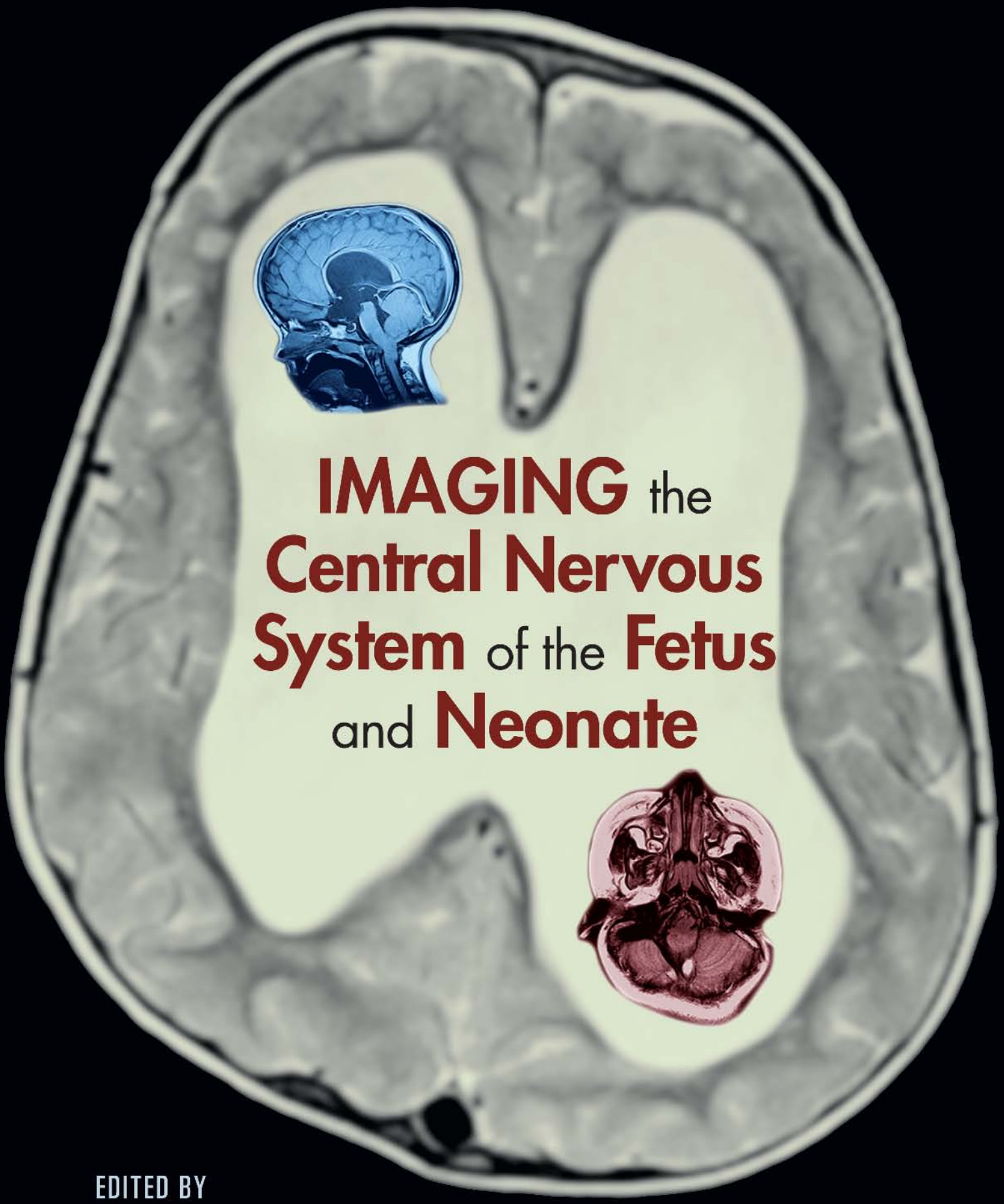

IMAGING the Central Nervous System of the Fetus and Neonate

EDITED BY

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Preface

One of the most significant areas of advance in clinical medicine over the last 20 years has been in the imaging technologies. It is difficult to point to the single method or application that has benefited most from those advances because nearly all specialities in medicine have been involved. Perhaps the most significant trend, however, has been the development and introduction of imaging methods that do not use ionizing radiation, such as ultrasonography (US) and magnetic resonance imaging (MRI). Imaging methods using x-rays or nuclear medicine products are the largest single man-made source of radiation burden to the population. Research and development into other methods that can replace techniques that use ionizing radiation is a justifiable goal in itself, for the benefit of both patients and hospital staff involved in imaging. It is difficult/impossible to provide accurate estimates of risk of imaging with ionizing radiation on an individual basis, but suffice it to say, the risks are small but present and must be taken into account when devising imaging policies.

The effects of ionizing radiation used in medical imaging in adults are divided into two types depending on the mechanism of risk accumulation with increasing dose. Non-stochastic effects occur in body areas such as the cornea where radiation will definitely have a deleterious effect that is dose-dependent. This is not usually a concern for patients but it is for staff involved in high-exposure procedures such as interventional angiography. Most of the concern for patient risk is the induction of malignant processes, which are described as being stochastic events, i.e., they are chance occurrences with the risk increasing with exposure. The risk of tumor development is not equal all over the body, some parts being quite resistant to radiation and others being very sensitive (ova, bone marrow, breast, thyroid, etc.). Irradiation of the ovaries and testicles presents concerns other than tumor generation in the individual, as there is risk of DNA damage that will be passed to a future offspring and could manifest as malformation or tumor.

When experts in radiation biology produce dose-related risks for radiation exposure in a medical environment they take account of the relative exposures of different parts of the body with different imaging methods because of the variation of radiation sensitivity, as described above. They take account of the patient's age as well, as it is highly likely that cells that are dividing rapidly are more susceptible to the damaging effects of radiation. Because an induced malignancy may take many years to develop, a lower age is an increased risk because there is more time for a problem to develop. Hence clinical imagers are very keen to limit radiation exposure in children wherever possible. It is imperative that the developing fetus should not be exposed to unnecessary radiation because of the known risks of teratogenicity and tumor formation. Although x-ray based methods of accessing the fetus have been used in the past, this is not the case now and even irradiating the mother during pregnancy should be performed only for well-considered reasons. Fetal assessment by imaging, therefore, is the realm of methods that do not use ionizing radiation.

The introduction of obstetric US into clinical practice in the late 1970s and early 1980s and its subsequent expansion has had a major effect on clinical practice. The majority of women are offered fetal screening in the second trimester, which may be supplemented by detailed anomaly scanning if problems are found. The widespread use of ultrasonography in neonatal imaging has cemented that method as the primary method of assessing the fetus and neonate. It is easy to predict that MRI should have a role in fetal and neonatal evaluation, if it is reasonable to extrapolate from the pediatric and adult population where US and MRI are used in a complementary fashion. The problems with using MRI have been many-fold including price, limited access, and practical issues that frequently require anesthesia/sedation in neonates and, until recently, have made imaging of the fetus a non-option. Many things have changed and the introduction of ultrafast MR imaging in the late 1990s made MRI of the fetus a realistic option. MRI generally is exceptionally good for neuroimaging and it is not surprising that most of the early work in fetal MRI has concentrated on the brain and spine.

This book describes the status of ultrasonography and MRI of the central nervous system of the fetus and neonate in the early part of the new millennium and attempts to explore the relative roles of each method. We have tried to be as current as possible and have included a section where we describe our view of future developments, but this is a rapidly expanding field and still driven by technological refinements in a major way.

We do have one request for workers who are active in this field or who are contemplating becoming involved, and that is the continuing need for vigilance about safety issues. All imaging methods work by perturbation of human tissues by the input of energy—be it x-rays in CT, sound waves in US, or radiofrequency (RF) pulses in MRI—and none of these can be considered totally safe. US, is thought to be totally safe for the majority of pregnant mothers and very few doctors using US are concerned about damaging effects of any description and they are probably right. Most of the new developments in US technology use greater power deposition when compared to the studies confirming the safety of US in earlier studies and continuing safety studies are required. MRI presents a range of potential safety issues, the two most important being temperature increases due to RF deposition and acoustic noise damage from the very noisy sequences used. Both of these are unresolved at present and are surprisingly difficult to study in the current environment. The acoustic effects on subsequent hearing acuity should be very easy to study; however, it must be appreciated that, as far as we know, “normal” pregnancies are not referred for fetal MRI. Any study, therefore, must rely on the small number of cases where a brain problem has been described on US but no abnormality was shown on in utero MRI or post-natal imaging and the child is shown to be otherwise developmentally and neurologically normal. Unless there are obvious and gross effects on hearing (which seems unlikely), that study will require a long-term multicenter study.

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SECTION 1

An Overview of Normal and Abnormal Brain Development

1.1
Early Development of the Neural Tube

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INTRODUCTION

The adult human body can be defined in terms of its three axes: anterior-posterior (future rostral-caudal), dorso-ventral, and, within the context of these, left-right. These axes are readily apparent in the external body appearance of the head, neck, trunk, back, and front. In addition, many of the internal body systems display similar axial form, and of these, the nervous system stands out as a pivotal example of a structure with defined anterior-posterior (A-P) and dorso-ventral (D-V) polarity. Indeed, an understanding of the development of the nervous system, and of the differentiation of the many discrete cell types within it, depends critically on an understanding of how a neural tube develops with A-P and D-V polarity.

NEURAL PLATE FORMATION AND NEURULATION

The central nervous system (CNS) (the presumptive brain and spinal cord) and peripheral nervous system both derive from an embryonic structure termed the neural tube. In humans, a neural tube with recognizable A-P and D-V axes is already apparent in the four-week-old embryo, neural tube development being initiated in Weeks 2 to 3 of embryogenesis. The neural primordium forms when a small cluster of specialized cells termed node cells, situated in the midline of the embryo beneath the embryonic epiblast (ectoderm), secrete antagonists of bone morphogenetic proteins (BMPs). BMP signaling causes epiblast cells to adopt an epidermal ectoderm fate, while antagonism of BMP signaling results in epiblast cells adopting a neural fate (1). Thus, under the influence of BMP antagonists, a cohort of cells within the epiblast ectodermal sheet, close to the midline node, are instructed to adopt a neural fate, becoming neuroectodermal cells of the neural plate (Fig. 1). Immediately after its induction, the neural plate elongates and, concomitant with this elongation, the node itself differentiates. Node-derived cells undergo convergent extension and ingression, and differentiate into a rod of axial mesoderm that underlies the midline of the induced neural plate (Fig. 1) (2). In posterior regions of the body axis, this rod of axial mesoderm is composed of notochord cells.

The powerful convergent extension movements of the embryo are a primary driving force behind the process of neurulation— the folding of the neural plate and fusion of its lateral edges to form the neural tube (Fig. 2). Neurulation transforms the medio-lateral axis of the neural plate into the ventro-dorsal axis of the neural tube. During neurulation, notochord cells continue to lie immediately beneath midline regions of the induced neural plate, and so come to underlie ventral-most regions of the neural tube while, as a result of delamination of the neural tube, surface epidermal ectoderm comes to overlie dorsal-most regions of the neural tube (Fig. 2).

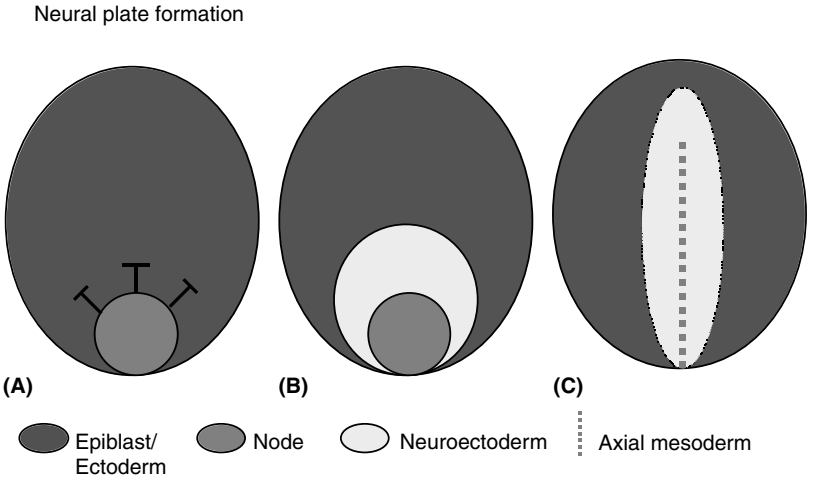

Figure 1. Neural plate formation. (**A**) Node cells secrete BMP antagonists. (**B**) Epiblast ectodermal cells adjacent to the node differentiate into a plate of neuroectoderm, termed the neural plate. (**C**) The neural plate elongates; concomitantly, node-derived cells undergo convergent extension, self-differentiating into axial mesoderm, and ingressing to underlie the midline of the induced neural plate.

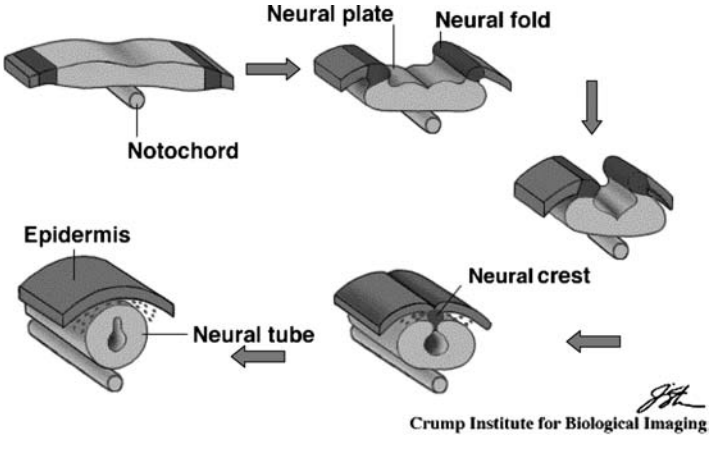

Figure 2. Neurulation transforms the medio-lateral aspect of the neural plate into the ventro-dorsal aspect of the neural tube. Notochord cells that lie beneath the medial aspect of the neural plate lie beneath the ventral aspect of the neural tube. *Source*: Modified from Ref. 4.

In the human, neural tube closure—the coming together of the lateral edges of the neural plate and formation of the dorsal-most aspect of the neural tube— initiates in more than one place. A primary site of closure occurs in hindbrain (rhombencephalic) regions, between somites 4–6, and proceeds both anteriorly and posteriorly (Fig. 3). A second site of closure, forming slightly later, initiates anterior to the optic chiasm and proceeds posteriorly. Final closure of the cranial anterior neuropore occurs at around 25 days, while closure of the caudal neuropore occurs approximately 2 days later (3). Neurulation is followed by formation of the cephalic flexures, converting the A-P axis into the rostro-caudal (R-C) axis that remains throughout fetal and post-natal life.

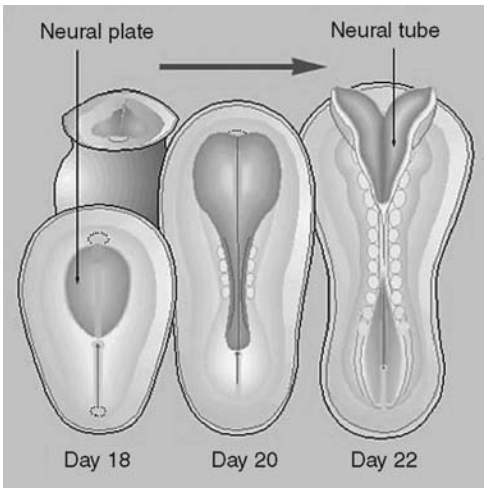

Figure 3. In the human, neural tube closure is initiated around Day 20, final closure occurs around Day 25. *Source*: From www.sciencemuseum.org.uk.

NEURAL PATTERNING

Immediately after neural plate induction and neurulation, signals act to pattern the induced neural tissue. The key function of these signals is to polarize the neural tissue, converting a plate/tube of overtly identical cells into a neural tube with recognizable A-P and D-V polarity. This, ultimately, will result in the correct formation of the many different neuronal and glial subtypes within the brain and spinal cord. The polarization of neural tissue is recognizable, first, in the early regionalization of neural tissue into distinct domains, and subsequently in the differentiation of the distinct neuronal and glial cells—all of which differentiate in a spatially and temporally predictable manner. This exquisitely regulated differentiation underlies the later co ordinated function of cells within the nervous system.

NEURAL PATTERNING: VENTRALIZATION IN THE POSTERIOR NEURAL TUBE

Among the processes that lead to polarization of the neural plate into a structure with A-P and D-V character, the best understood are the events responsible for ventralization of the neural tube. The appreciation of these events derives largely through experimental analyses of animal model systems, in particular, chick and mouse. However, the concepts and principles derived through these studies apply equally to human neural tube patterning.

Experimental embryological approaches in chick embryo have shown that the newly-diferentiated notochord acts as an "organizer" of adjacent tissues, including the overlying developing nervous system (5). The notochord secretes a signaling molecule called Sonic hedgehog (Shh) that appears to emanate away from the notochord in the form of a concentration (morphogen) gradient, such that very high levels of Shh protein are present close to the notochord, with low levels of Shh further away (6,7). A triangular wedge of cells in ventral-most regions of the neural tube therefore encounter the highest concentrations of Shh and, by a process of homeogenetic induction, these are induced to form a specialized group of cells, termed floor plate cells, that themselves secrete Shh (5). Subsequently, Shh synthesized by both the notochord and floor plate diffuses away from these two ventral sources, and establishes a concentration gradient within the neural tube, with highest concentrations ventrally, and diminishing concentrations more dorsally (Fig. 4A). Shh acts as a morphogen— a secreted signal capable

of eliciting distinct and predictable changes in cell fate in responding cells at distinct threshold concentrations (8,9). The fate changes are first instigated in neural cells by alterations in their transcription factor profile. Class 1 transcription factors which, prior to the action of Shh are expressed broadly in the neural plate and neural tube, are particularly sensitive to Shh signaling, and are repressed in response to low threshold concentrations of Shh. Class II transcription factors are induced, or de-repressed, in response to high threshold concentrations of Shh, and so come to be expressed in cells that occupy ventral regions of the neural tube (Fig. 4B).

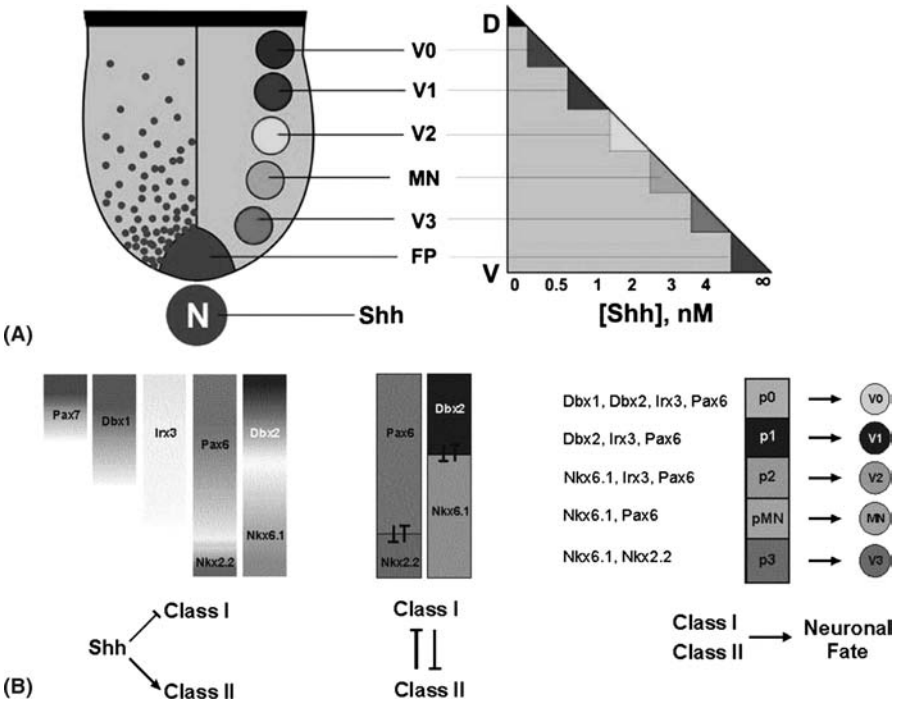

Figure 4. Sonic hedgehog (Shh) regulated transcription factors define ventral neural progenitor domains of the spinal cord. (**A**) A concentration gradient of Shh protein is established in the neural tube, in response to which five distinct progenitor domains are established. These predict the five distinct ventral neuronal subtypes that arise in the ventral spinal cord. (**B**) Shh regulates a series of transcription factors, repressing class I genes and de-repressing, or inducing, class II genes at distinct threshold concentrations (*left*). Negative cross-regulatory interactions refine and maintain progenitor domains (*center*). The combinatorial expression of homeodomain transcription factors in distinct progenitor domains determines the neuronal subtype that arises from each domain (*right*). *Abbreviations*: D, dorsal; Dbx, developing brain homeobox transcription factor; FP, floor plate; Irx, Iroquois homeodomain transcription factor; MN, motor neuron; N, notochord; Nkx, Nkx homeodomain protein; Pax, paired homeodomain protein; V, ventral; V0–V3, ventral interneurons 0–3. *Source*: From Ref. 10.

Distinct class I and class II transcription factors display differing sensitivities to the Shh morphogen, as a result of which Shh is able to elicit a complex transcription code in cells along the D-V axis, which in turn define distinct regional territories along the D-V axis. Importantly, this transcription factor code is instructive in neuronal and glial fate determination, and pre-figures and predicts the genesis of defined classes of differentiated neurons and glia. In this manner, the bilaterally symmetric organization

of the ventral CNS comes to form, with V3 interneurons differentiating closest to the floor plate, followed by (ventral to dorsal) motor neurons, V2, V1, and V0 interneurons (Fig. 4).

An outstanding question remains that of whether Shh acts alone to govern neuronal identity. Recent studies, in fact, indicate that additional signals may provide positional information, acting either in sequence or in parallel to Shh. Zinc finger proteins of the GLI family, which act as transcriptional mediators of Shh signaling, may play a crucial role in integrating the distinct signaling inputs, to effect a coherent program of neurogenesis (10,11).

NEURAL PATTERNING: DORSALIZATION OF THE CAUDAL NEURAL TUBE AND FORMATION OF THE PERIPHERAL NERVOUS SYSTEM

The principles involved in dorsalization of the neural tube are largely similar to those involved in its ventralization; however the signaling molecules required to pattern the dorsal neural tube are different from Shh (12). Members of the transforming growth factor β (TGFβ) family of signaling molecules, including BMPs, are expressed within the surface ectoderm (epidermis) that overlies the neural tube (Fig. 2). These appear to act, via a homeogenetic process, to induce their own expression within dorsal parts of the neural tube. TGFβs expressed in the surface ectoderm and dorsal neural tube signal to cells within the neural tube, changing their fate and inducing distinct classes of dorsal interneurons, including D1A, D1B, D2, D3, and D4 interneurons. The ability of TGFβs to induce distinct dorsal neurons appears to reflect, at least in part, their ability to elicit fate changes in response to distinct concentration thresholds. A widely accepted model thus suggests that a graded distribution of TGFβ signals is present in the dorsal neural tube, and induces a dorsal transcription factor code in a concentration-dependent manner. Numerous lines of evidence have suggested an antagonism between the ventralizing gradient of Shh and the dorsalizing gradient of TGFβs. Thus, the integration of Shh and TGFβ signaling patterns the dorso-ventral axis of the neural tube (10,11).

One facet of dorsalization that is very distinct to ventralization of the neural tube is the induction of neural crest cells. Neural crest cells are induced in dorsal-most regions of the neural tube, but do not remain confined to it. Instead, they migrate out of the dorsal aspect of the neural tube, follow a number of discrete migratory pathways, before settling in final target areas where they undergo terminal differentiation into the discrete components of the peripheral nervous system (13).

NEURAL PATTERNING: VENTRALIZATION OF THE ROSTRAL NEURAL TUBE

A wealth of evidence shows that Shh is required, not just for the differentiation of motor neurons and ventral interneurons in the spinal cord, but for the differentiation of classes of ventro-lateral neurons along the whole R-C axis. However, Shh elicits different outcomes in cell fate in the brain versus the spinal cord. Thus, for instance, in the hindbrain, serotonergic neurons form ventro-laterally, adjacent to Shh-expressing floor plate cells, and in the midbrain, dopaminergic neurons differentiate ventro-lateral to the floor plate. This occurs because a large degree of anterio-posterior (rostro-caudal) identity is already imposed on neural tissue, prior to its exposure to Shh. Final neuronal identity reflects the position of a cell within a Cartesian-grid of information, supplied by the patterning morphogen, Shh, and signals that convey distinct A-P identities on neural plate cells (6,14).

The signaling sources and signals that polarize the neural tissue along its A-P axis, and interact with Shh to impart distinct neuronal identities are beginning to be defined (15,16). Evidence suggests that members of the Wnt and FGF families of signaling molecules, together with retinoids, posteriorize the neural plate and neural tube,

the antagonism of these signals required to produce anterior identities. It is likely that anterior endoderm that borders the anterior edge of the induced neural plate, and a variety of posterior tissues, act as the source of such antagonistic signals, their integrated action producing an A-P regionalized neural plate, within which forebrain (telencephalon and diencephalon), midbrain (mesencephalon), hindbrain (rhombencephalon), and spinal cord domains exhibit distinct identities, manifest in their expression of distinct transcription factor codes (Fig. 5).

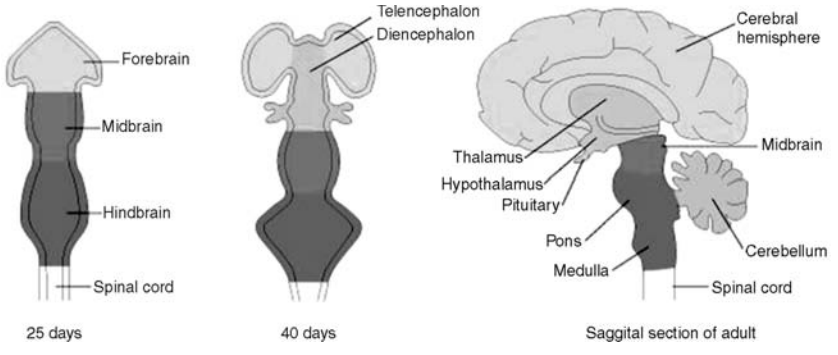

Figure 5. Antagonistic signals act along the A-P axis to produce a neural tube that is regionalized along the R-C axis. *Source*: From somna.npa.uiuc.edu.

PRECHORDAL MESODERM AND DEVELOPMENT OF THE HYPOTHALAMO-PITUITARY AXIS

In addition to imparting forebrain identity to neural tissue through its antagonism of posteriorizing signals, the anterior endoderm affects the character of extending axial mesoderm. Thus, although most of the node-derived axial mesoderm will form notochord, a small portion of anterior-most axial mesoderm encounters anterior endoderm and consequently differentiates into a structure termed the prechordal mesoderm (Fig. 6).

The prechordal mesoderm lies beneath the forebrain, and plays a pivotal role in patterning the forebrain, notably the hypothalamus (16,17). The concepts of hypothalamic patterning by prechordal mesoderm are broadly similar to those of neural patterning by the notochord. Signals from the prechordal mesoderm induce a floor plate-like structure in ventral-most regions of the hypothalamus that will form the infundibulum (median eminence), and initiate a transcription factor code within ventral hypothalamic territory that is translated into the differentiation of discrete classes of hypothalamic neurons. However, the signaling molecules that derive from prechordal mesoderm are distinct from those of the notochord. In particular, prechordal mesoderm expresses signaling factors of the TGFβ superfamily, including nodal and BMPs, that are not expressed by notochord. These co-operate with Shh to mediate the ability of prechordal mesoderm to induce and pattern both the hypothalamic infundibulum and neurogenic regions of the hypothalamus (16). The induction of the hypothalamus converts cells in the early eye field into hypothalamic cells, and hence splits the eye field into its predictable bilaterally symmetric arrangement. Subsequent to inducing the infundibulum and hypothalamus, the prechordal mesoderm retreats caudally. Consequently, the infundibulum comes to appose the underlying oral ectoderm, and induces immediately adjacent oral ectoderm to differentiate into Rathke's pouch, the precursor of the anterior pituitary (18). Thus, both the normal bilateral organization of the eyes, and the normal development

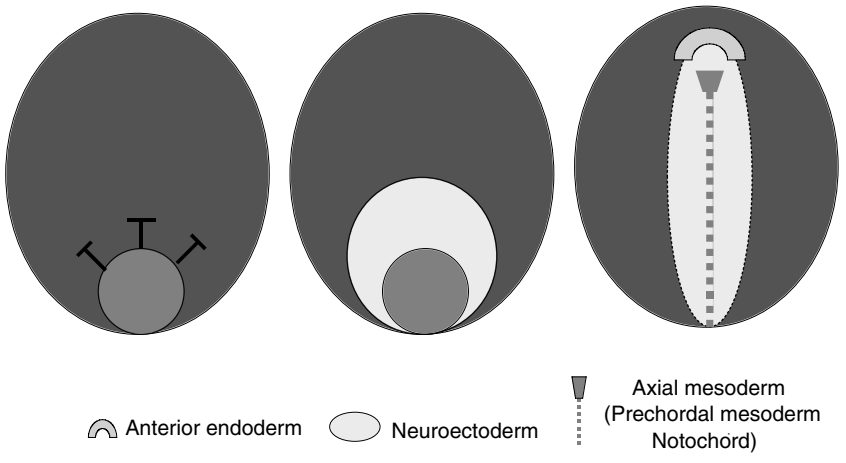

Figure 6. Anterior endoderm patterns the forebrain and prechordal mesoderm. Signals from the anterior endoderm appear to act on axial mesoderm after it has undergone convergent extension, specifying axial mesoderm to a prechordal mesoderm identity.

of the hypothalamo-pituitary axis are established through a series of inductive interactions that are initiated by the prechordal mesoderm.

SHH AND HOLOPROSENCEPHALY

The multiple effects of signals that derive from prechordal mesoderm and that act within the forming brain were first appreciated through analyses of the Shh-null mouse. This mutant mouse shows multiple dysmorphologies, including a lack of ventral cell types, holoprosencephaly, a nasal-like proboscis, cyclopia, and lack of a pituitary gland (19). The importance of Shh signaling in the human brain was recognized almost immediately afterwards, when studies revealed that holoprosencephaly in humans can be caused by Shh haploinsufficiency (20). This defect is characterized by an incomplete separation of the ventral forebrain, so that distinct cerebral hemispheres fail to form, and associated craniofacial abnormalities, including a proboscis-like nasal structure, cyclopia, cleft lip, and palate (Box 1 and Fig. 7). The severe lethality associated with these defects means that, although holoprosencephaly has an incidence as high as 1 in 250 conceptuses, only 1 in 16,000 live births are seen.

BOX 1. HOLOPROSENCEPHALY: Holoprosencephaly covers a wide spectrum of phenotypes, characterized by the incomplete cleavage of the forebrain (prosencephalon) into the right and left hemispheres, and the malformation of the diencephalon, telencephalon, olfactory, and optic bulbs. In the most severe case of holoprosencephaly, termed cyclopia, a single forebrain vesicle is formed without any evidence of division into left or right hemispheres. Here, a nose-like proboscis extends over a single, medial eye. In the next grade of holoprosencephaly, ethmocephaly, the eyes show a partial bilateralization, again separated by a proboscis-like structure. In cebocephaly, closely spaced eyes lie above a nose with a single nostril. In none of these cases does the prosencephalon divide to form the left and right hemispheres. In milder forms of holoprosencephaly, the prosencephalon splits to a varying, but not normal, degree. In such cases, the eyes are still close together, the nose is flat, and there is a cleft lip. The lesser grades of holoprosencephaly include various "midline" abnormalities including abnormally spaced eyes and dental anomalies such as a single central incisor. As detailed in the text, a variety of genetic and environmental factors can contribute to holoprosencephaly. Depending upon the genetic background and on the environmental factors to which an individual is exposed at a critical sensitive time-point, the same loss-of-function allele can give a wide variety of phenotypes.

Mutations in the Shh gene have been shown to cause both familial and sporadic cases of holoprosencephaly, but do not account for all cases. However, other genes that have been implicated in holoprosencephaly (21,22) have been shown to be crucial for normal forebrain development, and appear to govern the expression of Shh in the ventral forebrain. Several families with holoprosencephaly have a defect in the SMAD2 (TGIF) gene that is downstream of nodal signaling (23). Intriguingly, a number of studies suggest that nodal governs expression of Shh in the ventral forebrain (16). In a second group of families with familial holoprosencephaly, a chromosomal break-point interrupts the SIX3 gene (24). SIX3 appears to antagonize WNT signaling, and so allow the formation of early forebrain-like tissue. In mice with a targeted ablation of SIX3 (a SIX3 "knock-out" mouse), the ventral forebrain, including ventral-most Shh-expressing regions, fails to form properly (16).

Holoprosencephaly has also been seen as part of the Smith-Lemli-Opitz (SLO) syndrome (25). This syndrome is caused by loss-of-function alleles of the sterol delta-7-reductase gene (DHCR7) gene, a gene whose product acts in the final step of cholesterol biosynthesis. Cholesterol plays a critical role in the the production and reception of the Shh signal, and a prosaic interpretation of the holoprosencephaly seen in SLO syndrome patients is that the defects in cholesterol metabolism impact on Shh signaling, and so produce the same types of phenotypes as the lack of Shh. Indeed, using drugs to deprive pregnant mice of cholesterol will produce such syndromes in their offspring.

In addition to the genetic component to holoprosencephaly, environmental factors are also critical (26). Several teratogens can cause holoprosencephaly, one of them being the alkaloids of the plant *Veratum californicum*, another being ethanol. Veratrum alkaloids, such as cyclopamine block cholesterol synthesis and function, and prevent the reception of Shh, while ethanol is believed to impair the development of the prechordal mesoderm and neural plate.

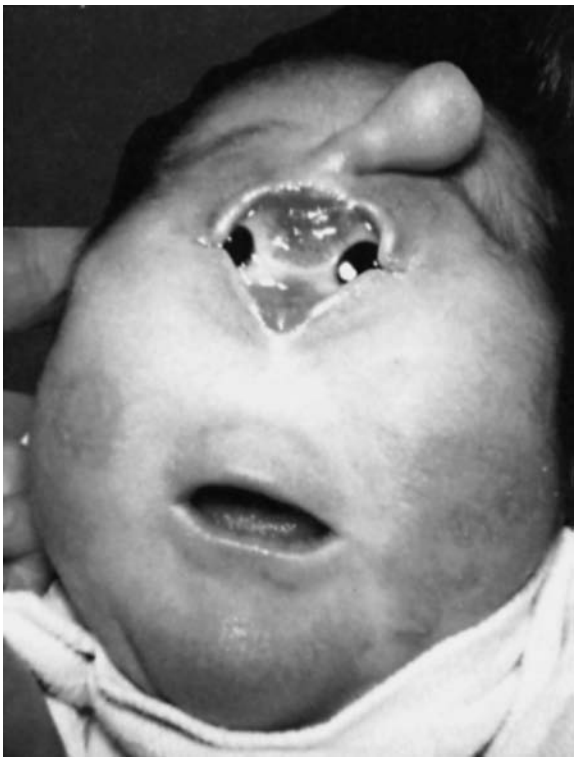

Figure 7. Cyclopia in a newborn. A proboscis-like structure is seen above the partially fused eye. *Source*: From M. Barr, Ann Arbor, Michigan.

In summary, holoprosencephaly shows phenotypic heterogeneity (one gene causing different phenotypes depending on the other genes in the organism), genetic heterogeneity (different genetic loci being able to create the same abnormal phenotype), and environmental causation (wherein teratogens are able to disrupt the genetic pathways required to form the normal phenotype). However, aberrancies in ventral midline Shh-expressing cells, or in the Shh pathway, both of which are critical to the normal development of the forebrain, appear to play a pivotal role in this disorder.

SUMMARY

Cell signaling plays a key role in the development of the nervous system, governing the differentiation of the numerous different neuronal and glial cells that are formed in embryogenesis. Critical groups of cells act as organizers of the developing neuroepithelium, providing sources of secreted signaling molecules that polarize the developing neural plate and neural tube, setting up a Cartesian-like grid of positional information. Key amongst these secreted signals are Shh, TGFβs, WNT, and retinoids. According to their position on the grid, cells acquire a distinctive signature of transcription factors, which ultimately directs their differentiation into distinct neuronal and glial subtypes. Our understanding of the embryonic development of cells within the neural tube has profound implications for our understanding of human congenital abnormalities and disease states that are manifest as dysmorphology and dysfunctions of the brain and spinal cord.

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1.2
The Supratentorial Brain

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THE SUPRATENTORIAL BRAIN

The classification of development of the human brain put forward in most clinical texts describes a series of sequential mechanisms occurring in utero. As well as helping to understand normal development this scheme allows many of the brain abnormalities seen in clinical practice to be explained (at least in part). The approach is useful but a number of points should be remembered:

- The described events do not occur sequentially but overlap to a considerable degree. This explains the coexistence of different types of malformation and why they are associated. It is virtually impossible to give the exact gestational age at which the abnormality was formed.
- Some of the more common brain malformations are difficult to explain using the simplistic classification.
- Considerable alteration in microscopic structure occurs after the brain has formed on a macroscopic scale. Myelination and synaptic organization are examples that commence before birth but continue post-delivery that can produce a wide range of clinical problems.

In spite of those problems the traditional approach outlined below is helpful in the clinical environment.

PRIMARY NEURULATION

Around 15–17 days post-conception, the embryo has the form of a trilaminar disc consisting of endodermal, mesodermal, and ectodermal elements. The central portion of ectoderm undergoes structural changes, influenced by the mesodermal element called the notochord. The specialist ectoderm is called the neural plate and this undergoes considerable thickening when compared to the adjacent non-neural ectoderm. The neuroectoderm begins to fold and after 20 days post-conception the edges meet in the midline, fuse, and separate from the non-neural ectoderm. This process is called dysjunction and occurs at different times at different levels of the central nervous system but the cephalic end of the neural tube should be closed by 26 days post-conception. The whole process of forming the neuroectoderm and closing the neural tube is called primary neurulation.

Failure of primary neurulation at the cranial end of the neural tube produces abnormalities such as anencephaly and cephalocoeles. Anencephaly occurs when the majority of the neural tube at the cranial end fails to form. This is a severe malformation that often results in spontaneous abortion or therapeutic abortion after detection or