 1.8).[69] Partial or complete agenesis of the corpus callosum occurs in two-thirds of cases. Venous structures may be included in the cyst, and anomalous venous drainage (aberrant sinuses and deep veins) is present in about one-half of patients and may complicate the surgical approach to these lesions.[69]

Timing and Clinical Aspects. Onset of the most severe lesions is probably no later than the approximate time of anterior neural tube closure (24 days), or shortly thereafter. Infants with encephaloceles not uncommonly exhibit associated malformations.[62,70] A frequently co-occurring CNS anomaly is subependymal nodular heterotopia.[71] The most commonly recognized syndromes associated with encephalocele are Meckel syndrome (characterized by occipital encephalocele, microcephaly, microphthalmia, cleft lip and palate, polydactyly, polycystic kidneys, ambiguous genitalia, and other deformities)[72] and Walker-Warburg syndrome (see Chapters 6 and 33). These disorders, as well as several other less common syndromes associated with encephalocele, are inherited in an autosomal recessive manner.[62,70,73] Maternal hyperthermia between 20 and 28 days of gestation has been associated with an increased incidence of occipital encephalocele,[70] as well as with other neural tube defects (discussed later).

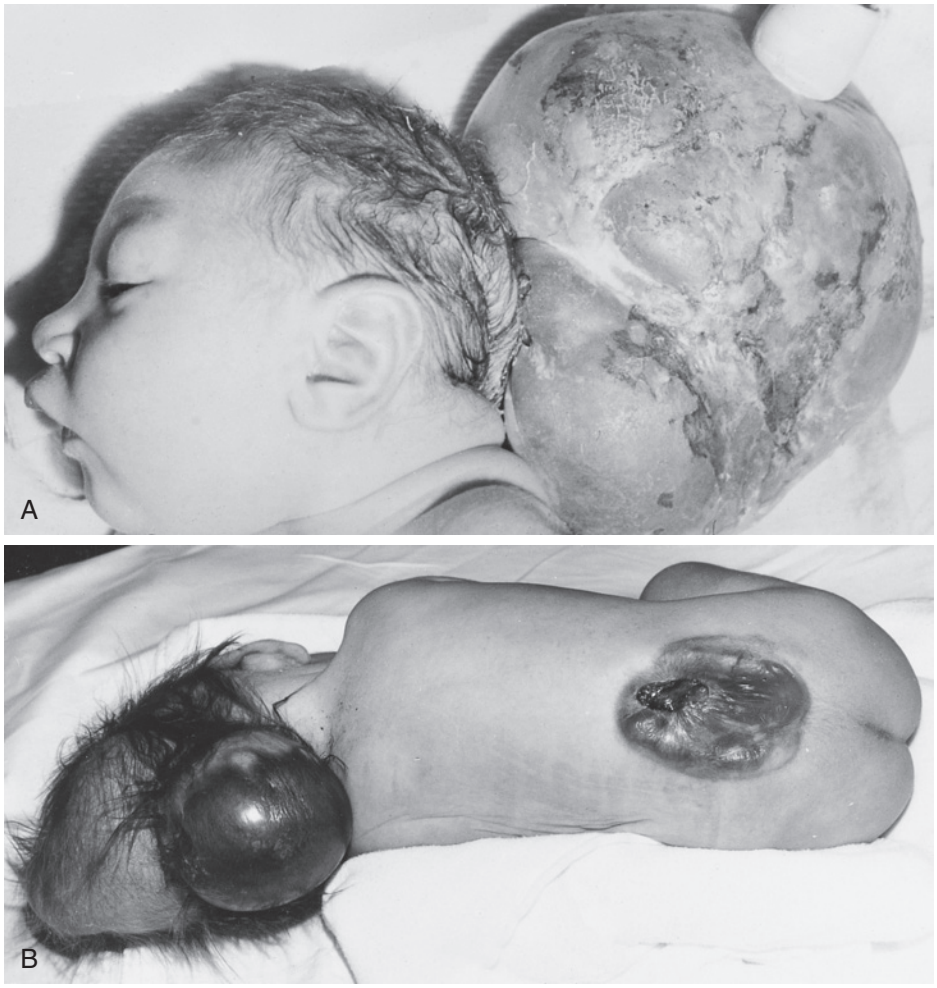


Figure 1.6 Encephalocele. (A) Newborn with a large occipital encephalocele. (B) Newborn with both an occipital encephalocele and a thoracolumbar myelomeningocele. (Courtesy Dr. Marvin Fishman.)

Diagnosis. Skin-covered encephaloceles have normal maternal serum and amniotic fluid AFP levels. Diagnosis by fetal ultrasonography in the second trimester has been well documented.[74-78] As with myelomeningoceles, *open* encephaloceles are often associated with decreased extraaxial CSF spaces by fetal imaging. Diagnosis before fetal viability has been followed by elective termination; later diagnosis may require delivery by cesarean section.

Management and Outcome. Neurosurgical intervention is indicated in most patients.[62,64] Exceptions include those with massive lesions and marked microcephaly. Surgery is necessary in the neonatal period for ulcerated lesions that are leaking CSF. An operation can be deferred if adequate skin covering is present. Preoperative evaluation has been facilitated by the use of computed tomography (CT) and especially magnetic resonance imaging (MRI) scans.[69,79,80] The outcome is difficult to determine precisely because of variability in selection for surgical treatment. In a combined surgical series of 40 infants,[64,65] 15 infants (38%) died, many of whose complications can be managed more effectively now in neurosurgical facilities. Of the 25 survivors, 14 (56%) were of normal intelligence, although often with motor deficits, and 11 (44%) exhibited both impaired intellect and motor deficits. Not surprisingly, prognosis varies inversely with the extent of herniated neural tissue, with cranial meningoceles (i.e., no obvious neural tissue in the cyst) having the best prognosis. Outcome is more favorable for infants with anterior encephaloceles than those with posterior encephaloceles. Thus, in one series of 34 cases, mortality was 45% for infants with posterior defects and 0% for those with anterior defects. Normal outcome occurred in 14% of the total group with posterior defects and in 42% of those with anterior defects.[62]

Spinal Dysraphism

In the following we first consider disorders of primary neurulation, usually open neural tube defects, because these originate earlier in embryonic development and are by far the most common and clinically relevant spinal dysraphic

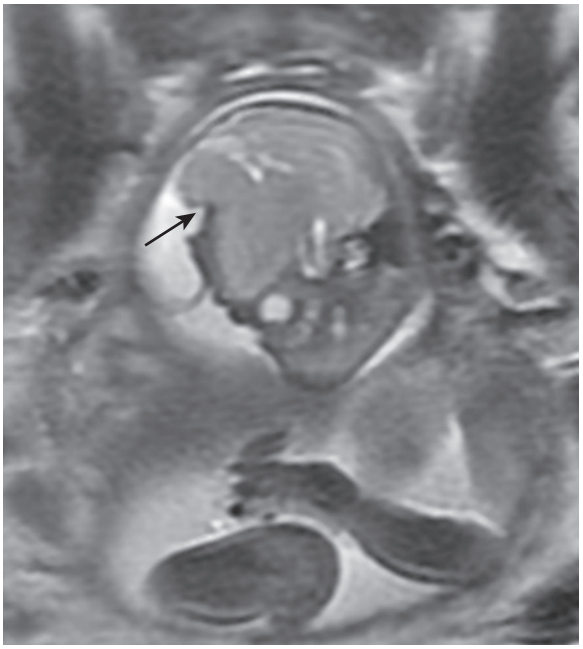
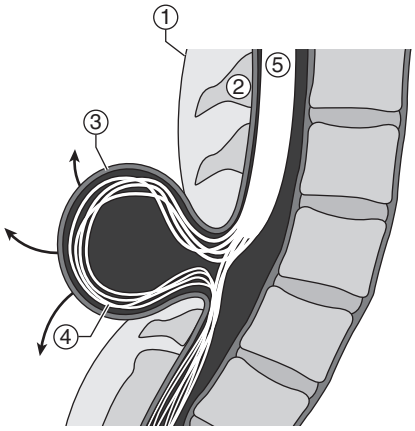


Figure 1.7 Frontoparietal encephalocele. Fetal magnetic resonance imaging (T2-weighted) angled sagittal view showing herniation of brain parenchyma through cranial defect *(arrow)*.



① Skin
② Bony spinal element
③ Dysplastic meningeal tissue
④ Herniating neural tissue
⑤ Spinal cord

Figure 1.9 Diagram of myelomeningocele. Note herniation of neural tissue through the bony spinous defect, dorsal displacement of the cord by ventral cerebrospinal fluid (CSF) collection, cyst covered by dysplastic meningeal tissue, leakage of CSF, and lack of skin coverage.

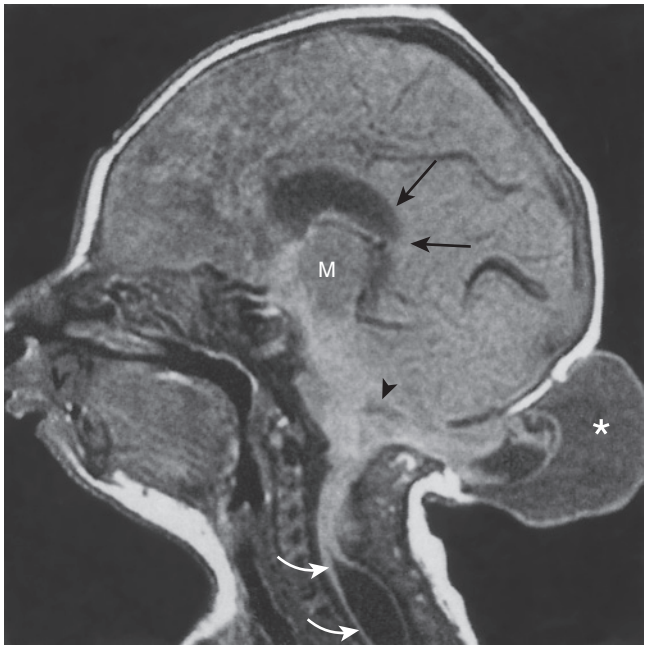


Figure 1.8 Fetal magnetic resonance imaging (MRI) showing occipital encephalocele. Midline sagittal spin echo 700/20 MRI scan demonstrates a low occipital encephalocele containing cerebellar tissue. The cystic portions *(asterisk)* within the herniated cerebellum are of uncertain origin. The posterior aspect of the corpus callosum *(straight black arrows)* is not clear and is probably dysgenetic. The third ventricle is not seen, but the massa intermedia (M) is very prominent. The tectum is deformed and is not readily identified. The fourth ventricle *(arrowhead)* is deformed and displaced posteriorly. A syrinx *(curved white arrows)* is present in the middle to lower cervical spinal cord. (From Castillo M, Quencer RM, Dominguez R. Chiari III malformation: imaging features. *AJNR Am J Neuroradiol*. 1992;13:107–113.)

conditions. Thereafter we discuss disorders of secondary neurulation, which more commonly result in closed neural tube defects.

Disorders of Primary Neurulation in the Spine

There are two major disorders of primary neurulation above the sacral level, namely, myelomeningocele and myeloschisis. The essential difference between these two lesions is that a cystic component is present in myelomeningocele (at least initially), consisting of dysplastic meningeal tissue usually leaking CSF, whereas in myeloschisis the neural placode is completely exposed, with no cystic meningeal or cutaneous covering and often continuous CSF leakage from the spinal central canal. Myelomeningoceles are usually displaced in a dorsal direction beyond the level of the surrounding skin, by a collection of CSF ventral to the cord (Fig. 1.9). Conversely, myeloschisis lesions are usually adherent to the anterior wall of the vertebral canal and are therefore either flush with, or below, the plane of the surrounding skin (discussed later). The terminology used for both these lesions has been inconsistent. Some authors use the term *myelomeningocele* for cystic lesions that contain abnormal neural tissue, even if the cystic lesion is skin covered (i.e., a closed defect).[81,82] The term *myeloschisis* has also been applied inconsistently, with some authors using the term for open lesions extending down most of the neural tube, a lesion that others refer to as rachischisis.[72] Myelomeningoceles are the most common open dysraphic lesion of the spinal cord by far, have been subject to the most investigation, and have shown some response to medical and surgical intervention (discussed later). In addition, most cases of myelomeningocele now survive. For these reasons, the following discussion focuses largely on myelomeningocele.

Myelomeningocele

Anatomical Abnormality. The essential neural defect in myelomeningocele is restricted failure of primary neurulation with varying degrees of posterior neural tube closure. Approximately 80% of lesions occur in the lumbar (thoracolumbar, lumbar, lumbosacral) area, presumably because this is the last area of the neural tube to close.[64] Myelomeningoceles are represented by a neural plate or abortive neural tube–like structure (placode) in which the ventral half of the cord is relatively less affected than the dorsal. Most of the lesions are associated with dorsal protrusion of the neural tissue, such that a sac is created on the back (Figs. 1.10 and 1.11; see also Fig. 1.9). Bony effects of the overlying tissue include failure (lack of fusion or an absence) of vertebral arch development (spina bifida), with bilateral broadening of the vertebrae and lateral displacement of pedicles, leading to a widened vertebral canal.[29] The caudal extent of the vertebral changes is usually considerably greater than the extent of the neural lesion. Soft-tissue covering consists

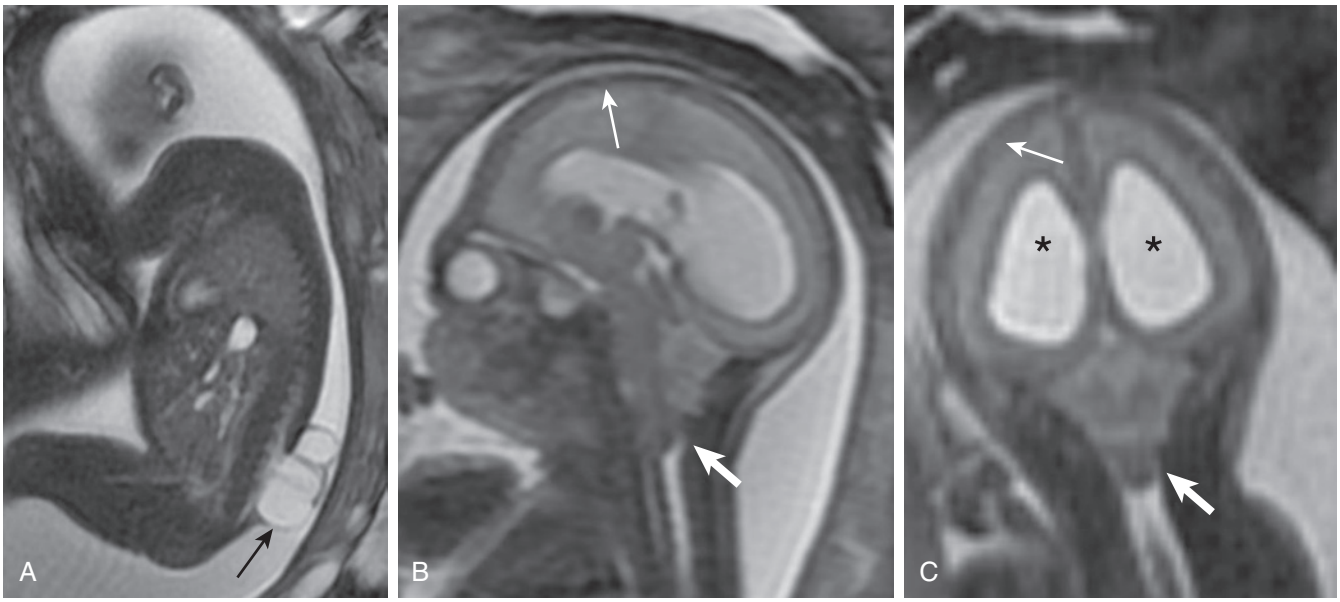


Figure 1.10 Lumbar myelomeningocele. T2-weighted fetal magnetic resonance imaging showing (A) sagittal view of the lumbar myelomeningocele *(arrow)*; (B) sagittal and (C) coronal views of the crowded posterior fossa with downward herniation of the brain stem and cerebellum (Chiari II) *(black arrow)*, paucity of extraaxial cerebrospinal fluid *(thin arrows)* around the brain, and moderate hydrocephalus *(*)*.

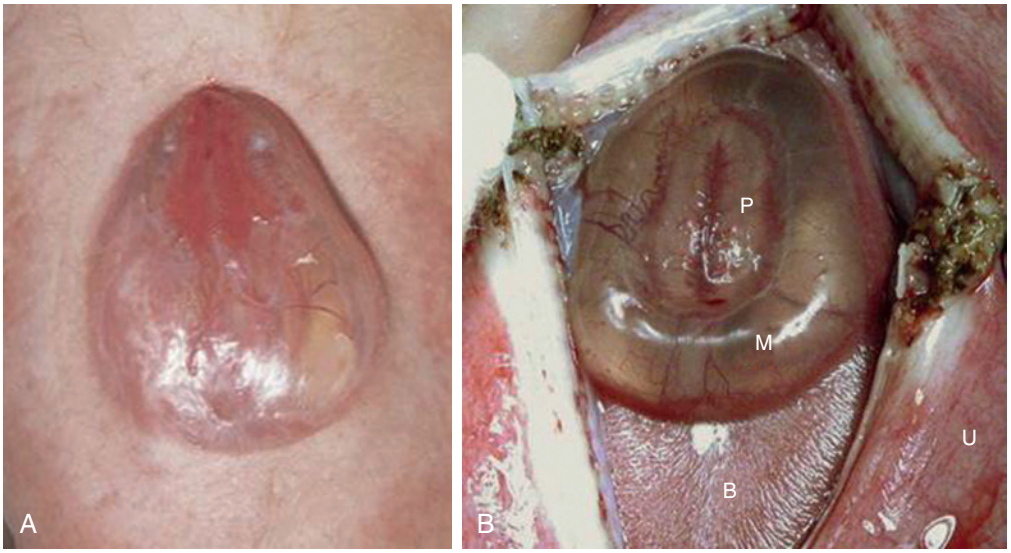


Figure 1.11 Myelomeningocele. Thoracolumbar myelomeningocele (A) in newborn. (B) Lumbar myelomeningocele exposed and viewed through hysterotomy site (B) during fetal repair. Note neural placode rising above the level of the surrounding skin. (*U*, uterus; *B*, fetal back; *M*, MMC sac; *P*, exposed neuroplacode). (A, Madan SS. Paralytic conditions in childhood. *Surgery*. 2004; 25:166–170. Copyright © 2007. B, Danzer E, Johnson MP. Fetal surgery for neural tube defects. *Semin Fetal Neonatal Med* 2014;19:2–8. Copyright © 2013 Elsevier Ltd.)

of a porous cystic sac of dysplastic meningeal tissue and a deficient skin cover.

Cervical myelomeningoceles are rare and differ in embryology, prognosis, and management from myelomeningoceles at lower spinal levels (discussed later).[43,83] These lesions are cystic and meet criteria as myelomeningoceles because they contain neuroglial tissue and CSF. However, unlike lower myelomeningoceles, the spinal cord is normal or near normal and remains within the spinal column. A stalk of neuroglial of fibrovascular tissue extends through a small midline gap between the dorsal columns of the spinal cord, passes through the bony spinous defect, and across the CSF-filled cyst to attach to the cyst wall, thereby tethering the spinal cord.[82,83] Unlike most other myelomeningoceles, these cervical lesions are almost always covered by full-thickness skin (i.e., *closed*) without CSF leakage.[81,84] Cervical myelomeningoceles are commonly associated with occult spinal lesions in other areas, such as hemivertebra, syringomyelia, and diastematomyelia (discussed later). Chiari II lesions are common in cervical myelomeningoceles, but intracranial neural lesions commonly associated with more caudal myelomeningoceles (such as fused thalami, callosal anomalies, and cortical malformations) are rare.

Timing. The onset of a typical myelomeningocele is probably no later than 26 days of gestation,[3] when the posterior neuropore closes.

Etiological Considerations. Prevention of myelomeningocele and other neural tube defects necessitates understanding of their causes. Recognized causes of such defects include (1) multifactorial inheritance, (2) single mutant genes (e.g., the autosomal recessively inherited Meckel syndrome), (3) chromosomal abnormalities (e.g., trisomies of chromosomes 2, 7, 9, 13, 14, 15, 16, 18, and 21 and duplications of chromosomes 1, 2, 3, 6, 7, 8, 9, 11, 13, 16, 20, and X), (4) certain rare syndromes of uncertain modes of transmission, (5) specific teratogens (e.g., aminopterin, thalidomide, valproic acid, carbamazepine), and (6) specific phenotypes of unknown causes (e.g., cloacal exstrophy and myelocystocele).[50,85-89] In rodent models of neural tube defects, more than 240 gene mutations have been identified.[90] Recent human studies suggest that a variety of genetic mutations may play a role, likely through complex polygenic interactions, possibly with superimposed epigenetic influences to produce the different neural tube defect phenotypes.[47,91] Of defects resulting from these causes, most cases (≈80%) are encompassed within the group in which the neural tube defect is the only major congenital abnormality and inheritance is multifactorial (i.e., dependent on a genetic predisposition that is polygenic and influenced by minor additive genetic variations at several gene loci).[92,93] Overall, genetic factors are thought to play a role in 60% to 70% of these cases. Environmental influences may play an important role on this substrate. Less than 10% of neural tube defects are part of syndromic conditions.[94]

Factors establishing the combined influence of both genetic and environmental influences are summarized in Tables 1.3 and 1.4. Factors establishing the *genetic role* include (1) a preponderance in female patients, (2) ethnic differences that persist after geographical migration, (3) increased incidence with parental consanguinity, (4) increased rate of concordance in apparently monozygotic twin pairs, and (5) increased incidence in siblings (as well as in second-degree and, to a lesser extent, third-degree relatives) and in children of affected patients.[51,85-87,92,93,95-101] The possibility of important *environmental influences* is suggested particularly by large variations in incidence as a function of geographical location and time period of study (see Table 1.3). Particularly potent data to suggest environmental influences relate to long-term trends in incidence. For example, in the northeastern United States, an epidemic period could be defined between approximately 1920 and 1949, with a peak between 1929 and 1932.[102] Since the late 1980s, a prominent steady decline in incidence has occurred in both the United States and Great Britain (see earlier).[a] The *interaction of environmental and genetic influences* has been

TABLE 1.3 Factors Influencing Differences in Prevalence of Myelomeningocele

FACTOR	TIME PERIOD	PREVALENCE
Country		
England/Wales	1996	0.32
Finland	1996	0.41
Norway	1996	0.57
Northern Netherlands	1996	0.63
Region of country		
Northern China	1992–1993	2.92
Southern China	1992–1993	0.26
Time period		
Eastern Ireland	1980	2.7
Eastern Ireland	1984	0.6
Ethnic/racial (California)		
Non-Hispanic white	1990–1994	0.47
Hispanic	1990–1994	0.42
African American	1990–1994	0.33
Asian	1990–1994	0.20
Prenatal diagnosis and elective termination (England/Wales)		
Live and stillbirths	1996	0.09
Live and stillbirths and terminations	1996	0.31

Data from Mitchell LE, Adzick NS, Melchionne J, Pasquariello PS, et al. Spina bifida. *Lancet.* 2004;364:1885–1895.

TABLE 1.4 Maternal Risk Factors for Myelomeningocele

FACTOR	RELATIVE RISK
Previous affected pregnancy (same partner)	30
Inadequate intake of folic acid	2–8
Pregestational diabetes	2–10
Intake of valproic acid or carbamazepine	10–20
Low vitamin B_{12}	3
Obesity	1.5–3.5
Hyperthermia	2

Data from Mitchell LE, Adzick NS, Melchionne J, Pasquariello PS, et al. Spina bifida. *Lancet.* 2004;364:1885–1895.

[a]References 50, 51, 53, 87, 100, and 103-107.

TABLE 1.5 Correlations Among Motor, Sensory, and Sphincter Function, Reflexes, and Segmental Innervation

MAJOR SEGMENTAL INNERVATION[a]	MOTOR FUNCTION	CUTANEOUS SENSATION	SPHINCTER FUNCTION	REFLEX
L1–L2	Hip flexion	Groin (L1) Anterior, upper thigh (L2)	—	—
L3–L4	Hip adduction Knee extension	Anterior, lower thigh and knee (L3) Medial leg (L4)	—	Knee jerk
L5–S1	Knee flexion Ankle dorsiflexion Ankle plantar flexion	Lateral leg and medial foot (L5) Sole of foot (S1)	—	Ankle jerk
S1–S4	Toe flexion	Posterior leg and thigh (S2) Middle of buttock (S3) Medial buttock (S4)	Bladder and rectal function	Anal wink

[a]Segmental innervation for motor and sensory functions overlaps considerably; correlations shown are approximate.

demonstrated in experimental studies of the curly-tail mouse, in which a neural tube defect is inherited as an autosomal recessive trait.[9,108] Among *specific environmental influences*, a particularly important role for *folate deficiency* during the period of neural tube formation is suggested by experimental and clinical studies (discussed later). Other environmental factors, such as prenatal exposure to maternal hyperthermia, maternal diabetes mellitus, valproic acid (see Chapter 38), carbamazepine (see Chapter 38), maternal obesity, and low maternal vitamin B_{12} concentrations, also are of varying importance (see Table 1.4).[51,89,93,109-125]

The increased incidence of neural tube defects in siblings of index cases has had major importance for *genetic counseling*. Recurrence risks for neural tube defects are around 3% after a single affected pregnancy, increasing to 12% after two affected pregnancies.[126] However, precise estimates of risks in subsequent siblings must take into account the population under study (see Table 1.3). A striking relationship between recurrence risk and the level of the myelomeningocele in the index case has been shown.[97] Thus the risk for recurrence in a sibling was 7.8% if the index case had a lesion at T11 or above, but only 0.7% if the lesion was below T11. A decline in the risk of neural tube defect as birth order increases also has been defined[99,127]; for example, in a study in Albany, New York, the risk for subsequent affected siblings (1.4%) was significantly less than for previously affected siblings (3.1%).[98]

Maternal diabetes is associated with a threefold increase in birth defects, but this risk increases to 5.4-fold for neural tube defects and 170-fold for caudal cell mass dysplasias (discussed later).[128] At highest risk are pregnancies complicated by hyperglycemia around the time of conception (pregestational diabetes). Pregestational obesity is also a risk factor for neural tube defects. In one large population-based study, there was a fourfold increase in neural tube defects in women with body mass index (BMI) greater than 40.[129] Other studies have shown a significantly increased risk for neural tube defects when maternal pregestational BMI exceeds 30.[130,131] The association between neural tube defects and obesity is significantly stronger for spina bifida than for anencephaly.[132] Recent reports suggest that obesity-related neural tube defects are folate unresponsive.[133]

Clinical Aspects. The precise incidence of myelomeningocele is difficult to establish, in part because of differences in the terminology used in reports. The populations included in these studies are variable, with some including anencephaly, some only open neural tube defects, or some with a broad spectrum of neural tube defects.[134,135] Although there is a wide variation between[50,51] and within countries,[53,100] it is generally agreed that the incidence of neural tube defects has been decreasing in developed countries for the past three decades, even before the advent of folic acid supplementation (discussed later).[a] Factors implicated in this decline include dietary folate supplementation, improved antenatal diagnosis and, in some areas, elective termination.[139] Nonetheless, the global burden of neural tube defects (mostly anencephaly and myelomeningocele) remains high and estimated to exceed 300,000 cases per year, with highest prevalences in low- and middle-income populations.[140] At the same time, there has been a steady increase in the survival of myelomeningocele, with one study reporting survival rates of 71%, 69%, and 66% at 1, 10, and 20 years, respectively.[141]

Neurological Features. The clinical features of myelomeningocele relate primarily to the nature of the primary spinal lesion, as well as the presence and severity of associated complications, such as hindbrain herniation, hydrocephalus, and other intracranial developmental lesions.

The disturbances of neurological function, of course, depend on the level of the spinal lesion. Particular attention should be paid to examination of motor, sensory, and sphincter function. Moreover, in the first days of life, motor function subserved by segments caudal to the level of the lesion is common but then generally disappears after the first postnatal week.[142] Table 1.5 lists some of the important correlations among motor, sensory, and sphincter function, reflexes, and segmental innervation. Assessment of the functional level of the lesion allows reasonable estimates of potential future capacities. Thus most patients with lesions below S1 ultimately are able to walk unaided, whereas those with lesions above L2 usually are wheelchair dependent for at least a major portion of their activities.[143-148] Approximately one-half of patients with intermediate lesions are ambulatory (L4, L5) or primarily ambulatory (L3) with braces or other specialized devices and crutches. Considerable variability exists between subsequent ambulatory status and apparent neurological segmental level, especially in patients

[a]References 50, 51, 53, 54, 61, 87, 93, 103-105, 107, 109, and 13-138.

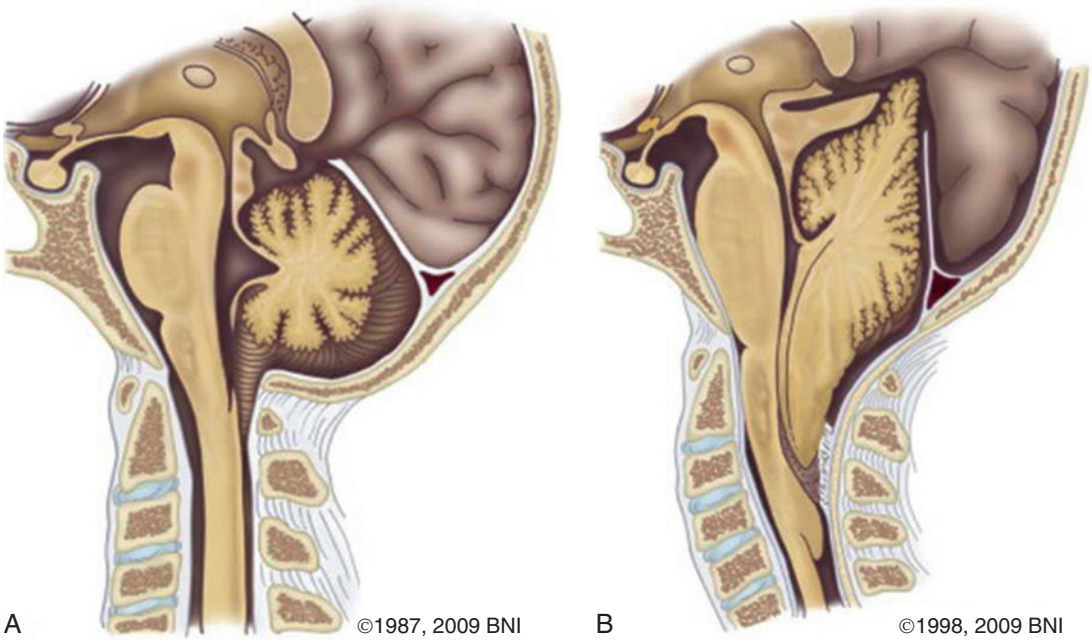


Figure 1.12 Diagrams of (A) normal posterior fossa and (B) Chiari II malformation. (Used with permission from Barrow Neurological Institute; Upper Cervical and Craniocervical Decompression. Gantwerker BR, Spine Surgery, Chapter 37, 377–388. Copyright © 2012, 2005, 1999 by Saunders, an imprint of Elsevier Inc.)

with midlumbar lesions.[144,149,150] Good strength of iliopsoas (hip flexion) and of quadriceps (knee extension) muscles is an especially important predictor of ambulatory potential rather than wheelchair dependence.[149,150] Deterioration to a lower level of ambulatory function than that expected from segmental level occurs over years, and this tendency is worse in the absence of careful management. In addition, patients with lesions as high as thoracolumbar levels, at least as young children, can use standing braces or other specialized devices to be upright and can be taught to *swivel walk*.[151,152] Indeed, continuing improvements in ambulatory aids and their use are constantly increasing the chances for ambulation in children with higher lesions (see Results of Therapy). Segmental level also is an important determinant of the likelihood of the development of scoliosis. Most patients with lesions above L2 ultimately exhibit significant scoliosis, whereas this complication is unusual in patients with lesions below S1.

Cervical myelomeningoceles are almost always associated with a normal neurological outcome if surgical detethering is performed in infancy.[81,153] Significant primary motor, sensory, bowel, and bladder deficits are rare.[43,83] Delayed or incomplete surgical detethering may result in progressive neurological deficits over time.

Associated Anomalies and Putative Mechanisms

Chiari Type II Malformation. The Chiari II malformation (Fig. 1.12) is a virtually ubiquitous complication of thoracolumbar, lumbar, and lumbosacral myelomeningocele. The central feature of this complex anomaly is a small posterior fossa, the contents of which are crowded and distorted.[79] A Chiari II malformation involves the midbrain and hindbrain (pons, medulla, and cerebellum) and cervical spinal cord and its components and associations are listed in Box 1.4. Features of the Chiari II malformation may be explained by the *unified theory*,[154,155] in which the ongoing spinal CSF leak results in failure of CSF *support* of the ventricles, including the fourth ventricle, which in turn leads to an underdeveloped small posterior fossa (with a low-set torcular and incomplete bony growth). The principles of the unified theory are supported by studies of fetal myelomeningocele repair showing reduced hindbrain herniation[156-158] and reduced brain stem compression.[159] The degree of hindbrain herniation does not appear to be related to the level of the spinal lesion.[154] However, some degree of hindbrain herniation is almost universally present in open myelomeningocele and remains the leading cause of death in the first 5 years of life.[160] The cerebellar hemispheres are underdeveloped,[158,161] but the cerebellar dysmorphology does not affect all cerebellar regions equally.[162] Compared with controls and corrected for reduced global volume, the anterior lobe is enlarged while the posterior lobe is reduced in size. Absence of brain stem nuclei, including the basal pontine and olivary nuclei, are also seen; these nuclei and the cerebellum have a common origin in the alar plate of the rhombencephalon.[163]

The *Chiari type II malformation* is responsible for both brain stem dysfunction (a serious complication in a minority of patients with myelomeningocele) and hydrocephalus, a serious complication in most patients with myelomeningocele (see earlier). Hydrocephalus associated with the Chiari type II malformation probably results primarily from one or both of two basic causes (see Box 1.4). The first is the hindbrain malformation that blocks either the fourth ventricular CSF outflow or the CSF flow through the posterior fossa. The second is at the aqueductal level, with aqueductal stenosis present in approximately 40% to 75%, and aqueductal atresia in an additional 10% of cases with Chiari II malformations.[127,163,164] Studies of human embryos

BOX 1.4 Complications of Myelomeningocele

Chiari II Malformation
Ubiquitous with lumbar-sacral myelomeningoceles

Temporal Features
Usually present by 2nd trimester

Etiological Features
Small posterior fossa is the fundamental mechanism; due to CSF leak from spinal lesion
Crowded and distorted contents

Anatomic Features
Small posterior fossa
Low-set torcular caudal herniation through foramen magnum (medulla, 4th ventricle, inferior vermis)
Rostral herniation through the tentorial notch (superior vermis)
Pressure/traction effects
Elongation and thinning of upper medulla and pons
Persistence of embryonic flexure
Cerebellar hemispheres may wrap around brain stem
Hydrocephalus due to disturbed flow dynamics from aqueduct, 4th ventricle, and subarachnoid space compression
Bony defects of foramen magnum, occiput and upper cervical vertebrae
Associated features of uncertain pathogenesis
Cerebellar dysplasia, hypoplasia or agenesis
Significant reduction of Purkinje cells
Absence of brain stem nuclei (basal pontine, olivary, other)

Clinical Importance
Stridor, apnea, cyanotic spells, and dysphagia may develop
Role in development of hydrocephalus

Hydrocephalus
Develops in 85%–90% of lumbar-sacral myelomeningoceles

Temporal Features
Most rapid progression occurring in first postnatal month
Dilation of ventricles before rapid head growth or before signs of increased intracranial pressure or both

Etiological Features
Chiari type II with obstruction of fourth ventricular outflow
Aqueductal stenosis
Impaired CSF flow through narrowed subarachnoid spaces and crowded posterior fossa

Importance
Requirement for shunt and its complications (especially infection) are a major cause of neurologic morbidity.

TABLE 1.6 Relation of Brain Stem Dysfunction to Mortality in Myelomeningocele

CLINICAL FEATURES	NUMBER	MORTALITY
Stridor	10	0
Stridor and apnea	4	25%
Stridor, apnea, cyanotic spells, and dysphagia	5	60%
Total	19	21%

Effective control correlated with ultimate neurological function.
Adapted from Charney EB, Rorke LB, Sutton LN, Schut L. Management of Chiari II complications in infants with myelomeningocele. *J Pediatr.* 1987;111:364–371.

and fetuses with myelomeningocele support the concept that the Chiari type II hindbrain malformation is a primary defect and not a result of hydrocephalus.[165]

Moreover, studies of a mutant mouse with defective neurulation (*Splotch*) provide insight into the mechanism by which myelomeningocele may lead to the Chiari type II malformation. Thus, in this model, it is clear that the Chiari type II malformation results from growth of the hindbrain in a posterior fossa that is too small. Hydrocephalus then results from the Chiari type II malformation, as described earlier. Additional support for this formulation is the demonstration that closure of the myelomeningocele in the second trimester of fetal life, before the most rapid growth of the cerebellum, results in upward displacement of the inferiorly herniated cerebellar vermis, expansion of the posterior fossa, improvement in CSF flow, and reduced need for ventriculoperitoneal shunting for hydrocephalus (discussed later; see Fig. 1.10).[157,166]

Clinical features directly referable to the hindbrain anomaly of the Chiari type II malformation (i.e., not to hydrocephalus) are probably more common than is recognized. In one carefully studied series of 200 infants, one-third exhibited feeding disturbances (associated with reflux and aspiration), laryngeal stridor, or apneic episodes (or all three). In one-third of these affected infants, death was "directly or indirectly attributed to these problems." Indeed, in this and similar series, at least one-half of the deaths of infants with myelomeningocele can be attributed to the hindbrain anomaly (despite treatment of the back lesion and hydrocephalus).[160,167,168] In a cumulative series of 142 infants, the median age at onset of symptoms referable to brain stem compromise was 3.2 months.[160] The clinical syndromes of brain stem dysfunction and their relation to mortality are presented in Table 1.6.[160,170,171] The 19 affected infants represented 13% of those with myelomeningocele. The principal clinical abnormalities in this and related studies reflect lower brain stem dysfunction and include vocal cord paralysis with stridor, abnormalities of ventilation of both obstructive and central types (especially during sleep), cyanotic spells, and dysphagia.[167-170,172-179] The full constellation of stridor, apnea, cyanotic spells, and dysphagia is associated with a high mortality (see Table 1.6). Such sensitive assessments of brain stem function as brain stem auditory-evoked responses, polysomnography, pneumographic ventilatory studies, and somatosensory-evoked responses are abnormal in approximately 60% in infants with myelomeningocele and are the neurophysiological analogues of the clinical deficits.[167,180-184]

The clinical abnormalities of brain stem function have three primary causes. First, they relate in part to the brain stem malformations, which involve cranial nerve and other nuclei, and are present in most cases at autopsy (Table 1.7).[163] Second, compression and traction of the anomalous caudal brain stem by hydrocephalus and increased intracranial pressure may play a role, especially in the vagal nerve disturbance that results in the vocal cord paralysis and stridor. Third, ischemic and hemorrhagic necrosis of brain stem is often present and may result from the disturbed arterial architecture of the caudally displaced vertebrobasilar circulation.[170]

Hydrocephalus. Several clinical features are helpful in evaluating the possibility of hydrocephalus. First, on examination, *the status of the anterior fontanelle and the cranial*

TABLE 1.7 Brain Stem Malformations in Myelomeningocele

Total With Brain Stem Malformation	76%
Defective myelination	44%
Hypoplasia of cranial nerve nuclei	20%
Hypoplasia or aplasia of olives	20%
Hypoplasia or aplasia of basal pontine nuclei	16%
Hypoplasia of tegmentum	4%

Adapted from Gilbert JN, Jones KL, Rorke LB, Chernoff GF, et al. Central nervous system anomalies associated with meningomyelocele, hydrocephalus, and the Arnold-Chiari malformation: reappraisal of theories regarding the pathogenesis of posterior neural tube closure defects. *Neurosurgery*. 1986;18:559–564.

TABLE 1.8 Cerebral Cortical Malformations in Myelomeningocele

Total with Cerebral Cortex Dysplasia	92%
Neuronal heterotopias	44%
Polymicrogyria (with disordered lamination)	40%
Disordered lamination only	24%
Microgyria, normal lamination	12%
Profound migrational disturbances	24%

Adapted from Gilbert JN, Jones KL, Rorke LB, Chernoff GF, et al. Central defects. *Neurosurgery*. 1986;18:559–564.

sutures should be noted. A full anterior fontanelle and split cranial sutures are helpful signs for the diagnosis of increased intracranial pressure. CSF leakage from the myelomeningocele provides decompression in this situation, and the signs of increased intracranial pressure may be absent or delayed. *Evaluation of the head size* provides useful information. If the head circumference is more than the 90th percentile, approximately a 95% chance exists that appreciable ventricular enlargement is present.[185] If the head circumference is less than the 90th percentile, an approximately 65% chance of hydrocephalus still exists.[185] The *site of the lesion* is also helpful in predicting the presence or imminent development of hydrocephalus. With occipital, cervical, thoracic, or sacral lesions, the incidence of hydrocephalus is approximately 60%; with thoracolumbar, lumbar, or lumbosacral lesions, the incidence of hydrocephalus is approximately 85% to 90%.[84,185,186]

Signs of increased intracranial pressure are not prerequisites for the diagnosis of hydrocephalus in the newborn and indeed are observed in only approximately 15% of newborns with myelomeningocele.[164] Serial ultrasound scans are important because progressive ventricular dilation, without rapid head growth or signs of increased intracranial pressure, occurs in infants with myelomeningocele[164,187] in a manner analogous to the development of hydrocephalus after intraventricular hemorrhage (see Chapter 24). The most common time for hydrocephalus with myelomeningocele to be accompanied by overt clinical signs is 2 to 3 weeks after birth; more than 80% of infants who have hydrocephalus with myelomeningocele and who do not undergo shunting procedures exhibit such clinical signs by 6 weeks of age.[152]

Other Central Nervous System Anomalies. Other anomalies of the CNS associated with myelomeningocele and the Chiari II lesion include cerebral cortical anomalies, callosal defects, small posterior fossa, with decreased size of the cerebellum. Perhaps most important of these are abnormalities of cerebral cortical development. In earlier studies, the pathological finding of microgyria was described in 55% to 95% of cases.[188,189] Whether this finding reflected a true cortical dysgenesis was not clear, but its presence was of major potential importance because of a relationship with the intellectual deficits that occur in a minority of these patients. Moreover, the occurrence of seizures in approximately 20% to 25% of children with myelomeningocele may be accounted for in part by such cortical dysgenesis.[190-192] This issue was clarified considerably by a careful neuropathological study of 25 cases of myelomeningocele (Table 1.8). Fully 92% of the brains showed evidence of cerebral cortical dysplasia, and 40% had overt polymicrogyria.[163] Thus impaired neuronal migration was a common feature. In addition, callosal anomalies, including hypoagenesis (reduced ventrodorsal extent) and hypoplasia (reduced thickness), are thought to occur to some degree in almost all cases of myelomeningocele.[193] In callosal hypogenesis, the rostrum, splenium, and posterior body are the most commonly missing elements.[79] Even when present, the posterior elements (i.e., isthmus and splenium) are the most commonly hypoplastic regions.[194] Thoracic myelomeningoceles are twofold more likely to have splenial agenesis than lower myelomeningoceles.[193] Up to 44% of myelomeningocele cases have callosal hypoplasia, in which the callosum is present in its entire rostrocaudal extent but is thinned.[195] More recent MRI studies using surface area and diffusion tensor analyses support the notion that the thinner corpus callosum results from fewer crossing axons.[196] Several studies have suggested that volume of the entire corpus callosum, as well as specifically the genu and splenium,[194,197] correlate with cognitive outcome.

Other anomalous features, such as cranial lacunae, hypoplasia of the falx and tentorium, low placement of the tentorium, anomalies of the septum pellucidum, anterior and inferior *pointing* of the frontal horns, thickened interthalamic connections, and widened foramen magnum, are of uncertain clinical significance. However, they are visualized readily to varying degrees with CT, MRI, and cranial ultrasonography.[72,198-200] Midbrain anomalies include tectal *beaking*, which is due to fusion of the colliculi and is evident in about 65% of cases. Anomalies in position of the cerebellum are observable in utero by ultrasonography or MRI.[201,202] Cerebellar dysplasia, including heterotopias, is definable neuropathologically in 72% of cases.[163]

Diagnosis. Maternal serum alpha-fetoprotein (AFP) levels and ultrasonography are the primary screening techniques for the prenatal diagnosis of neural tube defects. *AFP* is the major protein component of human fetal serum (Fig. 1.13) and can be detected 30 days after conception, peaking at between 10 and 13 weeks of gestation. Current recommendations are for maternal serum AFP testing between 15 and 20 weeks' gestation.[203] Increased levels of AFP in the amniotic fluid occur with open neural tube defects and anencephaly; the

mechanism for the elevated levels is thought to represent transudation of the protein from the membranes covering the lesion (see Figs. 1.9 and 1.11).[204] Positive maternal serum AFP testing should be repeated, since false positive tests are not uncommon.[205] Conversely, there are conditions other than open neural tube defects that may elevate maternal serum and amniotic fluid AFP levels, including abdominal wall defects such as omphalocele or gastroschisis. Until the mid-1980s, amniocentesis for detection of elevated levels of AFP in amniotic fluid was the most common, albeit invasive, procedure for suspicion of an open neural tube defect. Several reports in the late 1970s indicated that determination of *maternal serum AFP levels* was useful for screening for neural tube defects.[206-210] The largest study involved measurements in more than 18,000 pregnant women in the United Kingdom.[210] The optimal time for measurement was shown to be 16 to 18 weeks of pregnancy. Subsequent experience in Scotland,[206] Sweden,[211] Wales,[212] and the United States[213,214] confirmed the high sensitivity of the analysis of AFP in serum, and large-scale screening programs are now well established.[93,212,214,215] In situations where the origin of elevated maternal serum AFP remains in question, amniotic fluid levels of AFP should be tested and, if elevated, should be followed by acetylcholinesterase (AChE; primarily neuronal in origin) levels. Elevation of both AFP and AChE in the amniotic fluid confirms a neural origin for the elevated AFP.[216]

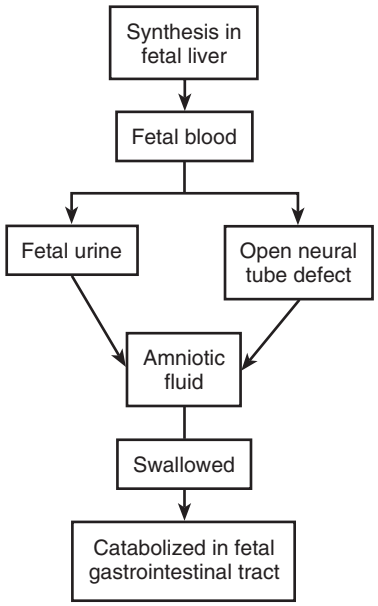


Figure 1.13 Physiology and pathophysiology of alpha-fetoprotein in utero.

The diagnosis and anatomical details of a fetal neural tube defect are confirmed by ultrasonography and MRI.[77,78,93,212,217-221] The earliest ultrasonographic features include changes in the configuration of the posterior fossa, in addition to the lesion itself. After 12 weeks' gestation the cranial markers of myelomeningocele (i.e., banana and lemon signs [Fig. 1.14], decreased extraaxial CSF, and small cisterna magna) become detectable by ultrasound and are useful supportive findings. Fetal MRI is the diagnostic study of choice in the fetal period and best delineates the anatomical details (see Fig. 1.10).

Management. The management of myelomeningocele has undergone major changes in recent decades, both in terms of primary prevention, as well as lesion repair in the newborn, and more recently in the fetus. The following briefly reviews current concepts in management.

Primary Prevention. Management of the patient with myelomeningocele, or of any patient with a neural tube defect,

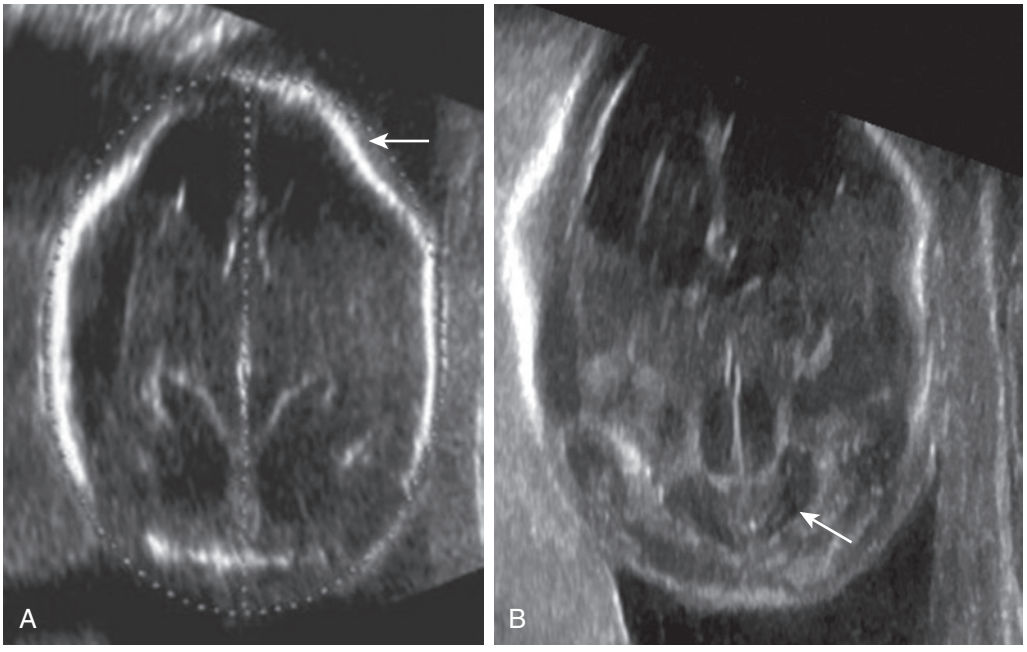


Figure 1.14 Fetal cranial ultrasound features associated with open neural tube defects. (A) The "lemon-shaped" cranium due to frontal bone scalloping *(arrow)*. (B) The "banana sign" of the compressed cerebellum *(arrow)*. (From Coady AM. *Twining's Textbook of Fetal Abnormalities*. Chapter 11, 223–263 Copyright © 2015, 2007, 2000 by Churchill Livingstone, an imprint of Elsevier Limited. All rights reserved.)

BOX 1.5 The Role of Folate in Neural Tube Defects

- 1959: Failed abortions using an FA antagonist were associated with an increase in NTDs.[423]
- 1965: Embryopathy of maternal FA deficiency includes NTD.[424]
- 1980–1983: MVI supplementation reduced NTD risk.[254-257,425]
- 1989: MVI supplementation beneficial effect corroborated.[258]
- 1989: Noncontrolled study of MVI/FA supplementation in early pregnancy leads to decrease in NTD.[245]
- 1991: Medical Research Council (United Kingdom) Vitamin Study. Large RCT of FA supplementation (4 mg/day) in women with previous NTD fetus showed an 83% reduction.[246]
- 1992: RCT of FA supplementation (0.8 mg/day) from 1 month preconception through first 8 weeks of pregnancy reduced the risk of a first NTD-affected fetus.[228]
- 1992: Centers for Disease Control and Prevention (United States) recommended FA supplementation (0.4 mg/day) for all women of childbearing age capable of becoming pregnant in the United States.[267]
- 1997: Despite increased public awareness, supplementation campaign proved disappointing; <1/3 women compliant and >50% of pregnancies in United States are unplanned.
- 1998: Fortification campaign implemented in the United States with goal of ensuring that women of childbearing age received the daily recommended dose of 400 μg/day
- 2002–2003: Several Canadian reports describe a 32%–54% decrease in NTD since dietary FA fortification.[275,426]
- 2010: United States report ~20% decrease in NTD since dietary FA fortification.
- 2015: Late high-dose (5 mg/day) rescue FA after early pregnancy diagnosis may be protective.[286]
- Currently: More than 75 countries have mandatory FA fortification programs.

FA, Folic acid; *MVI*, multivitamins; *NTD*, neural tube defect; *RCT*, randomized clinical trial.

should begin with the following question: How could this have been prevented? Indeed, *prevention* must be considered the primary goal for the future. Major advances have been made in this direction. Prenatal diagnosis of neural tube defects and termination of pregnancy involving an affected fetus are effective methods of *secondary* prevention. However, a method of primary prevention would be more widely acceptable. Evidence now shows that folate *supplementation* around the time of conception, and therefore neural tube closure, has a major preventive effect on the occurrence of neural tube defects.[a]

The effect of *multivitamin supplementation* (Box 1.5) before and during early pregnancy on recurrence of neural tube defects was first studied definitively by Smithells and colleagues[254-257,264] in a recruited series of women with histories of births of one or more previously affected children. The multivitamin supplement contained *physiological* quantities of vitamins, such as folate, riboflavin, ascorbic acid, and vitamin A. The results of the study were striking. Of 454 women taking supplements, only 3 (0.7%) had recurrences, whereas of 519 women not taking supplements, 24 (4.7%) had recurrences. Although the study was criticized for several methodological issues,[265,266] the data were promising. A subsequent study by Smithells and coworkers[258] showed a similarly striking effect. A noncontrolled study in the United States on women identified largely by elevated serum AFP levels, measured in a single regional laboratory, confirmed the beneficial role of folate-containing multivitamins.[245] Moreover, the beneficial effect of folate was related clearly to the time during pregnancy when neural tube closure occurs.

After the aforementioned study, the British Medical Research Council completed an extremely important multicenter study (Box 1.5).[246] Women were assigned randomly to four groups allocated to receive one of the following regimens of supplementation: folate and a multivitamin supplementation of "other vitamins," folate alone, "other vitamins" alone, or no folate or "other vitamins." The results were decisive in demonstrating the preventive effect and the specific role of folate (vs. other components of the previously used multivitamin preparations). The overall reduction in neural tube defects was 83%. The findings clearly had major implications for the primary prevention of neural tube defects. On the basis of this study, the US Centers for Disease Control and Prevention (CDC) recommended an increase in folic acid intake by 0.4 mg/day for women from the time they plan to become pregnant through the first 3 months of pregnancy.[246a] The folate was not recommended to be administered as a multivitamin preparation because of the potential danger for toxicity from excessive amounts of other vitamins in the multivitamin preparation. Because of the uncertainty of the degree of risk from the folate supplementation, the initial recommendations were directed only to women who had had a previous pregnancy complicated by a neural tube defect, as in the British study. Subsequently, two studies showed a preventive effect of periconceptional folic acid exposure on the occurrence of neural tube defects in populations of women without a prior affected child.[228,263] These observations were followed by the recommendation of the US Public Health Service and the American Academy of Pediatrics that "all women capable of becoming pregnant consume 0.4 mg of folic acid daily to prevent neural tube defects."[268]

The optimal methods of folate supplementation and dose of the supplement are not totally clarified.[269,270] Public educational campaigns, albeit useful, have not been entirely successful, especially because as many as 50% of pregnancies are unplanned, and only a few of the *nonplanners* are reached by such campaigns.[269,271] In 1998 the US Food and Drug Administration mandated fortification of all enriched grain products with folate (0.14 mg/100 g), which resulted in a 30% decrease in neural tube defects.[272] Similar programs have been instituted in many other countries and have resulted in an approximately 50% reduction in prevalence of neural tube defects.[a] However, the British Medical Research Council study used a 4 mg (rather than 0.4 mg) daily folate dose and achieved an 83% reduction in prevalence of lesions. Thus one expert in the field recommended a public health policy that includes "both the mandatory fortification of flour and a recommendation that all women planning a pregnancy take 5 mg of folic acid per day."[261]

Together these studies have led to the conclusion that folate supplementation was capable of reducing but not eradicating neural tube defects, giving rise to the notion of "folic acid–preventable spina bifida and anencephaly" (FAPSBA).

[a]References 9, 50, 51, 93, 103, 106, and 222-263.

[a]References 103, 106, 241, 244, 251, 259, and 273-276.

It is estimated that 50% to 72% of neural tube defects are preventable through folate supplementation.[277,278] The reduction in anencephaly and facial defects has been less striking than that of spina bifida.[279,280] In addition, in the postfortification era the initial decrease in neural tube defects has been sustained without further decline. In the United States, Hispanics continue to have the highest rate, whereas non-Hispanic blacks have the lowest rate. The decreases in prevalence of neural tube defects following fortification have been associated with increasing levels of serum and red blood cell (RBC) folate levels in the population and an almost complete eradication of folate deficiency. Recent studies have suggested that the majority of FAPSBA in the United States is prevented by fortification; however, more than 20% of women of childbearing age still do not attain the RBC folate levels known to decrease the risk of neural tube defects.[281,282] This has in turn led to recommendations for strategies that target specific RBC folate levels.[283]

The CDC has released a series of updates on global prevention of FAPSBA, as more countries instituted fortification programs. In 2006 the decrease in FAPSBA through fortification programs around the world was estimated at 6.8%,[284] in 2008 it was estimated at 9.1%, and in 2012 estimates ranged from 15.6% to 25.5%. The higher number of 25% is based on recent reports, suggesting that the threshold dose of folate necessary to prevent FAPSBA was lower than the originally proposed 0.4 mg/day. In addition, two recent case-control studies suggested that (1) full protection against FAPSBA was attained at levels lower than 0.4 mg/day, and (2) folate supplementation was no longer adding further protection against FAPSBA since the introduction of fortification.[272,285] Together, these studies suggested that most of the FAPSBA prevention in the United States was through fortification and that the vast majority of FAPSBA around the world could be prevented with fortification programs alone.

A population-based study in Denmark investigated the effects of two public health measures on the incidence of myelomeningocele, specifically recommendations for folic acid supplementation and second trimester (18–19 week gestation) fetal ultrasound screening.[139] The study concluded that recommendations for folate supplementation had no significant effect on the incidence of myelomeningocele because of lack of compliance. However, the second trimester prenatal ultrasound screening program was associated with a significant decrease in the rate of live-born babies with myelomeningocele.[139] Data from a large study in China suggest that late administration of folate might have a protective role against neural tube defects.[277] A strategy of high-dose (5 mg/day) folic acid rescue (to achieve rapid fetal levels) has been proposed for cases in which pregnancy is diagnosed before or in the provided time frame in women not taking folate supplementation.[286]

The mechanism of the beneficial effect of folate is not established. One report raised the possibility that autoantibodies against folate receptors are present in as many as 75% of women who have had a pregnancy complicated by a neural tube defect.[287] The autoantibody-mediated block of cellular folate uptake by folate receptors could be bypassed by administered folate, because the latter is reduced and methylated in vivo and is transported into cells by the reduced folate carrier. A related possibility is that the beneficial effect of folate could involve *the metabolism of homocysteine to methionine*, a reaction catalyzed by methionine synthase and necessitating a metabolite of folic acid (5-methyltetrahydrofolate).[a]

A critical enzyme in the synthesis of 5-methyltetrahydrofolate, *methylenetetrahydrofolate reductase*, is defective in 12% to 20% of cases of neural tube defects.[230,288] One biochemical result of this disturbance is an elevation of homocysteine, which has been shown to produce neural tube defects in avian embryos.[289] Another potential mechanism of a defect in homocysteine conversion to methionine is a disturbance in methylation reactions, for which methionine is crucial.[224,230] Transmethylations of DNA, proteins, and lipids have far-reaching metabolic consequences.[224,230]

Because some neural tube defects appear to be folate nonresponsive, other potential forms of nutritional supplementation have been explored. Inositol deficiency is the only known nutritional deficiency known to cause neural tube defects in mouse models.[292] In addition, inositol blood levels are significantly lower in pregnant women carrying a fetus with a neural tube defect.[293] Initial data from a randomized trial of periconceptional inositol supplementation in women with previous pregnancies complicated by neural tube defects are encouraging.[294]

Management After Fetal Diagnosis. The *two-hit* hypothesis for factors that determine the ultimate postnatal neurologic function of myelomeningocele survivors has significantly influenced fetal and delivery management of myelomeningocele. This hypothesis proposes that long-term neurologic function depends not only on the primary spinal defect but also on the accumulation of secondary, potentially treatable complications, including progressive injury to the exposed spinal neural tissue and the development of Chiari II lesions and hydrocephalus.[201,296,297] In fact, several lines of evidence have implicated these secondary insults in the majority of the ultimate deficit. Specifically, earlier studies showed preservation of exposed neural elements and absence of both hindbrain herniation and hydrocephalus in autopsies of early but not later gestation fetuses with myelomeningoceles.[298,299] Subsequent studies in midgestation fetuses showed loss of normal neural tissue at the level of the exposed tissue but not proximally.[300,301] In addition to direct trauma, noxious substances in the amniotic fluid, including meconium, have been implicated.[302] In myelomeningocele there is typically an accumulation of CSF in the subarachnoid space ventral to the cord at the level of the lesion (see Fig. 1.9); it has been suggested that the dorsal displacement of the cord exerts pressure on the dorsal cord neural elements by compression against the spinous defect.[303] Clinically, these observations are supported by the fact that fetal leg movements are often noted earlier in gestation in areas where they are lost after birth. Other studies in rodent and ovine models[304,305] suggested that secondary neural injury could be prevented or markedly attenuated and that normal hindbrain anatomy could be established after fetal closure of the spinal defect.[306,307]

On the basis of these experimental data, initial nonrandomized clinical studies of intrauterine intervention were performed in human fetuses with myelomeningocele.[156,157,166,308-311] These earlier studies reported a number of promising outcomes,

[a]References 9, 50, 222, 226, 230, 231, and 288-291.

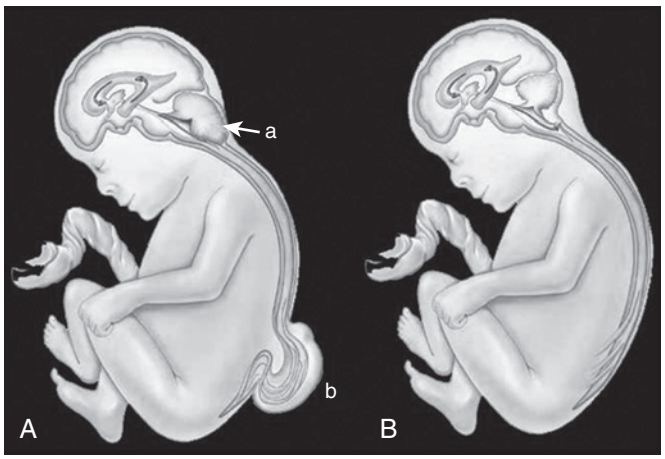


Figure 1.15 Pathogenetic formulation for the Chiari type II malformation and the effect of treatment. See text for details. In (A) Chiari malformation (a) and the open myelomeningocele (b) are shown. The negative pressure generated from drainage of cerebrospinal fluid from the open myelomeningocele (b) results in the inferior displacement of the cerebellum (a) and thereby the Chiari type II malformation. (B) After fetal closure, positive back pressure reduces the cerebellar hernia and expands the posterior fossa. (From Sutton LN, Adzick NS, Bilaniuk LT, Johnson MP, et al. Improvement in hindbrain herniation demonstrated by serial fetal magnetic resonance imaging following fetal surgery for myelomeningocele. *JAMA*. 1999;282:1826–1831.)

BOX 1.6 Outcome of Fetal Versus Neonatal Myelomeningocele Repair

Nonrandomized Studies—Prenatal Repair Associated With
- lower extremity function better than expected for anatomical level
- decreased hydrocephalus and need for VP shunt
- reversal of hindbrain herniation
- decreased brain stem dysfunction

10-Year Follow-up (n = 54)
- 79% community ambulators
- 9% household ambulators
- 14% wheelchair dependent
- 26% normal bladder function

Randomized Clinical Trial (MoM Study)—Prenatal Repair Group Had
- decreased need for VP shunt by 12 months (40% vs. 82%)
- improved motor and mental function by 30 months (25% vs. 67%)
- decreased moderate-severe Chiari II malformations (25% vs. 67%)
- increased independent orthotic-free ambulation (42%–21%)
- anatomical remodeling of posterior fossa
- increased rate of prematurity, chorionic membrane separation, and premature rupture of membranes
- increased need for postnatal cord untethering
- threatened or partial dehiscence of hysterotomy site (25%)

including lower extremity function better than predicted from the anatomical level of the lesion,[166] a significant decrease in hydrocephalus,[166,312,313] and the need for postnatal shunt placement.[166,311] Initial clinical reports also corroborated earlier experimental findings by showing reversal of hindbrain herniation as early as three weeks after human fetal myelomeningocele closure (possibly underlying the decreased need for shunt placement), as well as significantly fewer functional brain stem deficits (Box 1.6).[159,166] On the basis of these experimental and preliminary clinical results, a three-center randomized clinical trial of open prenatal versus conventional postnatal myelomeningocele repair was performed, in which the fetal surgery group with spinal lesions between the T1 and S1 levels underwent open surgical repair of the spinal lesion before 26 weeks' gestation. The trial was terminated early for demonstrated benefit in the experimental fetal surgery group.[314] Specifically, the fetal repair group required significantly fewer (40% vs. 82%) ventriculoperitoneal shunt procedures by 12 months of age, improved motor and mental composite scores at 30-month follow-up, and fewer (25% vs. 67%) moderate to severe Chiari II malformations (Fig. 1.15). There was an overall improvement in the functional versus anatomical spinal level, as well as an increased incidence of ambulation without orthotic devices in the fetal surgery group. Specifically, 42% versus 21% of fetal surgery cases were walking independently at follow-up (Box 1.6). However, the fetal repair group had a significantly higher rate of prematurity, chorionic membrane separation, and premature rupture of membranes, especially among those performed before 23 weeks' gestation,[315] and required more postnatal surgical untethering of the spinal cord. In addition, although no uterine ruptures occurred, 25% of women in this group had threatened or partial dehiscence of the hysterotomy site. Subsequent reports from the same center have corroborated those from the clinical trial but have shown that fewer than 30% of cases referred for evaluation actually underwent fetal myelomeningocele repair.[316]

Measurements of the posterior fossa and its contents in three groups—(1) normal controls and cases with myelomeningocele undergoing (2) fetal repair and (3) postnatal repair—provided evidence that the fetal repair group underwent postoperative anatomical remodeling of the posterior fossa that approached that of the normal controls, whereas postnatal repair cases failed to do so.[317]

Long-term follow-up at a median age of 10 years of 54 patients who underwent fetal myelomeningocele repair *before* the MoMS (Management of Myelomeningocele Study) clinical trial showed that 79% were community ambulators, 9% were household ambulators only, 14% were wheelchair dependent, and 26% had normal bladder function (Box 1.6).[318]

Earlier attempts at endoscopic closure were abandoned for an open hysterotomy approach, used during the MoMS trial. Following reports of the maternal and pregnancy complications of open hysterotomy, such as premature labor and uterine scar dehiscence, endoscopic approach was reexplored. However, the technical approach to the fetal spinal closure was significantly more challenging and associated with a paradoxical increase in prematurity and mortality.[319,320] Most recently, a phase 1 trial (10 cases) of endoscopic fetal myelomeningocele repair, in which a biocellulose patch is used to seal the CSF leakage, obviated the need for dural repair.[321] Initial results are promising, especially in the reversal of hindbrain herniation; the need for postnatal CSF shunting for hydrocephalus was similar to that in the MoMS trial. Clearly larger studies are needed to perform side-by-side comparisons of the open versus endoscopic approaches to fetal repair of myelomeningocele.[314,321] Other

experimental approaches are currently being investigated, including in utero stem cell transplantation,[323,324] but these have to date not entered into clinical care.

Management of Labor and Delivery. The optimal route for delivery of the fetus with an open neural tube defect remains controversial.[325] Proponents of the *two-hit hypothesis* argue that both labor and passage through the birth canal are likely to cause secondary traumatic neural injury. Consistent with the possibility of mechanical injury during labor, the results of a retrospective review of 160 carefully studied cases of myelomeningocele suggest that *delivery by cesarean section* before the onset of labor may result in better subsequent motor function than vaginal delivery or delivery by cesarean section after a period of labor.[325] Overall, infants delivered by cesarean section before the onset of labor had a mean level of paralysis 3.3 segments below the anatomical level of the spinal lesion, compared with 1.1 and 0.9 for infants delivered vaginally or delivered by cesarean section after the onset of labor, respectively. This variance is large enough to make the difference between the child's being ambulatory or wheelchair bound. Thus scheduled delivery by cesarean section before the onset of labor should be considered for the fetus with myelomeningocele, particularly if prenatal ultrasonography and karyotyping rule out the presence of severe hydrocephalus, chromosomal abnormality, or multiple systemic anomalies. Unfortunately there have been no prospective randomized trials comparing vaginal versus abdominal delivery to date, and in studies suggesting the benefit of cesarean delivery, comparison has been to historical controls.[325,326] As such, the mode of delivery currently remains the obstetrician's preference.

Postnatal Management. In developed countries with antenatal screening programs, most cases of myelomeningocele are diagnosed in the fetal period. Fetal imaging with ultrasound and/or MRI may allow for meaningful assessment of both acute neurological function at birth as well as long-term neurodevelopmental prognosis of the infant. Although most newborns with myelomeningocele are able to maintain vital functions, there is a higher than usual risk of cardiorespiratory failure that may require a period of extraordinary life support. In severe cases of hydrocephalus, Chiari II malformation, or associated malformations, it is reasonable to initiate discussions during pregnancy that allow the family to consider the level of intervention they would wish for their child if extraordinary life support is needed. The next step is to decide whether the newborn with myelomeningocele should receive anything more than conservative, supportive care (e.g., tender nursing care and oral feedings). Most neurosurgeons in the United States would advise early closure of the back lesion and, if needed, a CSF-diversion shunt.[160,327,328] Although the therapies are best discussed by the appropriate surgical specialists, a brief review is necessary here.

Early Postnatal Management. The prevalent notion is that *early closure of the back lesion* (within the first 24–72 hours) is optimal. The rationale for this approach has been the prevention of infection and the loss of motor function that may occur after the first days of life (see earlier). The prevention of infection is supported by several studies.[329,330] Conversely, in a large study of 110 infants with myelomeningocele, there was no significant difference in the rate of ventriculitis or lower extremity paralysis between infants undergoing early (first 48 hours) versus late (3–7 days) closure of the back lesion.[331] On balance, it would appear most prudent to close the back as promptly as possible (within the first 24–72 hours) but not to feel compelled to proceed so rapidly as to interfere with rational decision making. In addition, value for the use of prophylactic antibiotics from the first 24 hours of life to the time of surgery is suggested by the results of two studies.[331,332] In the later and larger study, ventriculitis developed in only 1 of 73 infants (1%) receiving broad-spectrum antibiotic prophylactic therapy, compared with 5 of 27 (19%) who did not receive antibiotics.[332]

Details of the operative repair of myelomeningocele are discussed in other sources.[327,333,334] Techniques to minimize the risk of subsequent development of tethered cord are important.

Long-Term Management of Associated Lesions

Management of Hydrocephalus. The management of the commonly associated hydrocephalus depends, first, on identification of the condition in the affected child. The findings of rapid head growth, bulging anterior fontanelle, and split cranial sutures are obvious, and an ultrasound scan can define the severity and the pattern of the ventricular dilation. More difficult is identification of low-grade hydrocephalus, often with no clinical signs, with CSF pressure in the normal range and with ventricles that are moderately dilated but not necessarily increasing disproportionately in size (often called *arrested* hydrocephalus). Later observations of similar patients have demonstrated a discrepancy in performance versus verbal intelligence quotient (IQ) scores, with the latter higher than the former. This discrepancy is considered consistent with a hydrocephalic state, which benefits from placement of a shunt.[335,336] Studies suggest that earlier use of shunt placement with resulting decreased ventricular size is associated with improved performance scores, especially in the cognitive domain (see the next section).[336]

Ventriculoperitoneal shunts are the primary form of the CSF-diversion technique used currently.[168,337] Although randomized controlled studies are not available, current evidence suggests that intelligence is better preserved if ventriculoperitoneal shunts are performed more liberally.[338,339] Such an apparent benefit for the early treatment of hydrocephalus is supported by data suggesting that the degree of ventriculomegaly identified in utero or the size of the cerebral mantle in the first week of life correlates significantly with subsequent intelligence if the hydrocephalus is treated.[340,341] This conclusion must be interpreted with the awareness that the incidence of shunt complications varies depending on the clinical circumstances and that shunt complications have a major deleterious effect on intellectual outcome.[185,342,343]

The dominant deleterious shunt complication is *infection.* In a study of 167 infants with myelomeningocele, the mean IQ of infants with shunt placement for hydrocephalus complicated by infection was 73; with shunt placement for hydrocephalus and no infection, the mean IQ was 95.[344] The mean IQ in infants with myelomeningocele but no hydrocephalus was 102. The similarity of IQ in infants with and without hydrocephalus suggests that the hydrocephalus per se, if adequately treated and not complicated by infection, does not have a major deleterious effect on intellectual outcome.

Management of Brain Stem Dysfunction Associated With the Chiari Type II Malformation. Management of the clinical abnormalities of brain stem dysfunction (see Table 1.6) associated with the Chiari II malformation is difficult. Infants with stridor and

obstructive apnea generally respond effectively to improved control of hydrocephalus; any additional benefit for cervical decompression is less clear.[170,172] However, infants with severe symptoms, especially cyanotic episodes related to expiratory apnea of central origin, do not respond effectively to current modes of therapy.[170,172] With progression of the condition, mortality rates in such infants exceed 50%. In a study of 17 infants who had brain stem signs in the first month of life (swallowing difficulty, 71%; stridor, 59%; apneic spells, 29%; weak cry, 18%; aspiration, 12%), and in whom functioning shunts were in place, decompressive upper cervical laminectomy resulted in complete resolution of signs in 15 (two infants died).[179] Postoperative morbidity was least when surgery was carried out within weeks rather than months after clinical presentation.

Management of Orthopedic, Bowel, and Urinary Tract Complications. Myelomeningocele is almost invariably complicated by disturbances in urinary and bowel function, as well as orthopedic complications. The management of these groups of complications is a major problem after the newborn period and is discussed in greater detail elsewhere.[345-350] Of note, orthopedic and urinary tract difficulties are very important determinants of patient and family perceptions of quality of life in adolescence[351]; careful discussion of these complications is important during prenatal counseling, since they are issues that factor significantly into parental decision making.[340,350] Dysfunction of the lower urinary tract (urethral sphincter and bladder), particularly the inability to accommodate and eliminate urine at low pressures, presents a major risk for the subsequent development of vesicoureteral reflux, ascending dysfunction of the upper urinary tract, and eventually renal dysfunction.[345,352] Mechanisms for this disturbance include dyssynergy between contracting/relaxing muscular function of the bladder and urethral sphincter, and fibrosis and irreversible hypertrophy of bladder musculature. Indeed, in a study of 36 infants, 13 of 16 who had subsequent deterioration of the urinary tract had incoordination of the detrusor-external urethral sphincter in the newborn period. This incoordination was followed by such deterioration in 72% of the newborns. Thus urodynamic evaluation in the newborn provides critical information about the urinary tract and helps determine the optimal type and frequency of follow-up management. Early evaluation and aggressive surveillance of bladder function, together with clean intermittent catheterization and antimuscarinic medications, decrease the need for future bladder surgery[353] and result in continence in up to 85% of patients.[144,345-347,350]

Ongoing monitoring of urinary function is important, since postoperative adhesions between the lower spinal cord and the repaired dural linings (often in association with dermoid inclusion cysts)[354] may result in cord tethering and stretch with progressive neurologic and urologic dysfunction. Such secondary cord tethering has been reported in up to 25% of repaired myelomeningocele cases by the age of 8 years.[355,356] In one study, more than 30% of children with normal bladder function in early infancy subsequently developed urological dysfunction requiring cord detethering.[357] Of note, fetal repair of myelomeningocele does not appear to have any beneficial effect over postnatal repair in the long-term requirement for bladder catheterization, anticholinergic, or antibiotic use.[358,359] Other techniques currently being evaluated are microsurgery to create a somatic-autonomic reflex that can be activated by cutaneous stimulation,[360] as well as Botox injections into the bladder muscle.[361]

Upper limb dysfunction is not uncommon in cases of myelomeningocele and hydrocephalus and includes spasticity and/or cerebellar signs unilaterally or bilaterally. Such dysfunction may be present in up to two-thirds of myelomeningocele cases. Upper extremity dysfunction also may result from associated cortical, brain stem, cerebellar, and callosal anomalies[362] or progressive severe Chiari II lesions.

Results of Therapy. Results of therapy are difficult to establish because of the wide-ranging spectrum of approaches that have been taken over the past 70 years, and until recently no randomized clinical trials were available.[314] Over the same time span, the overall supportive management of the newborn has advanced dramatically, making historical comparisons difficult. The approaches have been as disparate as the proposal of active neonatal euthanasia in the Netherlands (in the wake of the Groningen Protocol)[363,364] as recently as 2004 to in utero repair of the spinal lesion.[314] In the 1950s *conservative therapy* (i.e., no early surgery) was the standard of care and provided an approximate measure of the natural history of the disorder (Box 1.7).[365] Approximately 50% of patients managed conservatively were dead by 2 months of age, 80% by 1 year, and 85% to 90% by 10 years. Of the survivors, 70% were ambulatory (with or without aids), and their mean IQ was 89.

In the 1960s *aggressive therapy* became the standard, with the advent of early closure of the myelomeningocele and improved techniques of dealing with the hydrocephalus, which included unselective early operation of the primary lesion. The results of this approach were, in some ways, disappointing (Box 1.7).[144,365-367] Although mortality decreased markedly (40%–50% of patients were alive at age 16 years), the quality of life suffered notably. Of the larger number of survivors, 55% were confined to wheelchairs, and most of these children were incontinent, with a mean IQ of 77.[365] Approximately 30% of survivors exhibited epilepsy.[366]

Because the policy of unselective early operation appeared to cause a larger number of severely handicapped children who required an enormous amount of medical supervision and

BOX 1.7 Outcome of Myelomeningocele as a Function of Therapeutic Approach[a]

"Conservative" Therapy: 1950s
Mortality: 85%–90% by 10 years
Survivors: 70% ambulatory; mean IQ, 89

"Aggressive" Therapy (Unselected Early Closure of Primary Lesion and Treatment of Hydrocephalus): 1960s
Mortality: 40%–50% by 16 years
Survivors: 45% ambulatory; mean IQ, 77

"Selective" Therapy (Selected Early Closure of Primary Lesion and Treatment of Hydrocephalus): Early 1970s
Mortality: 55% (most were selected for no early closure)
Survivors: 80% ambulatory; 85% IQ >75

"Aggressive-Selective" Therapy: Late 1970s to Present
Mortality: 14% by 3–7 years
Survivors: 74% ambulatory; 73% IQ >80

[a]See text for references.
IQ, Intelligence quotient.

in-hospital therapy, and whose families required a great deal of social support, Lorber[367] advocated *selective therapy*, the use of strict criteria for treatment. The criteria were designed to exclude patients who would die despite therapy or, if they survived, would be very severely handicapped. Adverse prognostic criteria were identified as follows: (1) severe paraplegia (no lower limb function other than hip flexors, adductors, and quadriceps), (2) gross enlargement of the head, (3) kyphosis, (4) associated gross congenital anomalies, and (5) major birth injury. Shortly after the published recommendation to use such criteria, Stark and Drummond[339] reported their experience with 163 patients with myelomeningocele at a medical center (Edinburgh) that had been using criteria comparable to those recommended by Lorber for 7 years (1965–1971; see Box 1.7). Approximately 50% of the Edinburgh patients were considered to have the most favorable prognosis and were selected for early closure of the back lesion and subsequent vigorous therapy. The more severely affected 50% were given only symptomatic therapy. More than 70% of the treated patients were alive at 6 years of age, whereas more than 80% of the untreated patients were dead by 3 months of age. Of treated patients, approximately 80% were ambulatory with or without aids, and 87% were free of upper urinary tract disease. The level of intelligence was higher in the selectively treated patients than in the previously reported, unselectively treated patients.[368] Thus only 15% of patients selected for therapy exhibited an IQ of less than 75, whereas 33% of patients unselectively treated had an IQ of less than 75. The improvement in intellectual function was associated with a more liberal use of shunting procedures for hydrocephalus, a relationship noted by others.[338] In later series of children similarly selected for therapy, treated survivors exhibited a similarly better outcome than with earlier *aggressive* therapy.[369-371]

The use of selective criteria for the institution of therapy for myelomeningocele in the newborn period presented at least *two major problems.* First, some infants who could possibly have had a favorable outcome were excluded and were allowed to experience a poor outcome or to die. Second, some infants who were selected for early vigorous therapy had a poor outcome.

Perhaps in part because of the problems encountered with the use of selective criteria, as just noted, *aggressive therapy* has been favored *in the past 2–3 decades* in most centers in North America. Moreover, results of such therapy appear to be superior to those reported previously for selective therapy (see Box 1.7). For example, in one series of 200 consecutive unselected infants who were treated aggressively, mortality was only 14% after 3 to 7 years of follow-up. Of the survivors, 74% were ambulatory at least a portion of the time, and 87% were continent of urination. The apparent improvement in outcome relative to the earlier results of aggressive therapy relates to several factors, including improvements in diagnosis and monitoring of hydrocephalus (e.g., brain imaging), improvements in management of CSF shunts, more effective therapy of infections, and improvements in braces and other aids for ambulation.[160,168,372,373]

A largely *aggressive approach* that appears to *combine a degree of selection* (e.g., advising against early surgery for infants with major cerebral anomalies, hemorrhage, or infection; high cord lesions and *cord paralysis*; and advanced hydrocephalus) has yielded results similar to those just recorded for aggressive therapy.[168] Indeed, in a study of this *aggressive-selective* approach, fully 71% of infants were selected for early surgery because of the absence of the adverse initial findings noted. Of these infants, 79% of survivors exhibited *normal* cognitive development, and 72% were ambulatory.[168]

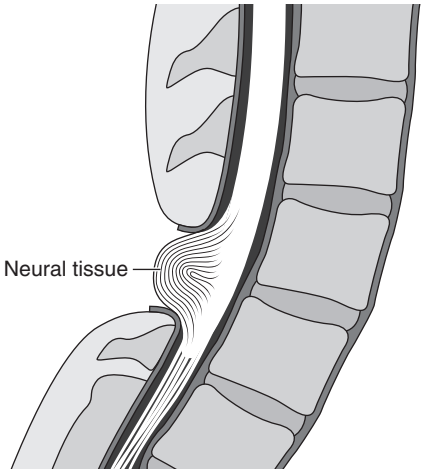


Figure 1.16 Diagram of myeloschisis. Note the ventral displacement of the underlying cord, the neural placode recessed below the cutaneous surface, and the lack of meningeal and cutaneous cover.

Conclusions. No easy answers exist to the questions of when and how to treat the newborn infant who has myelomeningocele. Advances in prenatal diagnosis and the option of pregnancy termination, especially in the presence of associated severe cerebral or systemic anomalies, will continue to alter the spectrum of infants observed in neonatal units. The initial results of fetal surgery, as noted earlier, is already having a significant impact on decision making.[314,374,375] Currently, concerning the newborn with the lesion in the absence of major irreversible parenchymal injury (e.g., complicating major hypoxic-ischemic encephalopathy or serious associated cerebral anomaly), the likelihood for intellectual impairment seems low, and aggressive therapy directed toward the back lesion and the hydrocephalus seems indicated to us. Indeed, even in the infant with major parenchymal disease, closure of the back lesion and placement of a shunt for hydrocephalus for the purposes of the infant's comfort and nursing care are reasonable. Although undue delay in onset of therapy is inappropriate, time for rational discussions with the family can be taken and should not compromise outcome. However, little enthusiasm can be marshaled for delaying decisions for management. Not only does delay lead to compromise in outcome for many patients, but it also puts the parents in an uncertain and nearly intolerable position. It is not trite to conclude that management of each patient must be determined individually. Perhaps no other problem in neonatal medicine necessitates as much perception and sensitivity on the part of primary physicians. They must be able to make as precise a prognostic formulation as possible in the context of current medical knowledge and the facilities available to them and the patient's family. Of equal importance, physicians must have the sensitivity toward the family and the patient that is needed to estimate the impact of the disease on everyone concerned.

Myeloschisis.

Although far less common than myelomeningocele, a brief review of myeloschisis is warranted (Fig. 1.16).

Anatomical Abnormality.

This form of open neural tube defect differs from myelomeningocele in several ways, including

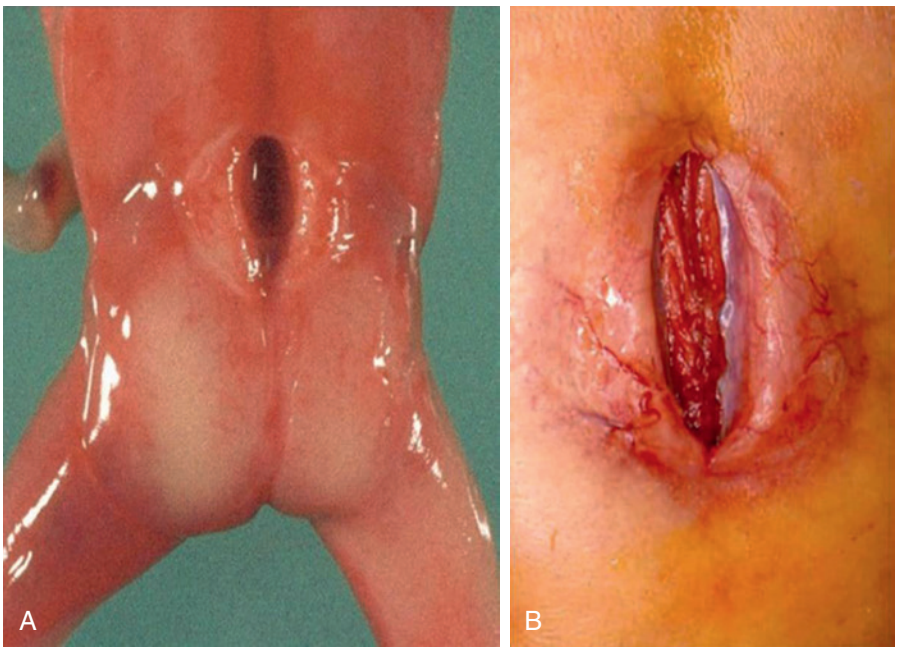


Figure 1.17 Myeloschisis. (A) Dorsal view of a 19-week fetus with myeloschisis and (B) close-up view of myeloschisis lesion. Note the absence of a cystic covering, direct exposure of the neural placode, which is recessed below the surrounding skin surface, and cerebrospinal fluid leakage from the central spinal canal. (A, Courtesy Dr. Joseph R. Siebert, Children's Hospital and Regional Medical Center, Seattle, WA; B from Moore KL. *The Developing Human*. 17, 379-416.e1; Copyright © 2016 by Elsevier, Inc. All rights reserved.)

a lack of an overlying cyst of dysplastic meningeal tissue; consequently, the spinal central canal continuously leaks CSF (Fig. 1.17). Therefore it is not surprising that myeloschisis is almost universally complicated by a Chiari malformation and hydrocephalus. The lack of redundant tissue also makes closure of myeloschisis more difficult. The neural placode is level with the overlying skin or even recessed (see Fig. 1.17) because, unlike most myelomeningoceles, myeloschisis lesions are not displaced dorsally by a ventral pocket of CSF but rather are displaced ventrally by tethering to the anterior wall of the vertebral canal.

Timing. Onset of myeloschisis is no later than 24 to 26 days p/c.[2]

Disorders of Secondary Neurulation

Occult (Closed) Spinal Dysraphism

Anatomical Abnormality. Occult dysraphic states are characterized by overt abnormalities involving vertebral overlying dermal structures or both and by neural lesions that are often subtle or even nonexistent (Fig. 1.18 and Box 1.8). The term *closed neural tube defect* is often used interchangeably with *spina bifida occulta* and considered synonymous with disorders of secondary neurulation. These disorders are distinguished from the disorders of primary neurulation not only by their usual caudal locus but also particularly by the presence of intact skin over the lesions. However, these closed or *occult* lesions may occur at spinal levels above those normally formed by secondary neurulation. A basic relation to disorders of primary neurulation is indicated by the finding that 4.1% of siblings of patients with occult dysraphic states exhibit disorders of primary neurulation, most often myelomeningocele or anencephaly.[376]

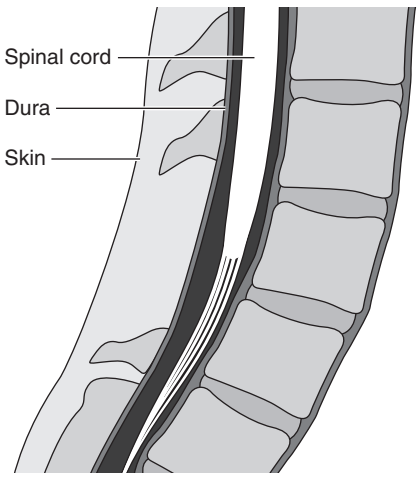


Figure 1.18 Diagram of spina bifida. Spina bifida refers only to the bony midline defect.

BOX 1.8 Neonatal Clinical Features Most Suggestive of Occult Dysraphic State

- Abnormal collection of hair
- Subcutaneous mass
- Cutaneous abnormalities (hemangioma, skin tag, cutis aplasia, pigmented macule)
- Cutaneous dimples or tracts

The *principal developmental abnormality* involves the separation of overlying ectoderm from the developing neural tube, a developmental event often termed *disjunction* (see Table 1.2 and see earlier). Failure of this separation impairs the insertion of mesoderm between the ectoderm and neural tube and, as a consequence, results in disturbed development of vertebrae and related mesodermal tissue. Although disturbances in disjunction may occur at any level of the neuraxis, they are most common in the region of the caudal neural tube and are thus often classified among disorders of caudal neural tube formation.[377] The disjunctional failure results most conspicuously in ectodermal abnormalities, dermal tracts and sinuses, abnormalities of mesodermally derived tissue (e.g., vertebral defects, lipomatous masses), and caudal neural tube abnormalities. Of note, unlike disorders of primary neurulation, the incidence of closed spinal dysraphism has not decreased since the recommendation for antenatal folate supplementation.

Because caudal neural tube formation by the processes of canalization and retrogressive differentiation results in the conus medullaris and filum terminale, it is not surprising that almost invariable and unifying findings in these disorders are abnormalities of the conus and filum. The conus is usually prolonged, and the filum terminale is thickened. Moreover, these structures frequently are *tethered* or fixed at their caudal end by fibrous bands, lipoma, extension of dermal sinus, or related lesions. This fixation is thought to impair the normal mobility of the lower spinal cord, and as a consequence, movements of the trunk such as flexion and extension transmit tension through the prolonged conus to the spinal cord and cause injury.[378-380] This explanation of the neural injury complements the *traction* concept (i.e., because of its tethered caudal end, the cord sustains a traction injury caused by the differential growth of the vertebral column and the neural tissue). This latter concept of differential growth as the sole cause of the injury is contradicted by the finding that differential growth is slight between approximately the 26th week of gestation, when the cord is at the level of the third lumbar segment, and maturity, when the cord is at the level of the first or second lumbar segment.[165,381] Nevertheless, contributory importance for traction associated with tethering in the genesis of the injury is indicated by studies of the mitochondrial oxidative metabolism of the cord in vivo in affected patients by dual-wavelength reflection spectrophotometry.[382] Thus distinct disturbances observed intraoperatively improved markedly on release of the tethered cord.

With the occult dysraphic states, as noted earlier, the neural lesion is often rather subtle, and the major overt abnormality involves mesodermally derived structures (especially the vertebrae), the overlying dermal structures, or both. Thus vertebral defects occur in 85% to 90% of cases and consist most commonly of laminar defects over several segments; other skeletal abnormalities include a widened vertebral canal and sacral deformities.[3,64,79,378,380,383-385] Approximately 80% of affected infants exhibit a dermal lesion in the lumbosacral area, consisting of abnormal collections of *hair*, cutaneous *dimples* or *tracts*, superficial cutaneous *abnormalities* (e.g., hemangioma), or a subcutaneous *mass* (Box 1.8; discussed later).

Timing. The neural lesions, in approximate order of time of origin during neural development, are myelocystocele, diastematomyelia-diplomyelia (Fig. 1.19), meningocele-lipomeningocele (Fig. 1.20), lipoma (other tumors), dermal sinus with or without *dermoid* or *epidermoid* cyst, and *tethered cord* alone (Box 1.9). Less common (although related) lesions include anterior dysraphic disturbances, such as neurenteric cyst and anterior meningocele, and the *caudal regression syndrome*. This latter rare disorder is characterized by dysraphic changes primarily of the sacrum and coccyx, with atrophic changes of muscles and bones of the legs; the neural anomalies range from minor fusion of spinal nerves and sensory ganglia to agenesis of the distal spinal cord.[386] Approximately 15% to 20% of patients are infants of diabetic mothers, and approximately 0.3% of infants of diabetic mothers exhibit the lesion.[387-391] (Infants of diabetic mothers also exhibit a 15- to 20-fold increased risk, relative to infants of nondiabetic mothers, of anencephaly or myelomeningocele.)[388] Because the lower genitourinary tract and anorectal structures are developing simultaneously and in close proximity to the caudal neural tube, lesions of the caudal neural tube are not uncommonly associated with anorectal and genitourinary abnormalities.[79] One such clustering of malformations is the omphalocele-exstrophy-imperforate anus-spinal defect (OEIS) complex, which includes an *o*mphalocele, cloacal *e*xtrophy, *i*mperforate anus, and *s*pinal defects.[392] Indeed, the presence of such lesions should be considered in infants with abnormalities of caudal neural tube formation.

BOX 1.9 Disorders of Caudal Neural Tube Formation: Occult Dysraphic States

Order of Time of Origin During Development
Myelocystocele
Meningocele-lipomeningocele
Diastematomyelia-diplomyelia
Lipoma, teratoma, other tumors
Dermal sinus with or without "dermoid" or "epidermoid" cyst
"Tethered cord" (without any of the above)

Myelocystocele

Anatomical Abnormality. Myelocystocele is a localized CSF-containing cystic herniation of a distended central spinal canal that extends beyond the vertebral canal, while the spinal cord itself stays within the vertebral canal (see Box 1.9; Fig. 1.21). The lesion has two sacs, an ependymal-lined sac emanating from a ballooning hydromyelic central canal and an outer dural sac containing neural and fibrotic tissue. Myelocystoceles are most common in the cervical and lumbosacral regions. Lumbar or *terminal myelocystoceles* (see Fig. 1.21) are of caudal mass origin and may be associated with other features of the caudal regression syndrome, such as severe vertebral defects and other elements of the OEIS complex (discussed previously), making them among the most severe malformations of the newborn period.[3] Severe bladder, bowel, and lower extremity motor deficits are frequent complications of terminal myelocystoceles, and Chiari II malformations may develop later in gestation. These lesions need to be distinguished from sacrococcygeal teratomas (Fig. 1.22), OEIS complex, and myelomeningocele. Lumbosacral lesions may be part of a broader caudal regression syndrome, when they may be associated. The onset of this lesion is estimated to be 28 days of gestation.

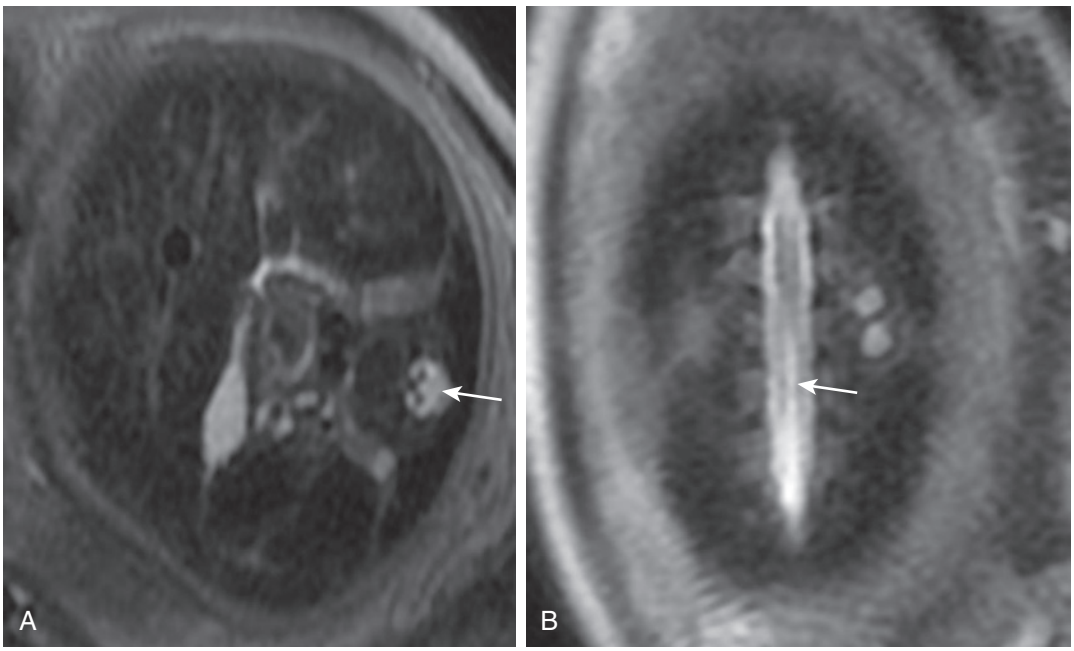


Figure 1.19 Diastematomyelia. Fetal magnetic resonance imaging (T2 weighted) showing axial (A) and coronal (B) views through the spine. Note the bifid shape of the spinal cord in both views *(arrows)*.

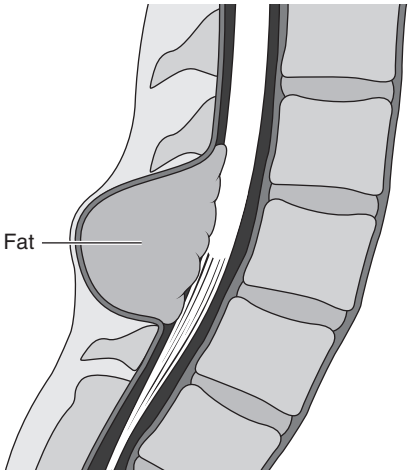


Figure 1.20 Diagram of lipomeningocele. Note skin and dural covering, with bone defect and lipomatous mass adherent to the spinal cord elements.

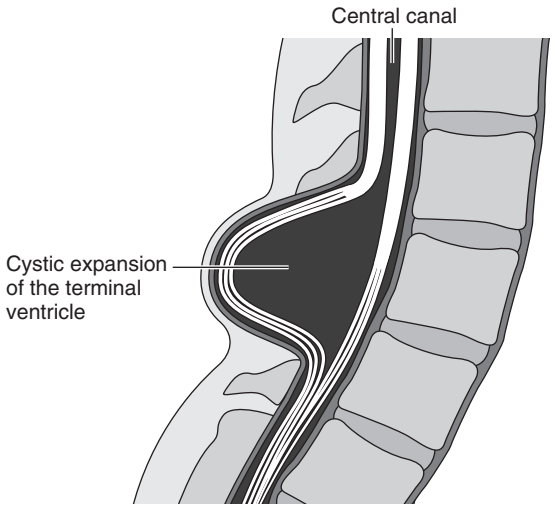


Figure 1.21 Diagram of a terminal myelocystocele. Note the expanded ventriculus terminalis and central canal protruding through the bony defect, which is covered by meningeal and cutaneous layers.

Meningoceles

Anatomical Abnormality. The fundamental abnormality in meningoceles is confined to the vertebral arches, with varying degrees of meningeal herniation (see Box 1.9; Fig. 1.23). The CSF-filled meningeal sac is covered by skin and usually contains no obvious neural elements. The underlying spinal cord is usually intact and remains within the vertebral canal. However, the cord may be malformed into a placode, and fragments of neural tissue may be present in the cyst. In addition, other occult spinal lesions may be present, and cord tethering may develop. By definition, meningoceles are skin covered and have no CSF leak. Lumbosacral meningoceles result from disturbances in secondary neurulation, while the embryology for cervical and thoracic meningoceles remains poorly understood. Posterior cervical meningoceles occur in the zone of primary neurulation but may involve more than one type of neurulation abnormality. It has been postulated that posterior cervical meningoceles are of preneurulation origin, starting during gastrulation when an abnormal endomesenchymal tract bisects the notochord and neural plate, causing a secondary disturbance in primary neurulation.[393] In this manner a midline attachment between the neural and cutaneous ectoderm persists after fusion of the neural tube.[393] The term *limited dorsal myeloschisis*[393,394] has been proposed for closed neural tube defects with a fibroneural

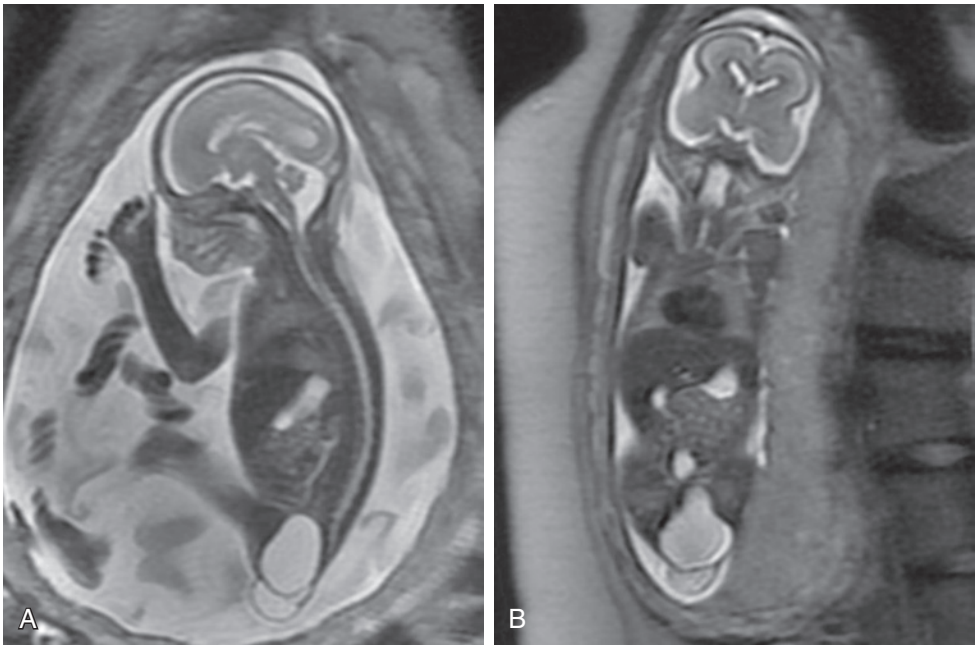


Figure 1.22 Sacrococcygeal teratoma. Fetal magnetic resonance imaging (T2 weighted) in the sagittal (A) and coronal (B) planes showing sacrococcygeal teratoma in a 24-week fetus.

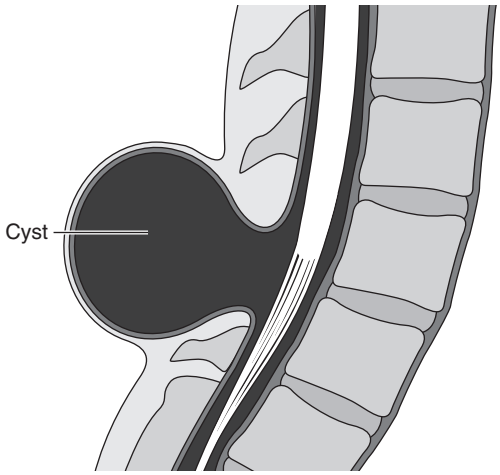


Figure 1.23 Diagram of meningocele. Note the herniation of a meningeal sac through the bony defect, without neural tissues entering into the cystic lesion. Note skin covering is intact, and hence there is no cerebrospinal fluid leak.

stalk (with or without dysplastic glial elements) that connects the spinal cord to the dome of the skin-covered meningeal sac.[395,396] In another variant, a cervical myelocystocele, the spinal cord remains in the vertebral canal, but a diverticulum of the central spinal canal extends into the meningocele. These lesions may be skin covered, partially covered, or open; when open, they are often associated with a Chiari II lesion. Unlike myelomeningoceles, which are most common in the lumbar region, meningoceles are most common in the thoracic spine. When meningoceles occur in the lumbar region, they are thought to result from abnormal secondary neurulation.[397] Lumbar meningoceles are rarely isolated and are not associated with hydrocephalus or neurological deficits, unlike disorders of primary neurulation.[3,385]

The neurological outcome of infants with meningoceles is usually normal or near normal, especially in early childhood. Later complications of cord tethering, such as disturbances in continence and ambulation, may develop. In a minority of meningoceles with placodes and neural elements in the sac (considered myelomeningoceles by some), as well as Chiari II malformations, the outcome is significantly worse. More cases are associated with infiltration of fibro fatty tissue that is contiguous with a subcutaneous lipoma (i.e., lipomeningocele).[3,398,399]

Diastematomyelia. The spinal cord in diastematomyelia is bifid.[a] The lesion is most common in the lumbar region. In some cases, the spinal cord is separated by a bony, cartilaginous, or fibrous septum protruding from the dorsal surface of the vertebral body, whereas in other cases no septum is present. (The term *diplomyelia* is sometimes used for the latter cases.) Because many types of duplications of the developing caudal neural tube may occur during canalization, it is postulated that persistence of these tubes could result in diastematomyelia. The duplications may occur because of splitting of the notochord with impaired induction of both the neural tube and the vertebrae.

Other Lesions (See Box 1.9). *Subcutaneous lipomata* with intradural extension are more common without an accompanying meningocele. Less commonly, other *tumors* may be observed.[402-405] By far the most common of these tumors is teratoma, although neuroblastoma, ganglioneuroma, hemangioblastoma, and related neoplasms, presumably originating from germinative tissue in the primitive caudal cell

[a]References 3, 79, 380, 384, 385, 400, and 401.

mass, or arteriovenous malformation, may occur. Congenital *dermal sinus* consists usually of a dimple in the lumbosacral region from which a small sinus tract proceeds inwardly and rostrally. The tract may enlarge subcutaneously into a cyst that contains predominantly dermal structures (*dermoid*) or epidermal structures (*epidermoid*). Extension of the tract into the vertebral canal may cause neurological symptoms as a result of compression, tethering, or infection. These lesions result from an invagination of ectoderm that is carried by the canalized neural tube as it separates from the surface.[2,3] With *tethered cord*, the conus is prolonged, the filum abnormal, and the caudal end of the cord fixed by fibrous bands.[3,79,378,380,385]

Relative Frequency. The relative frequency of the several occult dysraphic states differs somewhat, according to the source of the cases. Thus, in one large surgical series of 73 patients, dermal sinus with or without cyst accounted for approximately 35% of cases; lipoma accounted for approximately 30% of cases. Diastematomyelia and anterior meningocele were much less common.[383] Very frequent accompanying features, and sometimes the sole and predominant abnormalities, were the prolongation of the conus and a defective filum terminale. In a series of 144 cases of caudal lesions observed in a children's hospital, as in the surgical series, lipoma was similarly common (40% of cases), and diastematomyelia was similarly uncommon (4% of cases), but dermal sinus with or without cyst accounted for only 10% of cases.[404] Sacrococcygeal teratoma comprised 12% and myelocystocele 8% of cases in this less selected series. In another children's hospital–based series of 104 cases, data were similar, except that diastematomyelia accounted for approximately 25% of cases.[385]

Clinical Aspects. In the newborn period, the clinical features most suggestive of an occult dysraphic state are the *dermal stigmata* (see Box 1.8). Thus abnormal collections of hair, subcutaneous mass, superficial cutaneous abnormalities, (e.g., hemangioma, skin tag, cutis aplasia, pigmented macule), or cutaneous dimples or tracts should raise suspicion of a disorder of caudal neural tube formation.[378,380,385,402,406-413] The incidence of associated spinal dysraphism with various cutaneous stigmata in one large series was as follows: "hairy patch," 4 of 10; subcutaneous mass, 6 of 6; hemangioma, 2 of 11; skin tag, 1 of 7; cutis aplasia, 1 of 1; "simple dimple" (midline, <5 mm, and <2.5 cm above the anus), 0 of 160; atypical dimples, 3 of 13; and atypical dimples and other skin lesions, 5 of 7.[410] Although neurological deficits are most unusual in the newborn, motor or sensory disturbances in the legs or feet or sphincter abnormalities occasionally may be detected.

The most common clinical presentations for occult dysraphic states later in infancy include delay in development of sphincter control, delay in walking, asymmetry of legs or abnormalities of feet (e.g., pes cavus and pes equinovarus), and pain in the back or lower extremities. Recurrent meningitis is an uncommon, although dangerous, feature. Similarly, rapid neurological deterioration, although unusual, may occur (discussed later). In the older child or adolescent, the major clinical features are gait disturbance, abnormality of sphincter function, development of a foot deformity, and scoliosis.

Management. Management of the newborn with a skin lesion suggestive of an occult dysraphic state usually includes radiography of the spine. However, before the age of 1 year, ossification of the posterior spinal elements is insufficient to be certain that no abnormality is present. Moreover, even in older infants and children, 10% to 15% of patients with occult dysraphic states have normal spine radiographs. An important noninvasive initial evaluation is ultrasonography, a procedure made possible in the newborn in part because of the poor ossification of posterior spinal elements.[414-416] Visualization of the spinal cord, subarachnoid space, conus medullaris, and filum terminalis and real-time ultrasonographic observation of the mobility of the cord have allowed identification of a variety of occult dysraphic states.[415,416] If both radiography and ultrasonography findings of the spine are normal, no neurological signs exist, and the only clinical finding is a simple dimple or flat hemangioma, many clinicians consider further radiological study to be unnecessary in the neonatal period and clinical follow-up appropriate. Our inclination most often, however, is to perform an MRI.

If a skeletal abnormality or other abnormality is present on the radiographs or sonogram, or if the findings are equivocal, MRI is clearly indicated. MRI has added enormously to assessment (Fig. 1.24).[79,401,407,417,418] MRI is especially valuable for demonstrating the sagittal and coronal topography of the intravertebral and extravertebral components; only bony lesions are not as effectively visualized by MRI as by CT. Indeed, CT is especially useful in demonstrating anomalous bony structures and diastematomyelia spurs.[385,411]

Surgery is performed primarily to *prevent* the development of neurological deficits.[385,400,406,411] The optimal timing of surgery in the infant with few or even no neurological signs is controversial, but the combination of excellent preoperative imaging with MRI, microsurgical techniques, and intraoperative monitoring of cord function by evoked potentials has so decreased morbidity that treatment in the neonatal period before the onset of symptoms has been recommended.[380,419,420] Moreover, neurological deficits may develop in young infants suddenly, and these deficits may persist partially or totally, despite prompt surgical treatment.[378,380,421,422] The mechanism of this sudden deterioration may represent vascular insufficiency produced by tension on a tethered cord, angulation of the cord around fibrous or related structures, or a direct effect of a tumor (e.g., lipoma) or cyst. Surgical release of the tethered cord combined with removal of the tumor or cyst will prevent such deterioration and may partially reverse deficits recently acquired.

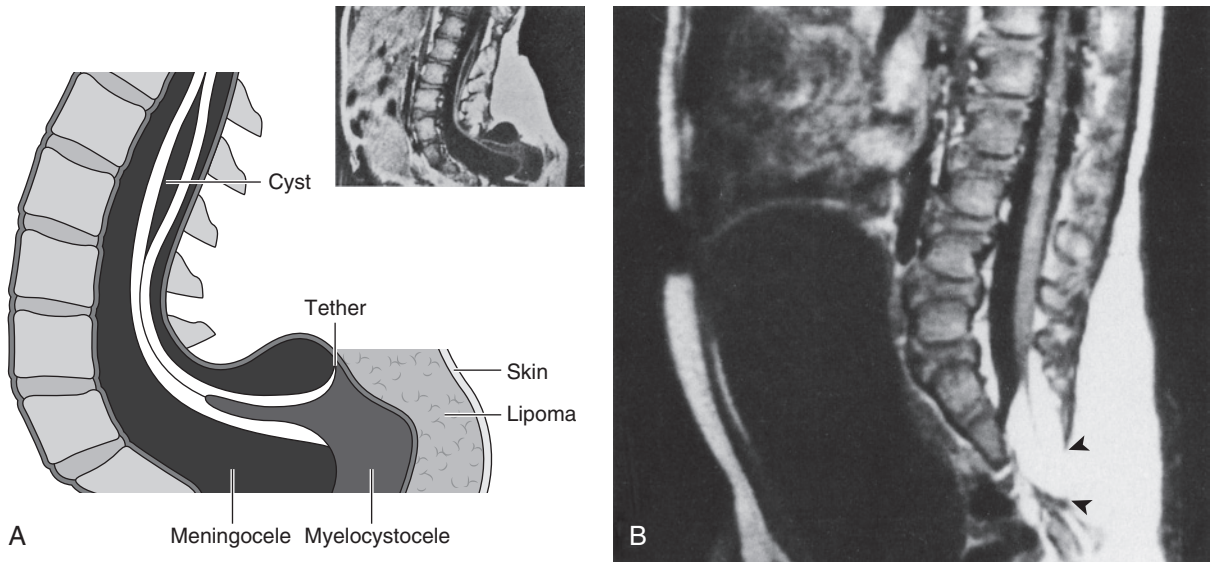


Figure 1.24 Disorders of caudal neural tube formation (A) Myelocystocele: artist's drawing of the meningocele surrounding the myelocystocele and related abnormalities. *Inset:* T1-weighted magnetic resonance imaging (MRI), sagittal view, showing a T12–L3 intramedullary cyst, terminal myelocystocele, meningocele, and lipoma dorsal and superior to the meningocele and myelocystocele. (B) Lipomyelomeningocele with tethered cord. Sagittal, partial saturation (T1-weighted) MRI, 5-mm-thick section shows spinal cord to extend to level of S1 and S2. At this level, a fatty mass envelops the distal spinal cord. The fatty mass extends through a vertebral defect *(arrowheads)* into subcutaneous soft tissues that are enlarged by the lipoma. (A, From Peacock WJ, Murovic JA. Magnetic resonance imaging in myelocystoceles: report of two cases. *J Neurosurg*. 1989;70:804–807. B, From Packer RJ, Zimmerman RA, Sutton LN, et al. Magnetic resonance imaging of spinal cord disease of childhood. *Pediatrics*. 1986;78:251–256.)

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