Formation, Maturation, and Disorders of Brain Neocortex

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The cerebral gray matter undergoes a complex but orderly developmental process, beginning with production of neuronal and glial precursors in the germinal zones lining the lateral and third ventricles, followed by migration of the neurons from the germinal zone to their eventual destinations. The neurons differentiate into several cell types (i.e., pyramidal cells, stellate cells) and organize into horizontal laminar aggregates and vertical columns, resulting in the production of normal cortical cytoarchitectonic patterns. Any disruption of the normal processes of neuronal generation and migration result in brain malformations, which can cause variable degrees of neurologic dysfunction. An understanding of the normal processes of gray matter development is essential to understanding the disorders of this development. Although this manuscript deals only with gray matter development, neuronal development is coordinated with, and dependent upon, the generation and development of nonneural cells, such as astrocytes and oligodendrocytes.

Neurogenesis

The vast majority of neurons and a large number of glial cells are generated in the germinal zones or the germinal matrices (1–3) (Fig. 1). In the early phases of cytogenesis, the germinal zones are located primarily at the ventricular surface. This germinal layer may be designated the ventricular germinal zone, the neural epithelium, or the neuroepithelium. As development proceeds, a subventricular zone forms immediately superficial to the ventricular germinal zone. It is not clear which of these germinal zones is primarily responsible for the generation of glial cells, as opposed to neurons and ependymal cells (4–6).

Altman and Bayer (6) postulate five stages of cell differentiation and migration in the cerebrum: 1) In the first stage, the neural epithelium lining the ventricle produces cells that migrate superficially to form the marginal layer (layer 1 of the cortex), 2) During the second stage, mitotic cells appear a small distance from the ventricular wall in the subventricular zone. Cells differentiating and migrating at this time appear to form the subplate layer. This is a transient cortical layer sometimes designated layer 7. 3) During the third stage, the neural epithelium shrinks while the subventricular zone expands and becomes the dominant germinal matrix. The major portion of the cerebral cortex (layers 2 through 6) derive during this stage. These cells migrate in an "inside-out" fashion, with layer 6 cells migrating first and cells of layer 2 migrating last. 4) During the fourth stage, a population of locally multiplying, presumably glial, cells becomes dispersed throughout the intermediate zone and the cortical plate. 5) Finally, during the fifth stage, the receding neural epithelium is transformed into a germinal source that does not display nuclear migration; this presumably represents the stage when it begins to produce ependymal cells.

The cerebellar primordia and the basal nuclei of the cerebrum begin to develop at Carnegie stage 14 (gestational age 32 days) (7). The cells that will form the deep cerebellar nuclei and the Purkinje cells of the cerebellar cortex are generated in germinal zones in the subventricular re-
Fig. 1. Normal neuronal migration.
A, Normal human brain pallaum at 16 weeks of gestation. Note the numerous migrating neurons packed in the deep intermediate zone (prospective white matter) at the level of the thalamocortical axons, and the underlying conspicuous germinative zone. (NEPE collection). C, cortical plate; I, intermediate zone; G, germinative zone.
B, MR image of fetal brain at 16 weeks gestational age shows wave of migrating neurons (open arrows) coursing from the germinative zone at the ventricular surface to the cortical plate (white arrows) at the brain surface.

Cell Migration

Movement of neurons from the germinal zone to their final destination is initially a simple process. Cells in the germinal zone elongate with the nucleus in the end of the cell that is most distal from the ventricular surface. After mitosis, the newly formed cells lie at some distance from the ventricular surface (4). As the cerebral hemispheres enlarge, and the distance to be travelled by the cells increases, more sophisticated translocation mechanisms evolve. Most of the neurons that will form the cerebral cortex migrate to their destinations along specialized radial glial fibers (RGFs) that span the entire thickness of the hemisphere from the ventricular surface to the pia (Figs. 2–4). These glial guides are grouped in fascicles of 3-10 radial fibers (10). Although the exact mechanism of the migration has not been established, the neurons are believed to interact
Fig. 3. Schematic hypothetical representation of radial glial cell (RGC) distribution pattern during the different developmental stages in the mammalian neocortex. A, Early embryonic stages; radial glial cells are regularly aligned. B, Migration stage of neurons destined for layers 6 to 4. The RGC are grouped in fascicles throughout the entire thickness of the neural tube from the ventricular zone to the pial surface. C, Mammalian RGC distribution during the migration period of neurons destined for layers 3 and 2. The migrating neurons defasciculate the radial glial fibers in the cortical plate via gradual neuronal saturation and glial dilution. In the human, this stage (C) starts after 15 weeks gestation. D, RGC distribution in the reeler mutant mouse when the last waves of migrating neurons reaches the cortical plate (embryonic day 17). There is no intracortical defasciculation of RGC in this mutant, so the cortex is disorganized. E and F, the RGCs gradually transform into astrocytes after the end of neuronal migration along radial glial fibers. Glial profiles seem to maintain their fasciculated pattern in the intermediate zone of the normal human fetus (E), the normal mouse (E) and the reeler mouse (F), and in the CP of the reeler mouse (F). In the cortical plate of the human fetus (E) and the normal mouse (E), this cytologic transformation or "involution" of glial elongated fibers occurs on previously defasciculated radial glial fibers. In the human, this glial transformation occurs gradually between 21 and 40 weeks of gestation, whereas in the mouse, this takes place between 1 and 3 weeks postnatally. G, Stage of full transformation of RGC into mature glia. V, lumen of neural tube; dark ovals, neurons; open ovals, glial cell bodies; dotted line, transition between the superficial cortical plate and the deeper intermediate zone. (Reprinted with the permission of the American Association of Neuropathologists, Inc, from Kadhim et al (99).)

with specific chemical markers on the surface of the radial glial fibers (4, 11, 12). Several neuronal and glial glycoproteins have been proposed to promote glial-to-neuron interactions: laminin, cytotactin, astrotactin, and NgCAM (for a review, see Ref. 13). The expression of these glycoproteins along the migratory corridors may be variable, since antibodies directed against them differentially block the neurons at different levels of their migrating pathway. Thalamocortical axonal bundles may play a role in the normal neuronal migration since they seem to temporarily impede neuronal migration (Fig. 2). Proteases may also play a role in the neuronal migration (14).

The process of neuronal migration is precise in that the final position of a neuron in the cortex can be predicted from its site of origin and the time of its final mitosis within the germinal zone (3, 4). The topographical end point of a neuron's migration can be predicted by knowledge of the course of the radial glial cell and the location of the origin of the glial cell within the germinal zone. The eventual cortical layer in which the cell will reside can be predicted by the known sequence of neuronal development and migration. As indicated earlier, neurons migrate from the germinal zone to the cortex in an "inside out" sequence. Those destined for the deepest cortical layer (layer 6) migrate first, followed by those destined for layer 5, layer 4, layer 3, and, finally, layer 2. The orderly production and migration of cells from the germinal zone to the cortex along the radial glial fibers has led to a concept of the "vertical neuronal-glial unit." This unit is comprised of the germinal zone that produces the cells destined for a certain region of cortex, the cells themselves, and the fascicles of radial glial fibers that guide the cells to their final destination (15) (Fig. 3). Recent experiments with retroviruses allowing the study of clonally related neurons, however, have shown that neurons originating from the same germinal precursor may display a wider cortical spatial dispersion than expected from an entirely rigid protomap (16).

The exception to the "inside out" rule of neuronal migration is that those neurons destined for the marginal layer (layer 1) seem to be the first to arrive in the cortex (2, 4, 17). The fact that the molecular layer forms first has led to speculation that the molecular layer in some way interacts with the subsequently migrating neurons of the lower layers in order to facilitate their separation from the radial glial fibers at the end of their migration. Caviness et al (18) have postulated that the molecular layer acts as a mechanical barrier to the further migration of the neurons. Marin-Padilla (2, 17) has suggested that termination of neuronal migration is initiated by synaptic contact with dendritic projections from the cells in the molecular layer. Furthermore, Marin-Padilla (2, 17) suggests that the neurons forming the molecular layer cease their migration upon reaching and interacting with corticopetal fibers from the mesencephalon. He proposes the existence of a primitive cortex, composed of layer 1 and the transient layer 7 (the subplate), that has functional
Fig. 4. Schematic representation of the intimate relationships between migrating neurons (N1-5) and the radial glial fascicles (dashed cells) in the embryonic mouse lower cortical plate. The neurons and the glial elements are reconstructed from micrographs of a series of sections cut in the coronal plane. During their migration, the neurons are entrapped into the glial fascicles and achieve an extensive and close relationship with their glial guides. Scale bar = 2 \( \mu \)m. (Reprinted with the permission of Elsevier Science Publishers, BV, from Gadisseux et al (11)).

synapses and resembles the cerebral cortex of lower animals such as amphibians. As layers 6 through 2 migrate to, and come to rest in, the developing cortex, they separate the molecular layer from the subplate. Several roles have been postulated for the subplate: production of neurotransmitters that interact with migrating neurons, waiting zone for corticopetal axons, formation of “pioneer” axons at early stages of neocorticalogenesis, and participation in the gyration of the cerebral surface (19, 20). By the time of birth, the subplate is barely discernible and, after birth, it disappears (2, 17), although some subplate neurons are still present in the white matter in adults (19). After neuronal migration has been completed, radial glial fibers transform into normal astrocytes (Fig. 3G), which may be of importance in the guidance of axons through the developing brain (21). Although the preceding discussion has centered mainly on neocortical development, it is important to note that similar processes occur in the remainder of the brain, with minor variations. For example, during the formation of the hippocampus, numerous phases of neuronal migration appear to occur, with the formation of secondary germinal zones after an initial migration of cells that are formed at the ventricular surface, and a complex subsequent migration (22-24). During formation of the cerebellum, the cells that will form the cerebellar nuclei and the Purkinje cells appear to migrate radially from the germinal zones bordering the fourth ventricle to their final locations (8, 9). Generation of these neurons begins at about the ninth gestational week. However, the cells that will form the granular cell layer of the cerebellar cortex originate in a second germinal zone that lies in the lateral portion of
the rhombic lips. From the secondary germinal zones, the young neurons migrate laterally and then circumferentially over the surface of the developing cerebellar hemisphere, where they form a transient external granular layer in which further mitoses occur. At the 16th gestational week, daughter cells from the external granular layer begin to migrate radially inward. Some of these cells form the "basket" and "stellate" cells of the molecular layer of the cerebellar cortex. Others migrate further inward along Bergmann glia cell guides, past the Purkinje cells, to form the (inner) granular layer of the cerebellar cortex. The external granular layer attains a maximum cell number in the first few postnatal months, then diminishes in size as the cells migrate radially inward (25). By the end of the first postnatal year, the cerebellar cortex achieves its adult threelayered histologic composition: outer molecular layer, middle Purkinje layer, and inner granular layer (25).

Disorders of Neuronal Generation and Migration

A large number of brain disorders result from variations in the processes of normal generation and migration of neurons. The causes of the abnormalities are varied and include congenital/genetic causes (Table 1) and maternal and environmental causes (Table 2). A full discussion of anomalies of neuronal migration in all of the disorders listed in these tables is beyond the scope of this manuscript. We will, therefore, focus on some classic pathologic entities that are well understood and discuss their supposed etiologies, clinical presentations, and radiologic and pathologic appearances.

The Radial Microbrain

The radial microbrain (15, 26) is an interesting and instructive anomaly. Evrard et al (26) described seven patients, born at term, that all had markedly reduced brain size (postmortem weight from 16–50 g) with normal gyral patterns, no evidence of gliosis or destructive lesions, and normal horizontal cortical thickness and lamination (ie, normal formation of layers I-VI) (Fig. 5). However, the overall number of neocortical neurons was reduced to 30% of normal. The authors suggested that these "microbrains" result from a severe reduction in the number of "vertical neuronal-glial units," each of which contains a normal complement of neurons and glial cells. They further postulated that the reduced number of neuronal-glial units was the result of a diminished number of proliferative units in the germinal zone. Interestingly, neuronal migration in these patients appeared normal, suggesting that control of cell proliferation and cell migration may be separate (15). Clinically, these patients had severe microcephaly in addition to associated extra central nervous system anomalies (acromicria, nephropathy). All died within 30 days after birth (26).

### Table 1: Syndromes associated with neuronal migration disorders

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<tr>
<th>Metabolic syndromes</th>
<th>Neuromuscular syndromes</th>
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<td>Zellweger syndrome</td>
<td>Walker-Warburg syndrome</td>
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<td>Neonatal adrenoleukodystrophy</td>
<td>Fukuyama congenital muscular dystrophy</td>
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<td>Glutaric aciduria II</td>
<td>Myotonic dystrophy</td>
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<td>Menke kinky hair disease</td>
<td>Anterior horn arthrogryposis</td>
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<td>Gm2 gangliosidosis</td>
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<td>Neuronal migration disorders</td>
<td>Neurocutaneous syndromes</td>
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<td>Incontinentia pigmeni</td>
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<td>Type I neurofibromatosis</td>
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<td>Hypomelanosis of Ito</td>
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<td>Encephalocranial cutaneous lipomatosis</td>
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<td>Tuberous sclerosis</td>
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<td>Epidermal nevus syndrome</td>
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<td>Multiple congenital anomalies syndromes</td>
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<td>Smith-Lemli-Opitz syndrome</td>
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<td>Potter syndrome</td>
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<td>Cornelia De Lange syndrome</td>
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<td>Meckel-Gruber syndrome</td>
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<td>Oro-facio-digital syndrome</td>
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<td>Coffin-Siris syndrome</td>
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<td>Bergeron syndrome</td>
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<td>Short small intestine syndrome</td>
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<td>Chromosomal syndromes</td>
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<td>Deletion 4P</td>
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<td>Deletion 17p 13 (Miller-Dieker syndrome)</td>
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<td>Skeletal dysplasias</td>
<td>Other CNS dysplasias</td>
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<td>Thanatophoric dysplasia</td>
<td>Acardi syndrome</td>
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<td>Joubert syndrome</td>
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<td>Idiopathic lissencephaly sequence</td>
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<td>Hemimegalencephaly</td>
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<td>Twin syndromes</td>
<td>Parabiotic twin syndrome</td>
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TABLE 2: Environmental causes of neuronal migration disorders

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<td>Toxoplasmosis</td>
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<td>Carbon monoxide poisoning</td>
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J. Microcephalia Vera

The term microcephalia vera, used in the sense defined by Evrard et al (15), includes several genetic and sporadic diseases. Most patients present with moderate developmental delay but no focal neurologic findings. Histologic exam of the cerebral cortex reveals severe depletion of the neurons of layers 2 and 3. Histopathologic study of one entire brain by Parain et al (27) revealed no migratory disorder, no heterotopias, and a depleted germinal zone (Fig. 6) at a gestational age of 26 weeks (which is the age of maximal volume in the germinal zone in normal fetuses (28)). (At this fetal age, the germinal zone consists mostly of glial precursors (15).) On gross pathologic study, these brains have thin cortices, shallow sulci, and markedly diminished callosal fibers (which originate and terminate in the outer cortical layers). Evrard et al (15) postulate that the cause of this disorder is early exhaustion of the germinal zone. One case of presumed microcephalia vera, studied by magnetic resonance (MR), showed a small brain with lissencephaly and thin cortex (Fig. 7).

Lissencephaly (Agyria-Pachygyria)

Lissencephaly and agyria-pachygyria are the terms used to describe brains with absent or poor sulcation. Agyria refers to brains or portions of brains with absence of gyri and sulci, whereas pachygyria refers to brains or portions thereof with few broad, flat gyri and shallow sulci. Lissencephaly ("smooth brain") is another term used to describe such brains. Complete lissencephaly is synonymous with agyria, whereas incomplete lissencephaly refers to brains with shallow sulci and a relatively smooth surface; incomplete lissencephaly is often used synonymously with agyria-pachygyria.

Two clinical pathologic types of lissencephaly have been identified (for a review, see Ref. 29). Type I lissencephaly usually has both agyric and pachygyric regions (Figs. 8 and 9). The histologic appearance of the cortex varies according to the brain area; the majority of the neocortex is that of a "4-layered" cortex, composed of a molecular layer, a disorganized outer cellular layer, a cell-sparse layer, and an inner cellular layer (probably composed of neurons whose migration has been prematurely arrested, Fig. 10) (30)). Some have postulated (30, 31) that the cell-sparse layer results from laminar necrosis, causing damage to the radial glial fibers and inhibiting further migration of neurons, which, therefore, remain in the inner cellular layer. Other hypotheses are based upon the supposed variation of the chemical...

Fig. 5. Radial microbrain. Cortex of a full-term neonate displaying the pathologic features described in the text. Normal cortical lamination and normal residual germative zone. C, cerebral cortex; v, ventricle. (Reprinted with permission of Paul H. Brookes Publishing Company, from Kadhim et al (95).)
control mechanisms of neuronal migration and neuronal-glial relationships along the radial extent of the migratory corridors. The clear-cut horizontal line of crossing between the thalamocortical pathway and the radial glial fibers (Fig. 2) seems to correspond to a chemical and/or mechanical variation of the migratory trajectory. The external sagittal stratum seems to be another concentric ring of chemical and/or mechanical heterogeneity in the intermediate zone. The migratory defect, whatever the cause, is postulated to occur between 12 and 16 gestational weeks (15, 32, 33). Other gross pathologic features of lissencephaly type I include dilatation of the trigones and occipital horns of the lateral ventricles (34-36) and hypogenesis of the corpus callosum (34).

Clinically patients with type I lissencephaly often have bitemporal hollowing, prominence of the occiput, and micrognathia (34, 35). The head size is normal to small at birth but progressive microcephaly commonly results from decreased head growth over the first few years of life (34, 35, 37, 38). Patients are hypotonic at birth, particularly centrally, but develop progressive appendicular spasticity (34, 35). Seizures, usually in the form of infantile spasms, generally begin within the first few months of life. As the infants mature, they are likely to develop focal motor seizures, absence spells, and grand mal seizures as well (34, 35). Anomalies of other organ systems are more common in the children with severe neurologic impairment (35, 38). Dobyns (35) has divided patients with type I lissencephaly into two groups, those with the Miller-Dieker syndrome, and those with isolated lissencephaly sequence. The distinctions between these groups are beyond the scope of this paper other than to comment that the clinical, pathologic, and radiologic manifestations are most severe with the Miller-Dieker syndrome (35, 38), and that a spectrum of severity is seen in the isolated lissencephaly sequence (38).

On imaging studies, patients with type I lissencephaly have a thickened cortex with broad, flat gyri and a few shallow sulci, diminished white matter, and shallow vertical sylvian fissures (31, 34, 35, 39). In severe cases, the brain may be completely agyric (Fig. 11); more commonly, areas of pachygyria are present, particularly in the frontal and temporal lobes (Fig. 12) (31, 33, 36). In the most severe cases, the corpus callosum is hypogenetic (34, 40). The trigones, occipital horns, and temporal horns of the lateral ventricles are usually dilated, probably because the calcaneal sulci and the hippocampi are incompletely formed (34).

Type II lissencephaly is characterized pathologically by a thickened and severely disorganized unlayered cortex, which is disrupted by penetrating vessels and fibro-glial bundles (33, 35, 41) (Fig. 13). The neurons are sometimes grouped in large, poorly established vertical columns that are poorly aligned with the neighboring columns (Figs. 14 and 15). Subcortical heterotopias are not rare. The cortico-subcortical deposition of the neurons is generally more superficial than in the
type I lissencephaly; consequently the “cortex” is thinner. The morphologic features can be highly variable, even in different regions of the same brain. The meninges are thickened and densely adherent to the cortex, obliterating the subarachnoid space and resulting in hydrocephalus (32, 33, 35, 41). The entirety of the cerebral hemispheres is involved. Furthermore, the cerebellar cortex displays a diffuse microgyric pattern. Associated anomalies include microphthalmia with retinal dysplasia, callosal dysgenesis, cerebellar cortical dysplasia, cerebellar vermian hypoplasia, and hypomyelination of the white matter (32, 33). The literature contains hypotheses of both genetic causes (42) and of a destructive process in the second half of the second trimester (15, 43).

As suggested earlier (26, 43, 44), this complex pathologic picture, including neuronal heterotopias and a severe prenatal hydrocephalus, suggests a destructive and cicatrizing factor or another abnormal mesenchymal process acting for a protracted period during gestation.
Classically, the clinical presentation of patients with type II lissencephaly is that of the Walker-Warburg syndrome (35, 41, 43). These patients are almost always severely abnormal at birth and may have severe congenital eye malformations, posterior cephaloceles, congenital hydrocephalus, or congenital hypotonia (32, 35). The hypotonia is usually profound and unchanging, with most patients dying in the first year of life, secondary to recurrent aspiration and respiratory illnesses.

Some authors (32, 35, 45–49) have pointed out similarities and apparent overlap of Walker-Warburg syndrome with Fukuyama's congenital muscular dystrophy. Santavuori (45) has proposed that the Walker-Warburg syndrome and Fukuyama's congenital muscular dystrophy are part of a spectrum of pathology with an intermediate form (muscle-eye-brain disease) consisting of congenital muscular dystrophy, congenital retinal dysplasia, hydrocephalus, hypomyelination of the white matter, and cerebral cortical dysplasia.

The imaging manifestations of type II lissencephaly are a thickened cortex with shallow sulci (which may appear intermediate between type I lissencephaly and diffuse polymicrogyria), microphthalmia (which may be unilateral or bilateral),
Fig. 12. Type I lissencephaly. SE (600/20) image shows the typical appearance in which some gyri and sulci (arrows) are present, especially in the temporal lobes.

Fig. 13. Type II lissencephaly in a 4-day-old human. The cortical plate is highly disorganized with deep ectopic groups of neurons (arrows). The features of type II lissencephaly are detailed in the text. (NEPE collection).

Fig. 14. Type II lissencephaly. The cortex is disturbed with poorly established vertical columns that are out of register. Human cortex, (NEPE collection).

Fig. 15. Type II lissencephaly. Eight-month-old patient with Walker-Warburg syndrome. SE (3000/120) image shows that the cortex is agyric, with poorly established vertical columns (compare with Fig. 14). The white matter is hypomyelinated. Hydrocephalus was present (but shunted) and the corpus callosum was hypogenetic.

and hypomyelination (Fig. 15). More severe cases will have hydrocephalus, vermian hypogenesis, cerebellar polymicrogyria, dysgenesis of the corpus callosum, and, occasionally, an occipital cephalocele.

Polymicrogyria

The term polymicrogyria refers to an abnormal macroscopic appearance of the brain gyration that is characterized by too many abnormally
small convolutions (Figs. 16–19). The macroscopic appearance is variable. In some cases, small gyri are separated by shallow sulci. In others, the gyri are wider but with minute indentations indicating the sites of sulci. Still other cases show small, irregular gyri without intervening sulci or with intervening sulci obliterated and bridged by fusion of the overlying molecular layers (32, 33). The basic cytoarchitectonic lesion in polymicrogyria is a mid-cortical ischemic laminar necrosis predominating in layer 5 (Figs. 18 and 20A) (50). Superficial to this necrotic cortical band, the cortex consists of normal layer 4, 3, and 2 neurons. The cortical laminar necrosis enhances the developmental growth difference between the inner and the outer cortical layers.

This mechanism seems to be at the origin of the polymicrogyric cortical overfolding (51). Because the late migrating neurons reach their normal positions before the laminar necrosis takes place, this type of microgyria originates after the 20th fetal week, and may be considered postmigratory.

In some instances, a varying type of localized pallial disorganization has been described in microgyria. Heterotopic neurons are found in the intermediate zone beneath a microgyric cortical area. This type of microgyria with heterotopic features originates slightly before the end of neuronal migration and may result from ischemia.

Variants of microgyria and some other morphogenetic mechanisms have been proposed. Four-layered microgyrias with a laminar necrosis localized or predominating in other layers than layer 5 have sometimes been reported. In the unlayered form of polymicrogyria, another variant, no cell-sparse layer is present (32, 52), making laminar necrosis less likely (for reviews of microgyric variants, see Refs. 52–57). Nonetheless, most authors suggest that many, if not most, causes of polymicrogyria result from ischemic cortical damage (15, 32, 52, 53, 58, 59). In an experimental model, Innocenti (60) has shown that the administration of ibotenate, an excitotoxic amino acid, can induce cortical laminar necrosis, supporting the ischemic etiology of polymicrogyria, since the extracellular concentration of excitotoxic amino acid is highly increased in cases of hypoxia-ischemia (61). Humphreys et al (62) have demonstrated that neurons can migrate through a laminar necrosis and Marin-Padilla (personal communication) has shown a possible late renewal of migration in the superficial cortical layers, suggesting that the disorganized outer layer(s) of the polymicrogyric cortex could be partly composed of neurons that arrived after the cortical injury had destroyed the normal or-

Fig. 16. Polymicrogyria. Bilateral polymicrogyria with vascular topography. (Reprinted with permission from Evrard et al (97).)

Fig. 17. Polymicrogyria in a 9-year-old human. Microgyria of the postmigratory type associated with CMV infection.
A. The cortex displays numerous small convolutions separated by shallow sulci.
B. Higher magnification reveals the cortical pattern expected with laminar necrosis. The “cell-sparse zone” is the result of necrosis in cortical layer 5 (arrows). (NEPE collection.)
Fig. 18. Polymicrogyria. High magnification of the laminar necrosis of layer 5 (arrows) in two adjacent abnormally small convolutions. (NEPE collection).

Fig. 19. Polymicrogyria. Note the thickened cortex and the abundant abnormally small convolutions in the absence of heterotopia in the underlying white matter.

Organizational mechanisms within the cortex. Nevertheless, most cases, the chronology and the histopathology favor the classical model of a postmigratory hypoxic-ischemic laminar necrosis.

Clinicopathologic correlations from the European Multicenter Study (63) and from the Brussels Neuropathological Collection emphasize two points. First, most of the cases of microgyria are due to perfusion failures provoked by cytomegalovirus. Other known etiologies include toxoplasmosis, syphilis, and maternal shock. The authors have seen a subsequent case in whom the mother had inhaled toxic hydrocarbon fumes during the 17th gestational week. Indirect evidence suggests that, even in cases of intrauterine infection, polymicrogyria results from perfusion failure (32, 33, 64). Second, serial ultrasound studies of the fetus show the occurrence of a break in the cranial growth curve around 30 weeks in our cases of microgyria due to cytomegalovirus infection.

A few isolated case reports give other clues as to the timing of the injuries that result in polymicrogyria. Barth (32) has observed two cases involving injury to the fetus at 12–17 weeks gestation that led to unlayered polymicrogyria, whereas two incidents of carbon monoxide poisoning in mothers at 18–24 weeks of gestation resulted in layered polymicrogyria. Moreover, experiments by Dvorak et al (53, 59) on newborn rats that had brain maturity roughly equivalent to a midgestational human infant, caused layered polymicrogyria. Barth (32), therefore, postulates that unlayered polymicrogyria results from early second trimester brain injury and that layered polymicrogyria results from mid to late second trimester injury.

Clinically, patients with polymicrogyria have an extremely variable presentation and course that seems to depend upon the location and extent of the cortical involvement. Patients with diffuse polymicrogyria, involving the entire neocortex, clinically resemble those with lissencephaly in that they have small heads, are hypotonic with subsequent appendicular spasticity, develop seizures (usually infantile spasms) at a very young age, and are severely developmentally delayed (65). Patients with bilateral focal polymicrogyria have a high incidence of generalized developmental delay, usually moderate in severity, and have spastic motor dysfunction that is usually bilateral. Language development is almost always delayed (65). Patients with unilateral focal polymicrogyria most often have congenital hemiplegia as their primary clinical manifestation. In the 60% of patients in whom developmental delay is present, it is usually mild to moderate. Seizure disorders are present in 70%–80% and are usually focal motor in type (65). The high incidence of epileptic manifestations in polymicrogyria correlates with the presence of lesions in layer 5, a potentially potent source of epilepsy, and with lesions of the adjacent layer 4, a source of inhibiting inputs onto layer 5 neurons.

On imaging studies, polymicrogyria can mimic pachygyria as the cortex is slightly thickened, and sulci are shallow (31, 66) (Fig. 21). The brain surface may be flat or infolded (Fig. 22). Although most commonly located in proximity to the syl-
vian fissure, polymicrogyria can be present anywhere in the brain. In general, the cerebral cortex in polymicrogyria is not as thick as it is in pachygyria. Cortical thickness in polymicrogyria usually is in the 5-7 mm range, compared to a normal cortical thickness of approximately 3 mm and a cortical thickness of >8 mm in almost all cases of pachygyria (34). Approximately 25% of patients with polymicrogyria will have abnormally prolonged T2-relaxation of the underlying white matter (65). Anomalous venous drainage is common in areas of polymicrogyria (33). Large draining vessels are especially noticeable in regions where the polymicrogyria is manifest as a large
Fig. 21. Polymicrogyria. Newborn with seizures and hypotonia.
A, Axial SE (500/15) image shows broad, flat gyri in the right frontal lobe with a thickened cortex (open arrows, compare with normal left side). An abnormal operculum is present on the right (closed arrow).
B, Axial SE (3000/120) image shows that the abnormal thickened cortex (arrows) remains isointense with normal gray matter.

infolding of abnormally thick cortex, a condition some authors have mislabelled as “type I schizencephaly” (67). Such vessels should not be mistaken for vascular malformations (68). Angiography is not indicated in these patients.

Schizencephaly

The term schizencephaly was first coined by Yakovlev and Wadsworth to describe gray matter lined clefts in the cerebral hemispheres, extending from the pia to the ependymal lining of the lateral ventricle (69, 70). The walls of the cleft may be in apposition (closed lip, or type I, schizencephaly) or separated (open lip, or type II, schizencephaly). The cerebral cortex surrounding the cleft may be normal or may be in the form of polymicrogyria, which extends for a variable distance along the surface of the adjacent brain (32, 33, 57, 58, 67). The gray matter lining the cleft is composed of disorganized, mature neurons in the form of unlayered polymicrogyria (32, 57, 58). Heterotopic gray matter may line the ventricle adjacent to the cleft (32, 33). In all probability, schizencephalies result from pathogenetic processes similar to those that cause polymicrogyria. Superficial cortical injuries result in flat polymicrogyria without cortical infolding. Injuries that extend more deeply into the cortex and destroy the superficial portions of the radial glial fibers or the surface molecules that promote neuronal migration, cause cortical infoldings lined by polymicrogyria. Injuries involving the entire thickness of the developing hemispheres, from pia to ependyma, cause schizencephalies (32, 71).

Patients with schizencephalies present clinically in manners similar to those with polymicrogyria. Patients with bilateral schizencephaly (approximately 35% (71)) have a high incidence of moderate to severe developmental delay, delayed language development, and motor impairment. In patients with unilateral clefts, clinical impairment is related to the size and location of the cleft. Large clefts are associated with a high incidence of moderate to severe developmental delay, whereas patients with small, unilateral clefts, although usually hemiplegic, have a high incidence of normal intellectual development (71). A small number of patients with schizencephaly will have poor visual acuity or nystagmus secondary to associated septo-optic dysplasia (72, 73).

On imaging studies, schizencephalies are seen as cerebrospinal fluid (CSF)-filled, gray matter-lined clefts that extend from the inner table of the calvarium into the lateral ventricle (Figs. 23 and 24). When the clefts have closed lips, a dimple will be seen in the ventricular wall where the cleft enters the ventricle (72, 74). Large vessels are often seen within the CSF within open-lip schizencephalies. The cortical gyral pattern may be dysplastic for a variable distance on one or both sides of the cleft (Fig. 23). Subependymal heterotopias may line the lateral ventricle adjacent to the cleft. The septum pellucidum is absent in 80%-90% of patients with schizencephaly.
Fig. 22. Polymicrogyria. Five-year-old with seizures and spastic quadriplegia.
A, Parasagittal SE (600/20) image shows the sylvian fissure to be in continuity with a sulcus in the parietal lobe (arrows).
B, Axial SE (2800/80) image shows deep infoldings of irregular, thickened cortex (arrows) in the parietal lobes bilaterally.

Occasionally, patients with open-lip schizencephaly will have an enlarged hemicranium on the side of the schizencephaly (Fig. 24), presumably resulting from CSF pulsations being transmitted through the cleft. Insertion of a ventriculoperitoneal shunt can, at times, dampen the CSF pulsations and diminish the calvarial asymmetry (M. Edwards, personal communication).

Heterotopias

Gray matter heterotopias are collections of normal neurons in abnormal locations secondary to an arrest of radial migration of neurons. The exact mechanism of the migration arrest has not been determined. Some authors have postulated that the arrest of neuronal migration results from damage to the radial glial fibers (31). Others have suggested premature transformation of the radial glial cells into astrocytes (15), or a deficiency of the specific surface molecules that promote migration along the radial glial fibers (12). Heterotopias have been associated with a wide variety of genetic, vascular, and environmental causes, including methyl mercury poisoning, exposure to ionizing radiation, fetal alcohol syndrome, trisomy 13, and multiple congenital anomaly syndromes, to name just a few (32, 33). Classically, heterotopias have been divided into three major types: 1) subpial heterotopias, that lie in the marginal zone or outside the brain in the leptomeningeal space (Figs. 25 and 26); 2) nodular heterotopias, that are conglomerate masses of gray matter that are situated near the wall of the lateral ventricle (Figs. 27–30); and 3) laminar heterotopias, that are bilateral, symmetrical ribbons of gray matter in the centrum semiovale (Fig. 31). Clinically, it is more useful to divide heterotopias into three...
Fig. 25. Subpial neuronal ectopia. Light microscopic image of human fetal neocortex, 24th week of gestation, shows discontinuity of the basal membrane (open arrows) and subpial neuronal ectopia. Beneath these ectopias, the laminar pattern of the underlying cortex is often distorted and, less frequently, perfectly preserved, especially in the fetal alcohol syndrome (Reprinted with permission from Evrard et al. [98]).

Fig. 26. Neuronal ectopias (arrows) in the marginal layer in a case of fetal alcohol syndrome. Human neocortex, 3-month-old. Note the highly disturbed laminar pattern in the underlying cortex. (NEPE collection).

groups: 1) subependymal heterotopias (Figs. 27–29); 2) focal subcortical heterotopias (Figs. 30 and 31); and 3) diffuse heterotopias (Figs. 32 and 33). Subpial heterotopias are not considered in this classification because they can only be diagnosed by biopsy or autopsy.

Patients with subependymal heterotopias tend to have mild clinical symptoms, normal development, normal motor function, and onset of seizures during the second decade of life. Seizures are usually mixed partial complex, and tonic-clonic (75). Patients with focal subcortical heterotopias have variable symptoms depending upon the quantity of neurons that have been arrested during migration. Patients with large, thick subcortical heterotopias may have normal motor function and normal development (75). Finally, patients with diffuse gray matter heterotopias (also referred to as "band heterotopias" (76) or "double cortex" (77)) tend to have moderate to severe developmental delay and an early onset of medically refractory seizures (76). Livingston et al (77), however, report two patients with "double cortex" and relatively mild clinical manifestations, indicating some variability in clinical presentation. This difference may relate to the thickness of the arrested layer of neurons (75).

On imaging studies, the hallmark of heterotopias, as with all anomalies of neuronal migration, is the isointensity with cortical gray matter on all imaging sequences and the lack of contrast enhancement (31, 74, 76, 78). Subependymal heterotopias are smooth, ovoid masses (Figs. 28 and 29) that grow into the adjacent lateral ventricle, often causing the ventricle to be narrowed. They can be differentiated from the subependymal hamartomas of tuberous sclerosis by their shape (hamartomas of tuberous sclerosis are irregular and often elongated) (79–92), their signal inten-
sity (subependymal hemartomas of tuberous sclerosis are usually iso- to hypointense com­pared to white matter (80, 82), not isointense with gray matter), and the fact that they do not en­hance after intravenous infusion of paramagnetic contrast (81). Focal subcortical heterotopias will sometimes appear to contain vessels or CSF, thereby mimicking tumors. Closer examination in these cases will show that the vessels and CSF are within infoldings of the cortex adjacent to the heterotopias (75). Patients with large subcortical heterotopias may show thinning of the overlying cortex, which is abnormally smooth and has shallow sulci. Such heterotopias may appear to exert mass effect on the adjacent ventricle or the interhemispheric fissure; however, upon further scrutiny of the images, the affected hemisphere is seen to be small and it becomes apparent that the mass effect is actually distortion of the hem­isphere caused by the dysplasia. Finally, diffuse gray matter heterotopias (band heterotopias) ap­pear as a circumferential band of gray matter that is deep to the cerebral cortex and separated from the cortex by a layer of normal-appearing
white matter (Fig. 33). The overlying cortex may appear normal, may have normal thickness with shallow sulci, or may be pachygyric. The degree of cortical gyral dysplasia seems to be related to the thickness of the band of gray matter heterotopias; i.e., the thicker the band of heterotopic gray matter, the more anomalous the overlying cortex.

**Tuberous Sclerosis**

Tuberous sclerosis is a complex, genetically determined, variably expressed multisystem disorder of cellular organization and proliferation resulting in hamartomatous growth, and occasionally neoplasms, in one or more organs. Affected individuals most commonly present in childhood with seizures and characteristic skin lesions. Myoclonic seizures that begin in infancy or early childhood are the presenting symptom in ≈80% of patients. Seizures increase in frequency as the patient gets older (79). Mental retardation is present in 50%-82% of affected individuals (79). The neuropathologic manifestations of tuberous sclerosis are described quite well in a number of sources (32, 82-85) and will not be discussed in detail here. Patients have subependymal hamartomas that are composed of a variable mixture of cell bodies, glial processes, and blood vessels and are covered by an intact layer of ependyma. Concentric spheres of calcium are deposited in the gliovascular stroma of these subependymal nodules (83, 85). These patients also have giant cell tumors that share many histologic features with the subependymal hamartomas (83, 84).

The cortical lesions of tuberous sclerosis are firm, slightly raised, smooth masses involving the crests of affected gyri. A central depression may
Fig. 32. “Bicortical” lissencephaly-diffuse heterotopia. Neocortex of a 3-month-old deceased infant with pachygyria, hydrocephalus, and verticalized Sylvian fissures. The clinical picture suggested atypical type 1 lissencephaly. A cousin was affected with a clinical and imaging picture suggesting type 2 lissencephaly. The key cytoarchitectonic data is the “double cortex” well illustrated on this photograph. The clear-cut upper limit of the “deep cortex” (arrows) could correspond with the limit of the external sagittal stratum. This case of “double cortex” has been reported (see Ref. 99). (NEPE collection).

be seen in some lesions in older patients, reflecting degeneration and retraction of tissue in the central regions of the lesion (83).

The central nervous system lesions of tuberous sclerosis are composed of cells best classified as neurons, cells best classified as astrocytes, and cells that are not easily classified (86). The neurons are always primitive or aberrant (86, 87). The astrocytes are aggregated in the subependymal nodule and the cortical hamartoma, rather than diffusely dispersed as in the normal brain (86). Stefansson et al (86) believe that patients with tuberous sclerosis have defective stem cells in all germ cell layers. In the neural epithelium, these stem cells evolve into both astrocytes and neurons but then lack the ability to integrate themselves into the brain (86). Some remain in the subependymal germinal matrix and proliferate there, forming subependymal hamartomas and giant-cell tumors. Others migrate to the intermediate zone or cortex but fail to differentiate, instead forming disorganized aggregates of cells (tubers) (86).

The lesions of tuberous sclerosis have characteristic appearances on imaging studies. The subependymal hamartomas tend to be located along the ventricular surface of the caudate nucleus, most often on the lamina of the sulcus thalamostriatus immediately posterior to the foramen of Monro (85) (Fig. 34). Less commonly, they may be present along the frontal and temporal horns of the lateral ventricles, or in the third or fourth ventricle. They are difficult to visualize on computed tomography (CT) in the first year of life since they rarely calcify until the end of infancy (88). In older infants, children, and adults, the subependymal hamartomas are readily recognizable on CT images as one or more calcified subependymal nodules that are often associated with cortical lesions (79, 82, 88, 89). On MR, subependymal hamartomas appear as irregular nodules that protrude into the adjacent ventricle and are isointense with white matter (80, 82, 90, 91). They are most easily visualized on short TR images where they contrast with the low signal intensity of the CSF in the ventricles. Nodules

Fig. 33. Band heterotopia. Axial SE (2800/80) image shows the migration of a thin layer of neurons (arrows) that has been arrested prior to completing migration to the cerebral cortex.
may manifest a variably low signal intensity on the long TR/TE images, the degree of hypointensity being dependent upon the extent of calcification (89, 90) (Fig. 34). Some subependymal nodules will enhance after administration of paramagnetic contrast material (81). In newborns, subependymal hamartomas may appear hyperintense to normal brain on short TR images (92) (Fig. 35).

Some subependymal masses of tuberous sclero-

Fig. 34. Tuberous sclerosis.

A, Axial contrast-enhanced SE (600/20) image shows multiple subependymal nodules (arrows). They are irregular and isointense to white matter, in contradistinction to heterotopias, which are round to ovoid and isointense to gray matter. Some of the hamartomas enhance after contrast administration.

B, Axial SE (2800/80) image. The subependymal nodules are less easily seen on the T2-weighted image than on the T1-weighted image in A.

C, Axial SE (2800/80) image at a higher level shows a cortical tuber (solid white arrow), which has a long T2 relaxation time and a strip of normal-appearing cortex overlying it. A line of hyperintensity (open white arrows) extends from the cortical tuber to the ventricular surface. This is believed to represent disorganized white matter along the pathway of migration of neurons and glial cells of the neuronal-glial unit from the germinal zone to the cortex (94).

Fig. 35. Tuberous sclerosis in a newborn. Axial SE (500/15) (A) and (3000/120) (B) images show cortical (closed arrows) and subependymal (open arrows) hamartomas. The short T1 and T2 relaxation times are sometimes seen in newborns and may represent calcification, the inherently long T1 and T2 of normal newborn brain, or both.
rosis are distinguished by their characteristic location near the foramen of Monro and a tendency to enlarge. These lesions are given the name "giant-cell tumors"; their incidence in tuberous sclerosis is \( \approx 5\%-10\% \). Giant-cell tumors are characterized on imaging studies by their increasing size, characteristic location, and intense enhancement after intravenous contrast administration. Their appearance on MR scans overlaps that of subependymal hamartomas, reflecting the overlap of their histologic appearance described above.

In newborns, they may have short T1 and T2 relaxation times compared with brain. The cortical hamartomas or "tubers" are the most characteristic lesions of tuberous sclerosis on pathologic examinations. The number of these lesions in the brains of affected patients varies widely from none to more than 30 (85). The appearance of cortical hamartomas on CT varies with the age of the patient (82). In infants, they appear as peripheral lucencies within broadened cortical gyri. The lucency diminishes with age, making noncalcified cortical hamartomas difficult to identify in older children and adults. The number of calcified cortical lesions seen on CT increases with age; by age 10, calcified cortical tubers are present in up to 50\% of patients with tuberous sclerosis (88). The MR appearance of cortical tubers also varies with age. In newborns, they may show short T1 and T2 relaxation times compared to normal brain (92) (Fig. 35). Tubers in older infants are characterized by long T1 and...

Fig. 36. Composite drawing summarizing cell disposition in various abnormal neocortical neuronal patterns: A, normal cortical pattern in radial microbrain; B, microcephalia vera; C, Zellweger disease; D, type I lissencephaly; E, normal structures; F, microgyria; G, atypical microdysgenesis; H, neuronal ectopia within the subarachnoid space; K, periventricular heterotopias; I to VI, numerals of neocortical layers; WM, white matter. (Reprinted with permission from Evrard et al [15].)
T2 relaxation times within enlarged gyri. The lesions seem to be circumscribed by an intact layer of cortex. Occasionally, a curvilinear streak of prolonged T2 extends from a tuber to the ventricular surface, representing disorganized white matter (94).

Summary

The anomalies of neuronal migration are a fascinating group of disorders that are surprisingly common. An understanding of the normal processes of neuronal generation and migration is of great help in the recognition of these disorders. In this manuscript, we have attempted to present this information, as well as the clinical, pathologic, and imaging manifestations of these disorders, in order to aid in the understanding, and, hopefully, the diagnosis of these disorders. Figure 36 summarizes the many findings in these disorders.

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