A Perspective:
The Role of Disordered Genetic Control of Neurogenesis in the Pathogenesis of Migration Disorders

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Key Words: Agyria-lissencephaly-pachygyria; Cortical dysplasia; Heterotopias; Migration disorders; Neurogenesis; Polymicrogyria.

INTRODUCTION

Malformations of the central nervous system (CNS) cover a wide variety of defects ranging from minor abnormalities identified incidentally at postmortem examination to severe anomalies that are lethal before or after birth. Although specific etiology is unknown for the majority, some of which are relatively common, such as Chiari 2 malformation with meningocele, there are others for which a pattern of autosomal recessive inheritance has been established, and a small number are known to result from radiation, toxins or infectious agents acting at a critical period of gestation.

Chromosomal abnormalities have been identified among an ever-growing number of cases, but a specific chromosomal change is not always found in all individuals with a particular malformation. For example, holoprosencephaly is present in 70% of infants with trisomy 13, but may be associated with trisomy 18, triploidy, as part of known autosomal and X-linked syndromes, or even in infants of diabetic mothers (1). Gurreri et al (1) studied 13 patients with holoprosencephaly in whom the chromosomal defect was found on chromosome 7q36, but they identified four other chromosomal anomalies in infants with this particular malformation.

A textbook addressing the subject of congenital malformations of the CNS, published in 1981, documented a linkage of at least 72 different chromosomal abnormalities in individuals with a wide variety of CNS anomalies and psychomotor retardation (2). Since that time the number has expanded greatly, as additional cases are continually reported.

However, even establishment of an association between a specific chromosomal abnormality and a given CNS defect leaves unresolved the specific mechanism or pathway through which the defective chromosome exerts its effect on the developing nervous system.

Moreover, although any one or more of the 46 chromosomes may be implicated in a developmental anomaly, identification of the specific gene or genes is a staggering undertaking. Consider, for example, that some 30,000 genes are expressed exclusively in the rat brain (3), and that the human brain presumably has at least as many if not more!

In view that it has not been possible to classify the majority of CNS malformations on the basis of etiology, it has been the practice to separate them into diagnostic categories on morphological grounds and, if possible, to suggest a putative pathogenetic basis. One such major diagnostic group includes a number of cerebral cortical dysplasias that are classified under the general rubric of ‘migrational disorders.’

Anatomical features of these migrational disorders suggest that there are other factors beyond a simple disturbance of the movement of neuroblasts from their site of origin to their permanent site in the cortex. Specifically, some malformed cerebella contain too few or too many neurons, abnormalities of neuronal size and type, and malorientation.

Extensive studies of the nematode, Caenorhabditis (C.) elegans, and Drosophila, the fruitfly, have demonstrated similar but obviously much less complex abnormalities of their nervous systems. In fact, development of the nervous system in these lower forms is an exceptionally complex process, specific stages of which are controlled by activity of multiple genes. Mutations of these genes lead to recognizable malformations in both the worm and fruitfly, each of which has a relatively simple nervous system, that of C. elegans, for example, being composed of only 302 neurons.

Comparison of the neurogenic genes and their effects in these lower forms with features of disordered human neurogenesis suggest that there may be analogous genes controlling normal development of the human brain, mutations of which are responsible for the observed anomalies.

In this paper I will describe the morphological features of the malformations comprising the group of human migrational disorders, review the process of normal human neurogenesis, present experimental data controlling neurogenesis (especially in C. elegans and Drosophila) and...
TABLE 1

Classification of Migrational Disorders

<table>
<thead>
<tr>
<th>Type</th>
<th>Putative cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lissencephaly</td>
<td>Unknown or AR*</td>
</tr>
<tr>
<td>A. Isolated lissencephaly sequence</td>
<td>del(17)(p13.3) or unknown AR</td>
</tr>
<tr>
<td>B. Miller-Dieker syndrome</td>
<td>In utero exposure</td>
</tr>
<tr>
<td>C. Norman-Roberts syndrome</td>
<td>Unknown or AR</td>
</tr>
<tr>
<td>D. Isoretinoin embryopathy</td>
<td>AR</td>
</tr>
<tr>
<td>E. Cerebro-cerebellar lissencephaly</td>
<td>AR</td>
</tr>
<tr>
<td>F. Cerebro-ocular dysplasia</td>
<td>Unknown or AR</td>
</tr>
<tr>
<td>1. Walker-Warburg syndrome</td>
<td>AR</td>
</tr>
<tr>
<td>2. Fukuyama type with muscular dystrophy</td>
<td>AR</td>
</tr>
<tr>
<td>G. Neu-Laxova syndrome</td>
<td>Unknown or AR</td>
</tr>
<tr>
<td>H. XK aprosencephaly syndrome</td>
<td>AR</td>
</tr>
<tr>
<td>Pachygyria-agyria</td>
<td>Unknown or AR</td>
</tr>
<tr>
<td>Cerebro-hepato-renal syndrome</td>
<td>AR</td>
</tr>
<tr>
<td>(Zellweger)</td>
<td>In utero exposure to radiation, toxins or unknown</td>
</tr>
<tr>
<td>HARD + E (hydrocephalus, agyria, retinal dysplasia, and encephalocoele) syndrome</td>
<td>AD**</td>
</tr>
<tr>
<td>Laminar heterotopias</td>
<td>Unknown or AR</td>
</tr>
<tr>
<td>Nodular heterotopias</td>
<td>In utero exposure to toxins, infectious agents, de-</td>
</tr>
<tr>
<td>Multiple nodular heterotopias with amentia and ventricular calcification</td>
<td>structive process or unknown</td>
</tr>
<tr>
<td>Polymicrogyria</td>
<td>Unknown or AR</td>
</tr>
<tr>
<td>Cerebral cortical dysplasia ± white matter and/or subependymal heterotopia</td>
<td>Potter sequence</td>
</tr>
</tbody>
</table>

* AR = autosomal recessive.
** AD = autosomal dominant.

conclude with a hypothetical construct of the neurogenetic defects that may be responsible for the neuroanatomical defects in humans.

CLASSIFICATION AND DEFINITION OF MIGRATIONAL DISORDERS

CNS malformations included in the category of 'migrational disorders' are listed in Table 1. Basically, the list can be simplified into several broad groups: agyria-lissencephaly-pachygyria, microgyria-polymicrogyria, dysplastic cortical architecture, NOS, and heterotopias. Exploration of the literature documents the complexity of these defects, namely that they vary widely within their special group and that they are often only a component of several involving the CNS, eyes and/or other organ systems, including muscle. This discussion will focus upon the cerebral cortical malformations and the heterotopias, leaving aside the many other specific aspects of individual syndromes that have been described. (For specific information on these see 2, 4-12.)

The severe malformations of cerebral cortex, specifically the agyria-lissencephaly-pachygyria and microgyria-polymicrogyria groups, are rare disorders, and individuals with such defects often die at birth (as in Neu-Laxova) or in childhood. The occurrence rate of Zellweger's disease is said to be 1:25,000-50,000, whereas heterotopias, ectopias and nonspecific dysplasia of cortical architecture are relatively common, especially in individuals with seizure disorders and/or mental retardation. An autopsy study of mentally retarded patients yielded an incidence of 3.3%, whereas 42% of surgical specimens removed for seizure disorders contained heterotopias (13).

Individuals with these types of cerebral malformations are typically mentally retarded and have seizure disorders which are often difficult to control with medication. There may be motor deficits of various types as well.

Agyria-Lissencephaly-Pachygyria

These descriptive terms are often used in combination, interchangeably or separately, although each differs in the precise meaning. The agyric brain is without convolutions, although in practice a brain totally lacking gyri or sulci of some kind is a rarity (Fig. 1). The companion term 'lissencephaly' indicates lack of sulcation or surface folding, the result being a smooth brain. Obviously, if a brain lacks gyral demarcation, it follows that sulci are also absent, hence the terms agyria and lissencephaly could be used interchangeably. On the other hand, pachygyria refers to a malformation characterized by abnormalities in two dimensions: surface gyri are broad and the cortex on cut section is unusually thick (Fig. 2). Brains with any of these malformations may be abnormally small (micrencephalic), of normal size or excessively large (megalencephalic). In some instances the hemispheres are unequally affected allowing a diagnosis of hemimegalen-
cephaly (14–16). However, such asymmetrical brains are not necessarily larger than normal; in fact, they may be too small or fall within the normal range.

A spectrum of cytoarchitectonic abnormalities has been described among this group (5–12, 16–20). Neopallial cortex is primarily affected and consists of three to five neuronal layers rather than the normal six. A common four-layered pattern consists of a molecular layer; a second, thin, poorly-defined superficial layer of nerve cells; a third consisting of a tangential plexus of myelinated fibers with a few neurons; and a thick disorderly fourth layer of neurons. Occasionally, the outer layer is abnormally cellular (6), but one of the most consistent features is misorientation of neurons. The cell bodies may be abnormal, both in size and morphology. There is a variable complement of abnormal, generally reactive, astrocytes. The cortical ribbon may be thin or there may be dispersal of neurons throughout the cerebral mantle leaving room for only a small amount of white matter adjacent to the ventricle.

**Microgyria**

This term is applied when the cerebral surface is composed of many small, irregular gyri demarcated by shallow sulci, giving it the appearance of a walnut shell or cauliflower (21) (Fig. 3A). In some instances, however, the gyri may be unusually broad or even normal and the disordered cortical ribbon may be discovered only upon sectioning. Cortical involvement may be focal (often localized to the region of the Sylvian fissures) or generalized, or combined with other types of cerebral malformations.

On section the cortical ribbon displays an irregular, wormy or 'festooned' configuration (Fig. 3B). In general, the disordered cortical ribbon is thinner than normal, containing from two to four recognizable layers. The four layers from outside in consist of the normally hypocellular molecular layer, the outer granular layer which may present the festooned pattern, a third, sparsely cellular layer (of Ranke) and a fourth layer of variable thickness composed of neurons of various sizes and shapes (6). If there are only three layers, the fourth is missing, and in the two-layered microgyric cortex the second layer widens and blends into the white matter (6). In some instances it is difficult to discern the laminae of a thoroughly disorganized cortex (22).

**Fig. 1.** Vertex view of agyric brain from 2 day old infant with 'HARD + E' syndrome (hydrocephalus, agryria, retinal dysplasia and encephalocele). Note almost total absence of gyralsulcal markings.

**Dysplastic Cortical Architecture, NOS**

It is not uncommon to observe cortical architectonic malformations that do not conform to any of the previously described patterns or malformation syndromes. These tend to be focal but may be widespread, and while they may be seen at necropsy, they are detected with increasing frequency in surgical specimens removed from individuals with intractable seizure disorders. Temporal lobe cortex is most frequently affected, although dysplasia may occur in any region of the cerebrum (23, 24).

The dysplastic cortical ribbon exhibits a variety of abnormalities, the most fundamental being replacement of the normal six-layered pattern by an apparently random distribution of maloriented neurons, many of which are large pyramidal-type cells. The ribbon often varies in

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**Fig. 2.** A. Lateral view of brain from 18 month old infant showing agryria-pachygyria primarily involving the frontal and temporal lobes. B. Coronal section of same pachygyric brain showing massive widening of cortex in all areas except for hippocampal formation. Note normal architecture of deep cerebral nuclei and rostral midbrain.

**Fig. 3.** A. Lateral surface of cerebral hemisphere of 3 year old child showing walnut-shell configuration of gyri in region of Sylvian fissure characteristic of micropolygyria. B. Coronal section of brain from 26 year old man demonstrating typical 'festooned' cortical ribbon involving gyri of the left Sylvian region. Note unilateral distribution of the lesion.
width from place to place and neurons tend to trail haphazardly into the white matter (Figs. 4, 5, 6).

Heterotopias

Two general types of heterotopias have been described, namely laminar and nodular (5, 6, 25–27) but it is common to find isolated or scattered small clusters of neurons in cerebral white matter of infants or children with or without other abnormalities. These randomly distributed neurons tend to disappear with age. The heterotopias, on the other hand, are more often clinically and pathologically significant.

Nodular heterotopias are the most common type. They are typically located beneath the ependyma of the lateral ventricles but may be found anywhere in cerebral white matter (6) (Fig. 7). They are primarily composed of neurons, vary in size and number, and are common in brains with microgyria, although they may be isolated findings or occur in association with other brain malformations (5).

Laminar heterotopias are rare. They consist of linear or multinodular arrays of neurons in the cerebral white matter paralleling the cortical ribbon but separated from it by white matter. The overlying cortex may be normal, dysplastic, pachygyric or agyric (5) (Fig. 8).

NORMAL NEUROGENESIS

Knowledge of normal developmental neuroanatomy is essential to understanding the pathogenetic concept of these cortical dysplasias as ‘migrational disorders.’ The process is exceptionally complex and a comprehensive review is beyond the scope of this paper; details may be found in a number of standard texts and papers (28–34). The brief summary to follow represents a bare outline of the essential features necessary to understand the process of migration and has been prepared primarily from the referenced sources.

The nervous system develops from the embryonic neural plate which forms the neural tube during the fourth postconceptual week. The neural tube consists of rapidly
proliferating, pseudostratified neuroepithelial cells that are oriented perpendicular to the inner and outer membranes of the tube. Nuclei of cells undergoing mitosis move toward the inner membrane and undergo division at that site; in the resting phase they are in a midposition. The germinal cells are attached to both the internal and external limiting membranes during interphase and prophase, but the external attachment is lost during metaphase when the cells round up and divide. At this point the daughter cells have one of four options: 1) both cells may re-enter the mitotic cycle and continue to proliferate; 2) one stem cell may continue to proliferate whereas the other loses the capacity for further mitosis (the young neuron) and migrates from the germinal zone toward the external surface of the neural tube; 3) the cells may enter a resting phase but retain the capacity to re-enter the mitotic cycle; or 4) they lose the ability to undergo mitosis permanently and move into the mantle layer to populate the cortex.

By the sixth postconceptual week, the number of cells in the wall of the neural tube has increased such that the rostral portion of the original primitive simple tubular structure has already been transformed into a holosphere presaging the configuration of the cerebrum. At this stage, there are three zones: the outer marginal, an intermediate, and the inner ventricular zone. The marginal zone con-
TABLE 2
Genes Controlling PCD in C. elegans

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
</tr>
</thead>
</table>
| 1. ced-3 and ced-4 | • Essential for "execution" of cell death  
                   • Acts within cells undergoing PCD  
                   • Gene products: ced-3: protein kinase-like molecule  
                   ced-4: Ca++ binding protein (may activate DNA endonuclease) |
| 2. ced-1 and ced-2 | • Necessary for engulfment of dying cells  
                   • Gene products most likely involved in recognition and process extension |
| ced-5–8 and 10 | • Participates in degradation of DNA in the dying cell |
| 3. nuc-1 | • Prevents cell death in cells fated to live  
                   • Analogous to human bcl-2 |
| 4. ced-9 | • Specifies which cells are to die  
                   • ced-1 prevents and ced-2 promotes cell death in specific neurons |

TABLE 3
Cell Death in C. elegans Consequent to Aberrant Genetic Activity

<table>
<thead>
<tr>
<th>Pathway of cell death</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Engulfment murder</td>
<td>A cell is &quot;murdered&quot; by a neighboring cell</td>
</tr>
<tr>
<td>2. Inappropriate activation of PCD</td>
<td>Loss of function of mutation of ced-9</td>
</tr>
<tr>
<td>3. Inappropriate phagocytosis</td>
<td>Mutations of lin-24 and lin-33 cause alterations in cells such that they become targets for phagocytosis by action of ced-2, 5 and 10.</td>
</tr>
<tr>
<td>4. Abnormal deaths</td>
<td>Mutations in mec-4 and deg-1 genes cause necrosis by swelling and cell lysis</td>
</tr>
</tbody>
</table>

Maintains the processes of the ventricular cells, young neurons and glia.

As development progresses there is continuous movement of postmitotic neuronal cells from the ventricular zone to the external limiting membrane of the marginal zone. These cells then reverse their path to locate in the cortical layer they are destined to occupy permanently. The normal developmental pattern is curious as there is an inside out population of the specific neuronal layers, immature neurons destined for the subplate and layer six comprising the first group to migrate, then those for layers five, four, etc. follow. Under the circumstances successive populations of young neurons must move through an increasingly cellular field in order to reach their permanent site. Studies of cerebral cortical development by Ghosh and Shatz have focused upon the first postmitotic neurons which establish themselves immediately below layer six and are called the "subplate neurons." Integrity of these neurons is critical to the establishment of normal patterning of connections from thalamus and in prevention of excessive cell death of the lateral geniculate nucleus (35).

Gliogenesis occurs at the same time as neurogenesis but continues long after neurogenesis is terminated. However, by the tenth week of gestation, the processes of the radial glia are serving as pathways along which the immature neurons migrate (33). Prior to the development of radial glia, early generations of migrating neurons normally move from the ventricular zone without guidance and apparently manage to do so without problems (36).

With some exceptions, the proliferation and migration of young neurons destined to form the cerebral cortex are completed by 20–24 weeks postconception. However, CNS development is not an uninterrupted chain of cellular proliferation, migration and eventual terminal differentiation and synapse formation. It has long been recognized that there is a simultaneous normal biological process of programmed cell death (PCD) during growth and differentiation not only in the embryonic and fetal nervous system but in other organs and parts of the body as well (37).

PROGRAMMED CELL DEATH

Programmed cell death includes necrosis, atrophy, and a type of PCD termed "apoptosis" (ancient Greek for seasonal 'falling off of tree leaves') (38–40). Detailed reviews of this fascinating biological phenomenon are available beginning with the discovery of this process by Kallius (41) and progressing to the pioneering work of Hamburger and Levi-Montalcini (42–44).

Neuronal cell death is a normal phenomenon during development of both the vertebrate and invertebrate nervous system, and a significant number of cells are destroyed, sometimes as many as 80% of those produced (43, 44). Information regarding this process in humans is sketchy, but studies of the nematode C. elegans have been exceptionally productive in identification of genes encoding the factors that promote and regulate cell death (45). This remarkable worm has been studied in great detail (46), and all somatic and nervous system cells have been counted during development and in the adult stage. A fixed number of 1,090 cells are generated, 131 of which are programmed to die (12%), most of these being neuronal (45).

The complexity of this process is astonishing considering 13 genes are involved in an organism with only a total of 959 cells in its entire body at maturity! The specific genes and the functions that they control are listed.
CONTROL OF NEUROGENESIS, NEURONAL NUMBERS, SIZE AND TYPE, AND NEURONAL–GLIAL INTERACTION

Other factors besides PCD modulate the exact number, size and type of cortical neurons and interaction between neurons and glia in the developing nervous system. Studies of Levi-Montalcini (47) and co-workers (48, 49) years ago established an important role for nerve growth factor (NGF) in neural development in both the peripheral and central nervous system. Its role in the CNS has not been completely delineated although it plays a major role in growth and maintenance of cholinergic neurons. Studies indicate that suppression or expression of trophic factor activity is under genetic control, specifically involving the c-fos and jun genes (50, 51).

Specific mechanisms controlling cell proliferation in the human neural tube and primitive nervous system are not precisely known. There is some evidence from study of yeast genes suggesting that one of the natural factors that starts and stops mitosis is akin to a maturation promoting factor (MPF) which is mitotic protein kinase (28). The decision to become a neuroblast is controlled by action of proneural genes upon groups of neuroectodermal cells. In Drosophila, five are involved in formation of sensory organs alone and at least one acts in the CNS (52, 53). These include four in the achaete-scute complex (As-C), daughterless (da), and wingless (for the CNS). Once committed, there is inhibition of neighboring cells to undergo similar development through cell interactions mediated by action of neurogenic genes (52, 54, 55).

There are six neurogenic genes in Drosophila that control cell–cell interaction pathways in the peripheral nervous system. Products of four named Notch (N), Delta (D1), Enhancer of split complex (E(Spl)-C) and mastermind (mam) encode for membrane proteins with epidermal growth factor (EGF)-like repeats. A fifth, neuralized (neu), may also be involved with the other four. A second pathway that possibly allows passive transport of small molecules across cell membranes is mediated by a neurogenic gene called big brain (bib) (52). Lack of function of any one of the neurogenic genes leads to neural hypertrophy (55).

Beyond involvement of these genes in control of both the number and type of neurons there are 15 other genes that function during the postneuroblast stage as neuronal precursor type selector genes (52, 54). Among these are the Helix-loop-helix (HLH) gene family. These consist of a family of transcription factors that involve a wide spectrum of growth and development systems. The As-C complex, noted above, belongs to this family (56). A new member is the gene NSCL-2, which appears to play a role in neurons undergoing differentiation (57). A second set of bHLH genes, Id, is also specifically expressed in neural precursors of the mammalian nervous system (58).

Other control genes regulate essential steps in development, some specifically involved in formation of the nervous system. These paired box genes (Pax) are found in Drosophila, mammals and other vertebrates, and are similar to homeobox (HOX) genes. Schmahl et al (59) observed striking cortical malformations, heterotopias, arachnoidal ectopia and increased volume of the forebrain germinal zone in mice with a point mutation at the Pax-6 locus. The latter observation is of special interest as it indicates interference of the normal migratory process of postmitotic cells from this germinative zone through genetic dysfunction.

Studies of mutations involving these genes have demonstrated anomalous nervous system development of various types as noted in Table 4.

Since glia are more easily studied in the laboratory, there is considerably more known about factors controlling their growth such as interleukin I, tumor necrosis factor (TNF), glial maturation factor (GMF), platelet-derived growth factor (PDGF), ciliary neurotrophic factor and insulin-like growth factor (ILGF) (28). These polypeptide growth factors mediate a variety of cell–cell interactions in the developing CNS, including signals which instruct cells to proliferate, migrate, differentiate or survive (60). Hormonal factors are most important during the fetal and postnatal periods, although some act during embryogenesis (61).

In contrast to genetic aspects of neuronogenesis, there is not a parallel body of data specifically regarding the genetic factors controlling gliogenesis. At the same time there is a vast literature describing morphology and function of various types of astrocytes and oligodendrocytes.

### TABLE 4

| Genetic Malfunction and Resulting Neural Abnormality in C. elegans and Drosophila |
|---------------------------------|----------------------------------|
| Gene group                      | Abnormality secondary to mutation |
| Prepattern and proneural        | No or too few neuronal precursors and neurons |
| Neurogenic genes                | Too many neuronal precursors and neurons |
| Neuronal precursor type selector genes | Transformation of neuronal type |
| Cell division and lineage genes | Alteration of cell division or cell lineage |
| Developmental control           | Disordered migration and cortical architectonic abnormalities |

Consideration of the concept of a migrational disorder must also include the possibility of some abnormality of glial development or function since the immature neuron (postmitotic neuroblast) utilizes glial processes as migratory pathways from the ventricular zone to its permanent site in the cortex.

Various types of cell adhesion molecules (CAM) appear to be involved in this dynamic process. These CAM are classified into three molecular families: immunoglobulin and integrin superfamilies, and the cadherin family (62, 63). Studies by Takeichi et al (64) suggest that different cell types in neural tissues acquire different sets of cadherins during development but that N-cadherin is the most important cell–cell adhesion molecule in maintaining the architecture of early neural tissues. In fact, overexpression of N-cadherin induced clumping of cells resulting in disorganization of tissue architecture.

It has been suggested that dysfunction of CAM interactions and linkages because of interference of very long chain fatty acids (VLCFA) is responsible for migrational abnormalities in infants with peroxisomal diseases such as Zellweger syndrome (65).

Komuro and Rakic (66) have shown that N-methyl-D-aspartate (NMDA) receptors regulate the migration of cerebellar granule cells along processes of Bergmann glial cells, but it is not known whether NMDA plays a role in migration of neurons in the telencephalon.

FORMULATION OF A HYPOTHESIS

Bielschowsky was the first to suggest an arrest of normal cell migration to account for the cortical malformations of microgyria and pachygyria, the difference between these two, in his opinion, being only the time in development at which arrest took place (21). Later, others suggested that polymicrogyria resulted from hypoxia producing cortical laminar necrosis after neuronal migration was almost completed (67, 68) or that the gyral abnormalities resulted from ischemia of the radial and unbranched cortical arteries at mid-gestation (69).

Bielschowsky’s hypothesis of disordered neuronal migration is an acceptable starting point as it provides a rationale for some of the observed anomalies: disordered cortical lamination, abnormal neuronal polarity, and the presence of heterotopic neurons in white matter and/or subependymal regions with or without overlying cortical anomalies.

While in utero hypoxia-ischemia may account for a few instances of polymicrogyria, there is no corroborating evidence in most cases. In fact, this cortical abnormality has been found in infants exposed to toxins, infectious agents and irradiation during the first half of gestation (5). In addition, some individuals with polymicrogyria have various malformation syndromes or other rare anomalies (5). Moreover, histological features of the polymicrogyric cortex vary; some apparently contain neurons from all cortical laminae, albeit in a disorganized pattern (22).

If the entire range of cerebral dysplasias covered by the general term ‘migrational disorders’ is considered, it becomes clear that the subtypes exhibit certain features requiring an explanation other than the simple possibility that the immature neurons somehow lost their way along the road from their birthplace in the ventricular zone to their permanent home in the cortex, or were secondarily damaged after they arrived.

Consider, for example, the pachygyric brain or one with linear or massive nodular heterotopias in the white matter. It is immediately obvious on gross examination that these brains contain too many neurons, and microscopic study documents not only that this is indeed true but that many of these neurons are larger than normal (16).

In light of advances in molecular developmental biology of the nervous system it seems reasonable to suggest that the morphological aberrations of cerebral cortical development characterized as ‘migrational disorders’ result from a complex disarray of the functional interaction of specific genes, trophic factors, cell adhesion molecules, other cell surface receptors and possibly other currently unrecognized factors responsible for CNS development similar in nature to those identified in C. elegans, Drosophila and other lower mammalian species.

Relevance of the many genetic mutations delineated in the nematode, C. elegans, and the fruitfly, Drosophila, to human neurogenesis may be challenged. However, Jan and Jan (52) argue that there exist considerable similarities between vertebrates and invertebrates and cite examples including HOX-containing genes involved in specification of cell fate in mammalian CNS, progressive determination of cell fate in the neural crest and hematoptoietic system, and involvement of proteins with the HhL motif in muscle fate determination. Moreover, they point out that many molecules used in essential cellular regulatory functions are highly conserved during evolution (e.g. transcriptional regulators, components of second messenger systems, regulators of cell cycle), and predict that many molecules important for specifying neuronal cell fate in invertebrates will also be found in vertebrates. Indeed, Vaux, Weissman and Kim (70) have demonstrated a homology between the human gene bcl-2 and the ced-9 gene of C. elegans. This is one of the genes involved in PCD referred to above (see Table 2). Lewis (71) has also reported duplication of HOX clusters in the genome of mice and humans four times, in each of four different chromosomes: 2, 7, 12 and 17. Yet another human complementary DNA has been isolated that encodes a widely expressed protein, hSos 1, that is closely related to Sos, the product of the Drosophila son of sevenless gene. This belongs to a group of genes that function in control of cell growth and differentiation (72).

Considering the rapid progress being made by molec-
TABLE 5
Hypothetical Construct of Neurogenetic Defects Producing So-called "Migrational Defects" in Humans

<table>
<thead>
<tr>
<th>Category of malformation</th>
<th>Defect of gene(s) controlling . . .</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agyria-lissencephaly-pachygyria</td>
<td>. . . neuroblast proliferation . . . programmed cell death . . . neuronal type . . . neuronal-glial interaction</td>
<td>. excessive or inadequate number of neurons . excessive or inadequate number of neurons . neurons too large or too small . too many or too few cells of a specific type . malalignment of neurons or failure of normal lamination</td>
</tr>
<tr>
<td>Microgyria</td>
<td>. . . neuroblast proliferation . . . programmed cell death . . . neuronal type . . . neuronal-glial interaction</td>
<td>. inadequate number of neurons . excessive destruction . unbalanced development of specific neuronal groups . failure of normal lamination and malalignment</td>
</tr>
<tr>
<td>Cortical dysgenesis, NOS</td>
<td>. . . neuronal-glial interaction . . . neuronal size . . . neuronal type</td>
<td>. failure of normal lamination and malalignment . abnormally large neurons . too many or too few neurons of a specific type</td>
</tr>
<tr>
<td>Heterotopias</td>
<td>. . . neuronal-glial interaction . . . neuroblast proliferation . . . programmed cell death</td>
<td>. neurons in abnormal locations . excessive number of neurons . too few neurons programmed to die</td>
</tr>
</tbody>
</table>

ular neurogeneticists, it may not be unreasonable to suggest that genes controlling the manifold aspects of human neurogenesis will be delineated in the future. Presumably, these would be homologs of the genes already identified in lower forms, designations and functions of which are described above.

On the basis of this expectation a hypothetical construct involving gene dysfunction in the pathogenesis of the migrational disorders is postulated and outlined in Table 5. Specifically, component features of this group of malformations suggest that there are multiple genetic disturbances involving control of the number of neurons that are produced and/or are programmed to die, the specific type and size of the nerve cell body generated, the interaction between neuroblast-neuron and radial glia, and the integrity of the glia. Activity of growth factors, hormones, etc. are also presumably under genetic control and must be included in any unified concept of the pathogenesis of these cerebral malformations.

Considering the complexity of these gene activities in 'simple' lower forms and the years of research that have been required to arrive at the current state of knowledge, the prospect for identification of the human homologs may appear overwhelmingly difficult. An old Chinese proverb teaches that a journey of a thousand miles must begin with a first step. Studies by molecular geneticists have already progressed beyond the first step, allowing the optimistic expectation that the goal at the end of the 1,000 miles is in sight.

SUMMARY

Morphological features of cerebral cortical dysplasias generally regarded under the umbrella term 'migration disorders' have been reviewed and critically analyzed against current knowledge of gene activity involved in neurogenesis. Although data are plentiful regarding the nature and role of these genes in lower forms, i.e. C. elegans and Drosophila, relatively few human homologs have been identified. Multiple genes are involved in various specific aspects of neurogenesis, i.e. neuroblast proliferation, PCD, migration, etc., and it is postulated that there are parallel gene actions in human neural development. A hypothetical construct of specific gene defects in human neurogenesis accounting for the morphological variations observed in the migration disorders is postulated.

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