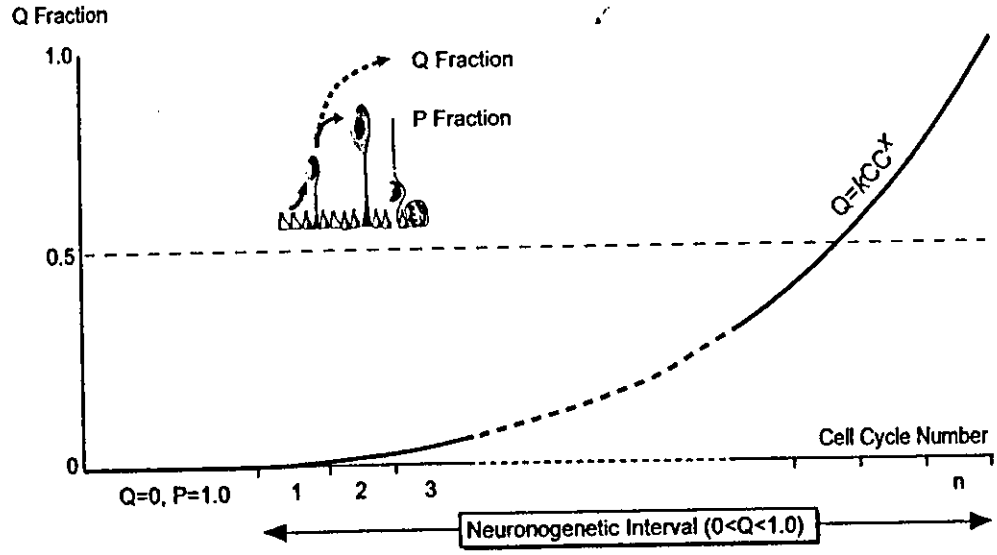

Fig. 1.4. The fraction of postmitotic cells exiting the cycle (Q fraction) increases non-linearly as the fraction continuing to proliferate (P fraction) with the successive cycles 1–n of the neuronogenetic interval (insert and lower panel). The number of cell cycles (1 through n) of the neuronogenetic interval in the neocortical PVE relates to the fractional advance of Q with cycles as $Q = kCC^x$ (plot, see text).

domain with "flexible hinges" has 24 repeats which are sites of proteolytic cleavage. In this regard, FLN1 is subject to extensive phosphorylation which alters its subcellular localization and its strength of binding to actin as well as to membrane receptors. Which of these domains is closest to the histogenetic disruption in periventricular heterotopia is not yet known. In any event, the gene product is essential to the sustained epithelial attachment of only a small portion of the total PVE, but for this population it is indispensable.

Neuronal Production within the Neopallial PVE

The neuronogenetic interval within the neopallial PVE is initiated when postmitotic neurons first exit the cell division cycle (Fig. 1.4) (Takahashi et al. 1995). The progeny of the previously exponential founder population then executes a finite series of cycles. With each cycle the fraction of postmitotic cells that exits the proliferative process (Q) increases, while the fraction that reenters S phase (P) decreases complementarily. Moreover, the duration of the cell cycle (T_C) also increases with each cycle, and – a matter of critical importance to the central thesis here – this increase is due solely to an advance in the duration of the G1 phase (T_{G1}).

The size of the proliferative population increases until $Q = P = 0.5$ (Takahashi et al. 1996). The size decreases with advance of Q beyond 0.5 and is exhausted of all proliferative activity with a final cycle where all postmitotic cells exit the cycle, that is where Q =

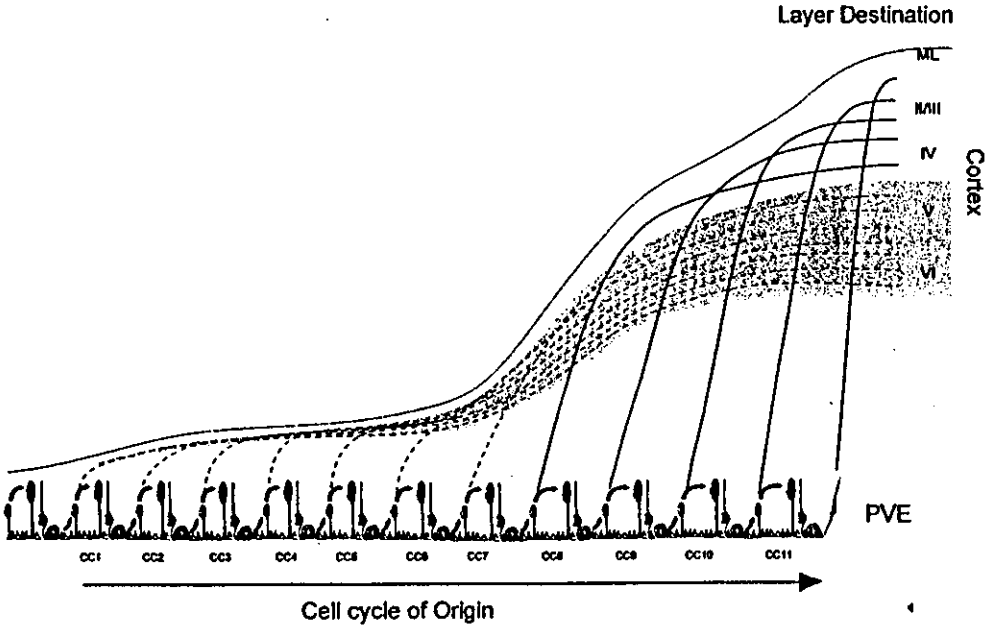

Fig. 1.5. The cells of the PVE execute a series of integer cycles (CC1–CC11 in mouse) in the course of which postmitotic neurons exit the epithelium and migrate across the embryonic cerebral wall to become assembled into neocortical layers more or less in inside-to-outside order with respect to their sequence of origin.

1.0, P = 0. Thus the duration of the neuronogenetic epoch is defined as a series of cycles through which Q advances from 0 to 1.0 and P declines from 1.0 to 0. The number of cycles through which the neuronogenetic process continues can be determined from the equation

$$Q = kCC^x, \text{ also expressed as } CC = (Q/k)^{1/x}$$

where k is a constant representing the fractional advance of Q with cycle and where the final CC is reached when Q is 1.0. We assume that the increasing fractional advance of Q with each cell cycle reflects the resultant of the full set of molecular operations required to process the P/Q decision for each cycle. In the mouse the exponent, x, has been experimentally determined to be 1.97, and the constant k, 0.009, thus giving approximately 11 cell cycles (Takahashi et al. 2000), which agrees with independent estimates of CC number made from measurements of cell cycle length (Takahashi et al. 1995).

The number of neurons arising with each cycle from a defined proliferative population corresponds to the size of that population multiplied by Q for that cycle (Takahashi et al. 1996). Thus, the number of cells arising in the course of the full neuronogenetic interval will be the sum of the production from each cycle in the series of cycles. In mouse, this corresponds to an average total production of about 140 neurons for each founder cell, that is a 140-fold multiplier effect of the proliferative process. If the exponent x in

the above equation is assumed to remain constant across species, we may estimate that 27 cell cycles in the 60 day neuronogenetic interval of monkey and perhaps as many as 34–35 in the 120 day neuronogenetic interval of man (Caviness et al. 1995, Takahashi et al. 2000) give the proliferative expansion associated with the larger neocortex of these species.

In all mammalian species, there is a systematic relationship between sequence of neuron origin and the particular subclass of neuron which is formed (Fig. 1.5) – that is, mechanisms of specification of neuronal subclass are coordinate with those proliferative mechanisms that regulate the sequence in which each subclass is formed (Caviness et al. 2000b). Specifically, the earliest neurons arising from the epithelium and destined for layers II–VI are those that will form layer VI, the latest are those that will form layer II, and those destined for the intervening layers arise approximately in order (Caviness and Sidman 1973, Fernandez and Bravo 1974, Rakic 1974, McSherry 1984, Bayer and Altman 1991). The mechanisms that govern these proliferative and specification operations of the PVE are universal to all regions of the epithelium, but do not occur simultaneously in all cortical regions. The sequence is initiated far rostrolaterally, advances caudomedially and at all times is staggered in its state of progression according to the rostrolateral to caudomedial (or principal) axis of the PVE (Fig. 1.6) (Caviness and Sidman 1973, Fernandez and Bravo 1974, Rakic 1974, McSherry 1984, Bayer and Altman 1991).

This property of the proliferative activity of the PVE is known as the *transverse neuronogenetic gradient* (TNG) (Fig. 1.6) (Bayer and Altman 1991). Moreover, the TNG actually corresponds at all times during the neuronogenetic interval to a shifting mosaic of cell cycle domains distributed from relatively higher to lower in the 11 cycle series along the principal axis of the epithelium (Takahashi et al. 2000) (Fig. 1.6). As a consequence of its complex mode of operation, considered in more detail elsewhere (Takahashi et al. 2000) the slope of the TNG at any moment in the neuronogenetic interval will be determined by the pattern of advance of T_C with cycle. In theory, this frequency shift gradient offers a mechanism for encoding positional information within the epithelium (Miyama et al. 1997). We have elsewhere illustrated how this gradient might contribute at fine grain, with other coarser grained mechanisms of positional encoding active in the PVE prior to the onset of neuronogenesis (Puelles and Rubenstein 1993, Shimamura et al. 1995), to encoding a protomap (Rakic 1988) of the neocortical architectonic representations within the PVE (Takahashi et al. 2000).

The essence of the observations just reviewed is that Q and T_{G1} are the only two regulated parameters of the proliferative process and that they advance in mouse in the course of 11 cycles, observing in their advance a rostrolateral to caudomedial gradient within the PVE (Caviness et al. 2000b, Takahashi et al. 2000). We have elsewhere proposed the G1 phase restriction point to be a plausible master regulatory mechanism for coordinate control of the constant k in the equation, $Q = kCC^x$, and thus the mechanism that determines the number of cycles and the multiplier power of the overall proliferative process (Fig. 1.7) (Caviness et al. 1999, Takahashi et al. 2000). The restriction point, a complex

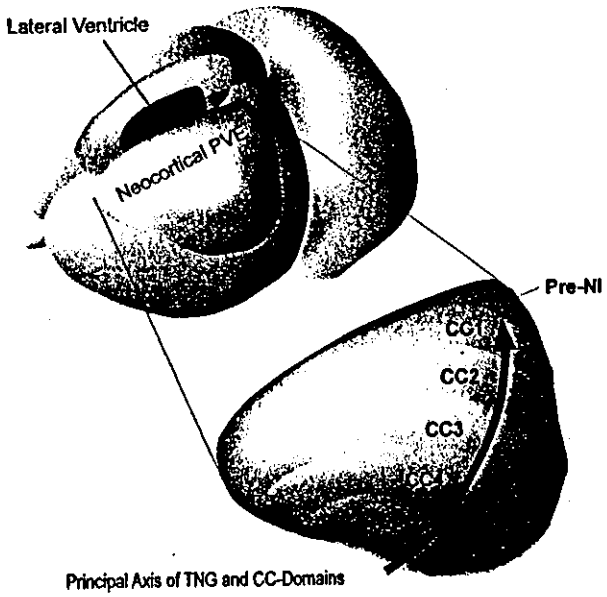

Fig. 1.6. The neocortical PVE of the embryonic mouse brain of the left hemisphere and cerebral ventricular cavity of the right hemisphere are revealed after the overlying cerebral wall is cut away (upper panel). The neuronogenetic interval is initiated far rostrolaterally with the first postmitotic cells entering cell cycle 1 (CC1) of the total 11 cycle series. Over the course of the initial 24 hours of the neuronogenetic interval in mouse, the leading edge (indicated boundaries) of domains of cells executing cycle CC1–5 propagates caudomedially, following the principal axis of the transverse neuronogenetic gradient. There is progressive contraction and eventual disappearance of the domain of cells that continue in the pre-neuronogenetic interval (Pre-NI) exponential proliferative state.

set of molecular actions governed internally by opposing facilitatory and inhibitory molecular mechanisms and responsive to a variety of cell external facilitatory and inhibitory agents, determines Q in proliferative vertebrate cells and also may govern variation in T_{G1} (Koff et al. 1993; Sherr 1993, 1994; Roberts et al. 1994; Massague and Polyak 1995). Moreover, the transcriptional profile of the P fraction is set by mechanisms inherent to the operation of the restriction point (Touchette 1992, Weinberg 1995, Brown and Schreiber 1996, Gerhart and Kirschner 1997). Thus, the mechanisms associated with Q and T_{G1} regulation are sufficient to coordinate the generation of the appropriate number of cells according to the cell class and also to serve to provide the mapping requirements of neocortical specification (Takahashi et al. 2000, Caviness et al. 2000b).

To date only the p27 "knockout" mouse can be taken to be a test of this hypothesis, and, at this time, it is a test of only a few of its provisions (Fero et al. 1996, Kiyokawa et al. 1996, Nakayama et al. 1996). The protein p27 is a principal intrinsic inhibitor at the restriction point; that is, augmentation of its action would be expected to augment Q, whereas an easing of its action would be expected to decrease Q. The knockout animals

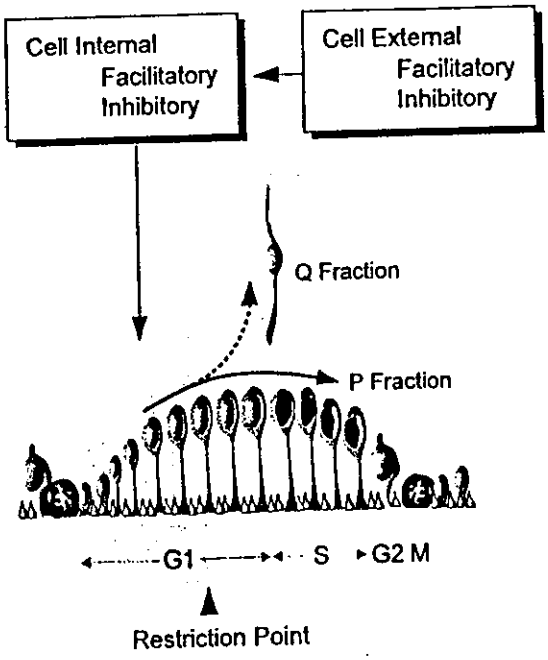

Fig. 1.7. The shape of cells of the PVE correlates with phase of the cell cycle. Cells undergo mitosis (M) at the ventricular margin, elongate through G1 phase (framed), then contract again through S and G2 phases. Facilitatory and inhibitory cell internal mechanisms, modulated by facilitatory and inhibitory cell external influences, act at the G1 restriction point (RP; closed arrowhead) to determine the proportions of postmitotic cells that will exit the cycle (Q fraction) or continue to proliferate (P fraction).

are larger by some 40% than normal animals, and, to a rough approximation, the enlargement is uniformly scaled across most body organs and across all brain regions. Thus, this animal illustrates a role of the restriction point in a general computation that determines cell number in the course of histogenesis of brain and most body organs. Since the animal is not infinitely large, it is clear that other proteins must also act as inhibitory checks at the restriction point in the animal null for p27. The loss of this protein produces a moderate increase in cell number in the neocortex (Goto et al. 1999). Its effect upon the operation of the TNG has not been established.

In humans, however, certain of the heritable extreme "primary" microcephalic disorders may reflect the consequences of molecular disruptions which modify both the operation of the cell cycle and that of the TNG (Caviness et al. 2000a). We suggest this because the outer cortical layers in these malformations tend to be preferentially blighted (Ross and Frias 1977) and it is greatly doubtful that the architectonic map is complete. Thus, in such disorders there might be accelerated advance of Q with cycle, acting to reduce the number of cell cycles, and also disruption of positional encoding specificity of the TNG.

MIGRATION AND STRATIFICATION OF THE CEREBRAL WALL

Neurons arising in the PVE must find their way to developing neocortex at the surface of cerebral wall (Sidman and Rakic 1973). The width and the structural complexity increase greatly as neuron production proceeds (Stensaas 1967a,b, 1968; Morest 1970). It is to be inferred from the dual origin of neurons, i.e. the neopallial PVE and basal fore-

brain regions, that there must be multiple routes of migration and, perhaps, as many mechanisms of guidance as routes (Fig. 1.2).

NEOPALLIAL PVE TO CORTEX

The most completely understood routes and mechanisms of migration are those of the long axon neurons from neopallial PVE to cortex (Fig. 1.2) (Rakic 1972, 1995). Neurons arising from the neopallial PVE migrate toward and into the cortex continuously (Takahashi et al. 1995), guided principally by the ascending fiber of the radial glial cell, a cell of astrocytic lineage which spans the full width of the cerebral wall (Rakic 1972, 1995; Misson et al. 1991). The somata of these specialized glial elements form a minor contingent of the proliferative population of the PVE (Levitt et al. 1981, Misson et al. 1991). Their rate of proliferation and fiber elaboration is such as to maintain a fasciculated fiber scaffolding of constant density throughout the migratory epoch of neocortical histogenesis (Gadisseux et al. 1987, 1989, 1990).

Migration of neurons generated in the PVE through the subcortical segment of this glial scaffold is disrupted in the heritable lissencephaly type I malformations in man (Fig. 1.8A) (Dobyns 1987, Dobyns and Truwit 1995). The structural evidence for this is the presence of heterotopia which is limited to the sagittal stratum and corona radiata (Caviness et al. 1989). Heterotopia extends to but not into the cortex itself, which is represented by a narrow but well formed laminar ordering of neurons that has the architectonic and cytologic features of layers VI/V (Stewart et al. 1975). The neuronal population of the heterotopia includes a range of types native to the neocortex and in particular neuronal types native to the outer cortical layers. Pyramidal forms are generally radially aligned (Caviness et al. 1989). The position of the heterotopic neurons indicates that the migrating neurons can make an initial attachment to the radial glial fibers and move for some distance before their progress is disrupted. Transmission occurs as a consequence of genetic disruptions on two different linkage groups (*LIS1*: chromosome 17p13; *DCX*: Xq22.3–23) where microdeletion and point mutation have both been implicated as mechanisms of genetic disruption (Reiner et al. 1993, 1995; Lo Nigro et al. 1997; des Portes et al. 1998; Gleeson et al. 1998; Pilz et al. 1998; Walsh 1999). The classic lissencephaly I phenotype is observed only in the male hemizygotic for the *DCX* mutation. The heterozygotic state of *DCX* mutation is also expressed in the female but the anomaly is very much milder, limited to a tangentially coursing band of heterotopia located at the level of the sagittal stratum and extending into the depths of the corona radiata (Barkovich et al. 1989, 1994; Livingston and Aicardi 1990; Vahldiek et al. 1990; Palmini et al. 1991; Soucek et al. 1992). Its width is variable from individual to individual, reflecting, it is thought, the variability of X inactivation (Walsh 1999).

Disruption of migration in both the *LIS1* and *DCX* malformations appears to reflect a disorder of assembly and management of microtubules. The protein products of both the *LIS1* and *DCX* genetic loci co-localize and co-assemble with microtubules and appear to be operationally microtubular associated proteins or "MAPs" (Sapir et al. 1997,

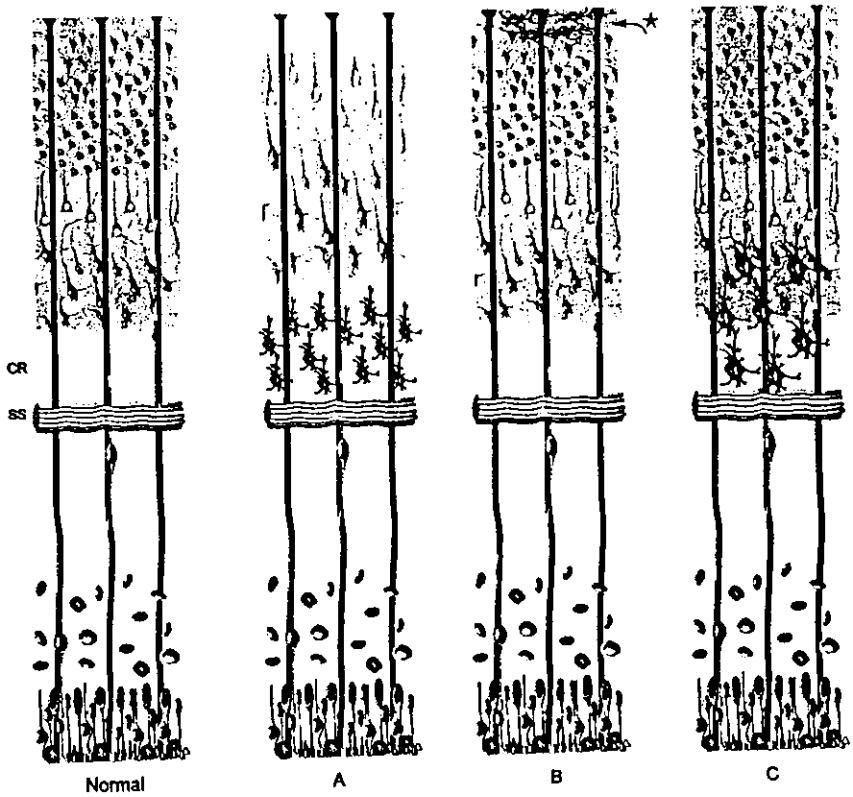

Fig. 1.8. In the course of normal neocortical histogenesis, neurons arising in the neopallial PVE traverse the intermediate zone of the cerebral wall, sagittal stratum and corona radiata in their ascent to the neocortex along radial glial guides (panel at left). Migration is arrested within the corona radiata in the Lis1 and related malformations (A), but at the transition between corona radiata and cortex in the Zellweger malformation and the focal dysplasias of tuberous sclerosis (C). Small clusters of heterotopias within the molecular layer may represent the consequences of disordered tangential migration of cells of the subpial granular layer (asterisk and arrow in B, see text).

Gleeson et al. 1998) As such they may be expected to contribute to migration via a role in microtubule organization and stability and more specifically to elaboration of leading process and translocation of the nucleus (Rakic et al. 1996). *LIS1* may also serve as regulatory subunit to the enzyme platelet activating factor (PAF) acetylhydrolase, which hydrolyzes PAF, potentially implicating it in mechanisms of nuclear translocation (Ricci et al. 1992, Hashimoto et al. 1993, Hattori et al. 1994).

Basal Forebrain to Cortex

The GABAergic neurons arising within the ganglionic eminence of the basal forebrain stream tangentially through the intermediate zone of the cerebral wall before ascending radially to the cortex itself (Fig. 1.2) (Anderson et al. 1997, Meyer et al. 1998, Lavdas et al. 1999). Other neuronal forms, arising even more remotely in juxtaolfactory PVE,

stream tangentially though the molecular layer (Brun 1965, Gadisseux et al. 1992, Meyer et al. 1998). This population, the "subpial granular layer", includes GABAergic neurons and, transiently, the Cajal–Retzius cells. The mechanisms of guidance, though not yet explicitly demonstrated, may depend upon the course of tangentially aligned fasciculated axons of the molecular layer (Anderson et al. 1997).

Small clusters of heterotopic neurons are regularly encountered in the molecular layer of the human brain and when abundant have been associated with impaired language facility or other cognitive deficits (Fig. 1.8B). In some instances they are associated with disruption of the glial limiting membrane, and may extend into the overlying leptomeningeal compartment (Caviness et al. 1978). Deformities with these same histological features may be induced by puncture or thermal injury to the cerebral surface (Rosen et al. 1992), and some of these may arise consequent to focal surface injury occurring late in the course of neuronal migration. In other instances there is no evidence of disruption of the glial membrane so as to suggest local tissue injury. Although not known to be transmissible by heritable mechanisms in man, such layer I heterotopias without evidence of injury are transmissible in mice by an autosomal recessive mechanism in the dreher mutant mouse (Nowakowski 1988, Sekiguchi et al. 1994) and by some more complitated mechanism in the NZB inbred mouse line (Sherman et al. 1990, 1992). They may be induced in normal mice by exposure to high levels of the neurotropin NT3 (Brunstrom et al. 1997, Ringstedt et al. 1998). This set of observations invites the hypothesis that heritable mechanisms, as yet undisclosed, but possibly related to the disregulation of neurotropins or the neurotropin TrkB receptor, may set the stage for layer I heterotopias in man.

Stratification

At the outset of neocortical histogenesis, the PVE and a narrow plexiform margin generated by the ascending processes of its cells comprise the full width of the cerebral wall (Sidman and Rakic 1982, Takahashi et al. 1995). The somata of the earliest cells to become postmitotic may translocate radially outward along the ascending process into the superficial "primordial" plexiform zone (Morest 1970, Nowakowski and Rakic 1981, Nadarajah et al. 1999). The subsequently generated long axon neurons ascend across the widening plexiform interval, following ascending radial fibers. Their laminar destination is more or less "inside to outside", that is, the neurons whose somata will form layer VI are the first and those of layer II are the last to be formed (Angevine and Sidman 1961, Hicks and D'Amato 1968, Rakic 1974). The laminar distribution of neurons arising with each successive cell cycle of the 11 cycle series in mouse is the same throughout the cortex (Fig. 1.5).

Postmigratory Cortical Morphogenesis

Among the earliest postmigratory events occurring within the cortex is the assignment of neuronal somata to their respective layers. Whereas neurons arise in the PVE and migrate

approximately in an "inside-to-outside" order with respect to their laminar destinations in the cortex, this correspondence is only approximate. Cells of multiple class and destined for multiple adjacent layers are formed and migrate into the cortex concurrently, and each layer receives cells born over multiple sequential cycles (Takahashi et al. 2000). Thus, mechanisms must operate following migration that enforce laminar class assignment.

A wide variety of dysgenetic states, variously designated microdysgenesis and characterized by mild degrees of malregistration of layers, appear to reflect low level derailment of these processes (Hardiman et al. 1988, Brodtkorb et al. 1992, Farrell et al. 1992, Mouritzen-Dam 1992, Caviness et al. 1995b, Mischel et al. 1995). Less common but well defined is a set of malformations where large scale heterotopia spreads through the lower reaches of the cortex into subjacent corona radiata. Among these are the malformations associated with the Zellweger syndrome and the focal cortical dysplasias of tuberous sclerosis (TS) (Fig. 1.8C). In the Zellweger disorder heterotopic neurons spread extensively through the centrosylvian region of the lateral hemispheric convexity and are more or less symmetrically distributed in the two hemispheres (Volpe and Adams 1972, Evrard et al. 1978). Heterotopia increases from laterally to medially across the cerebral wall, and there is an associated graded microgyric to pachygyric conformation of the overlying cerebral surface. The cellular forms distributed throughout the heterotopic field are similar to those seen in lissencephaly and are presumably neurons normally destined for cortex (Evrard et al. 1978). In addition, extending through the upper corona radiata there are distinctive columns of densely packed small cellular forms which have not yet been established to be neurons.

In TS there is a focal dysplasia that typically but not invariably occurs singly and is generally limited to a portion of a single gyrus generally deforming the gyrus such that it may be recognized with magnetic resonance imaging (Andermann et al. 1987, Barkovich and Kjos 1992, Raymond et al. 1995). It is distinctive for its associated anomaly of neuronal form. Cells of gigantic size bear neurofilaments and form synapses. Many of these are neuronal forms that distribute diffusely through cortical and subcortical fields, respecting no laminar assignments. There are for the present no certain indications of the cellular and molecular biological mechanisms that lead to migratory arrest associated with the pattern of heterotopia. Mutation in the Zellweger disorder leads to a failure of assembly of peroxisomes and is associated with failure of degradation of very long chain fatty acids and depletion of essential lipids normally synthesized in these organelles. In mice null for the *Pxr1* gene there is a comparable deficiency of peroxisomal assembly, and this disorder is also associated with failure of neuronal migration (Baes et al. 1997). The TS phenotype appears with two genetic loci. The *TSC2* (chromosome 11) gene encodes for the protein tuberin which is a GAP (GTPase activating protein) for Rab5 and potentially, by inference from its structure, a transcriptional co-regulator. It has extensive homology with the gene *gigas* in fly where cells in which this gene has been disabled replicate DNA through multiple cycles without intermediary mitosis. Giant multiploid cells reflecting this sequence disrupt retinal development (Ito and Rubin 1999). There may

also be homology with the flathead mutation in rats where large neocortical cell forms are associated with disordered cytokinesis, cell patterning abnormalities and exaggerated cell death (Roberts et al. 2000, Sarkisian et al. 2001). Given the gigantic and probably multiploid appearance of cells of the dysplasias in TS, it is plausible that they reflect the consequences of a corresponding molecular biological anomaly. TSC1 (chromosome 9) encodes a protein designated hamartin for which function has not been elucidated.

The mechanisms of migration arrest in the Zellweger malformation and respecting the focal dysplasias in TS remain to be elucidated, but the distance through which the cells have moved argues that migration begins normally. The anatomic evidence suggests that the arrest occurs toward the end of the migratory trajectory where migrating neurons must bypass postmigratory neurons upon entering the cortical zone. In this limited sense this pattern of distribution of heterotopia has affinity with the malformation associated with the reeler mutation in mice (Caviness and Sidman 1973, Pinto-Lord and Caviness 1979, Pinto-Lord et al. 1982, Caviness et al. 1988) and its phenocopies, scrambler and yottari (Gonzalez et al. 1997, Sheldon et al. 1997, Ware et al. 1997, Yoneshima et al. 1997). In these murine disorders movement of migrating cells is obstructed by an apparent failure of previously generated cells to detach from the radial glial fiber (Pinto-Lord et al. 1982). A pachygyric, microcephalic cerebral malformation associated with small cerebellum, thus far observed anatomically only from the perspective of MRI, has also now been found to be associated with null mutation of the homologous human gene (Hong et al. 2000). The gene at the reeler locus encodes a large secreted extracellular matrix glycoprotein. This protein probably influences cell migration by binding to a cell surface receptor which is an upstream station in the mdab signaling pathway that is apparently inactivated by mutation in scrambler and yottari as well as by engineered null states of the surface receptor for this pathway (D'Arcangelo et al. 1997, Sheldon et al. 1997, Ware et al. 1997, Rice et al. 1998, Trommsdorff et al. 1999). It remains to be determined if similar obstructions of migration and receptor interactions are involved in producing the heterotopia in TS and the Zellweger malformation.

Systems Optimization and Regressive Events

The progressive events of cell proliferation, migration and growth are offset by substantial regressive events that include the elimination of neurons by apoptotic cell death and of "exuberant" axonal and dendritic processes by "pruning". By extrapolation from the course of events in mouse and other mammalian species (Caviness et al. 1997, Takahashi et al. 2000), cell elimination by apoptosis should go forward rapidly during the late second and early third trimester in the human brain. Thus, in mouse, it is initiated in the immediate postnatal period, reaches peak intensity within several days and is essentially complete at 2 weeks (Takahashi et al. 2000). Pruning of process exuberance runs a much more prolonged cycle that is more or less concurrent with that of synaptogenesis (Lamantia and Rakic 1990, Bourgeois and Rakic 1993, Bourgeois et al. 1994, Innocenti 1995). By extrapolation from investigations in monkey these processes in the human

brain probably continue strongly through the third trimester, beyond birth and into the first 2–3 postnatal years (Caviness et al. 1997).

The intracortical regressive morphogenetic events proceed more or less concurrently across the entire face of the cortex, although the magnitudes are idiosyncratic not only with respect to architectonic field but even to layer within field. This pattern bears no relationship to the earlier enacted spatiotemporal operation of the TNG of the PVE (Bourgeois and Rakic 1993, Bourgeois et al. 1994, Gilmore et al. 2000, Takahashi et al. 2000). The tempo of volumetric advance picks up through the third trimester and the period around birth is one of unequaled rate of volumetric increase. Asymptote is approached by 3 years of age but volume is probably not maximum until mid- to late adolescence (Caviness et al. 1997). Substantial evidence indicates that the regressive events serve a larger agenda of systems matching directed toward circuitry optimization.

GYRIFICATION

A resultant but greatly conspicuous consequence of these collective morphogenetic processes is the gyrification of the cerebral exterior. Though in detail the patterns of folding are probably as unique to the individual as the fingerprint (Ono et al. 1990), this variability still observes a canonical general pattern that is systematically related to the underlying cytoarchitectonic fields (Rademacher et al. 1993). A plausible model for the mechanical forces necessary to induce folding has been borrowed from geological plate tectonics (Richman et al. 1975) and depends upon the facts that: (1) the six cortical layers are fixed in their radial registration by cytological apical dendritic structure and cannot slip tangentially relative to each other once assembled; (2) the infragranular layers V and VI have largely completed their cycle of volumetric increase at the end of the migratory phase; and (3) a massive cycle of growth is initiated in overlying layers II–IV, that is, the layers that will derive from cortical plate only after migration comes to an end. The systematic topographic patterning of gyrification must have some explanation different from the differential force model which is taken to account for the fact of surface folding. As a plausible model for the topographic specificity of the gyral pattern respecting cytoarchitectonic divisions, it has been proposed that folding occurs in such a way as to approximate densely interconnected regions as opposite faces of the same convolution (Van Essen 1997). Opposing faces of adjacent convolutions are less densely interconnected. Whereas this model is probably sufficient to account for patterns of distribution of the secondary gyri (as superior frontal) and tertiary gyri (as variable tributaries of superior frontal) that become established over the course of the last half of intrauterine development, it is probably not sufficient to account for the position of the primary convolutional (as sylvian, central) pattern emerging even before the end of the ffth gestational month (Chi et al. 1977). Dramatic changes observed in posterior hemispheric gyral pattern following prefrontal ablations in the fetal monkey illustrate the potentially powerful yet long range actions of these determinants of gyral pattern in the developing brain (Goldman-Rakic and Rakic 1984).

PROSPECTUS

In the "remote present" of the molecular biology of development it has been estimated that some 90% of the human genome is expressed in the brain, as much as 50% of the genome expressed only in the brain, and most genes are expressed by the time of birth (Caviness 1987). Whatever the actual numbers eventually to be attached to the genetic requirement for morphogenesis of the human brain, its processes must stand as the hungriest "information sink" in biology. We have presented here a generally coherent view of the cellular events through which neocortical morphogenesis unfolds. This framework is linked by observation and theory from beginning to end and has proved flexible, accommodating revisions and new entries as they arise. The relationship of the cellular processes that form this framework to the underlying molecular biological mechanisms and their genetic regulation is less secure. Clearly, the principles of information transform through which genome presides over the developmental origins of morphological phenotype are only weakly codified. Powerful, rapidly evolving methodologies in molecular genetics and other domains of biology, addressed to mutation induced disorders of the developing brain or in exploration of engineered genetic perturbations of brain development in mice, virtually daily provide new offerings. For the present, however, there are few generally defensible molecular biological mechanisms that have surfaced from these offerings and, as far as we are aware, no general theories of their genetic regulation (Gerhart and Kirschner 1997). We imagine with this perspective that future research will discover rules and algorithms of operation that will be crucial for clinical method and purpose.

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熱性けいれん
Febrile Seizures

飯沼一宇　東北大学大学院教授・小児医学/小児病態学分野

病態と診断

熱性けいれんは，「発熱に伴って起こるけいれんで，中枢神経系の感染によらないもの」と定義される．また，急性脳症や，代謝異常などの明らかな原因疾患のある場合は熱性けいれんとは考えない．大多数で38℃以上の発熱があり，初発は1歳に最も多く，最終発作は，3歳で，4歳以降ではほとんど見られなくなる．

NIHの合意会議では，①無熱性けいれんの家族歴，②発症前から存在する神経学的異常，③長時間（15分以上）のけいれんや局所あるいは片側のけいれんなどの非典型的けいれんのうち，2つ以上の危険因子を有しているとてんかんへの移行率が上昇すると結論された．

治療方針

A. けいれん時の対応

これには親への対応の仕方の指導と，医師が直面したときの対応がある．親への指導としては，慌てないこと．顔を横に向けて，衣服，特に首の回りをゆるめる．特に左右差，眼球の偏位などをよく観察する．口には指やものを入れない．時間をはかるなどを指導しておく．10分以上続く場合には救急車に搬送を依頼する．

医師の対応は，救急の対応などになるが，多くは短時間で止まるので，生命の危険がないかと，発作像をよく観察することと，危険が予測されることに対応することである．来院時には既にけいれんが消失していることが多いが，この場合はバイタルサインを確認して，異常がなければ何もする必要がない．

B. 日常の管理・発熱時の対応

発熱の原因はほとんどが感染である．熱性けいれんの既往のある場合には，なるべくこまめに体温を測定し，急激な体温上昇の初期を見極めることが大切である．しかし決して容易なことではない．早めに体を冷却することも重要である．頭部を冷やすこともよいが，血液循環を考えて，腋窩，鼠径部など動脈を触れる個所を氷で冷やすのも効果的である．

C. 抗けいれん薬の発熱時投与

過去の熱性けいれんで，持続が長い場合，および熱を出すと決まってけいれんに至る場合には，今後のけいれんを予防したほうがよいと考えられる．ダイアップ坐薬を使用するが，0.3－0.5 mg/kgを37.5℃位のときに挿入する．使用8時間以後でも発熱が持続していれば，もう1回使用する．8時間後に解熱していれば再度使用する必要はない．2度目の使用で24時間後まで有効と考えられる．軽度の眠気やふらつきが認められることがあることを家族にあらかじめ知らせておく．

4歳をすぎると発熱時けいれんの確率は極端に低くなるので，最終発作をすぎているかもしれないことを説明し，積極的に使わなくてもよいことを話す．

R 処方例　（2歳　体重12 kgの場合）

ダイアップ坐薬（4 mg）　1個

発熱の初期に1回使用，8時間以後にも発熱があれば，もう1回使用

小児のてんかん
Epilepsy in Childhood

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病態と診断

小児期には多彩なてんかんおよびてんかん症候群が発症し，その発作型も多様である．治療方針の決定には正確な診断が重要である．てんかん発作に似た発作症状は非てんかん性疾患でもみられ，治療にもかかわらず発作が遷延反復するときは発作間欠期脳波だけではなく，発作時のビデオ脳波記録の検討が必要である．類似の発作型を示しても，てんかん症候群の診断が異なり，予後が異なることがあるので，発症年齢や臨床所見，家族歴，画像，脳波所見などより包括的に，「てんかんおよびてんかん症候群の国際分類」と「てんかん発作の国際分類」の診断をし，治療方針を立てる．小児では発作間欠期脳波でも特徴的異波を呈することが多く，それと臨床所見を関連させれば，比較的正確に診断が可能である．

治療方針

てんかん治療の主体は薬物療法であるが，治療は長期間になることが多く，子供の健全な発達と，家族や学校，社会生活への適切な対応が重要である．良性てんかんと診断し，発作回数が少なく，1年に1－2回以下で，睡眠時のみのときは治療開始を先に延ばす．一方，各種薬剤にも反応せず，外科治療の適応とならない難治性てんかんでは，薬物の多剤過量投与を避け，発作と人生の質の間での妥協点を求めねばならないこともある．

A. 薬物療法

各発作型に対し，単剤治療が原則である．少量より漸増し，副作用の有無，血中濃度を参考にしながら，投与量を調節する．第1薬から第2薬への変更時には，第2薬の血中濃度が上昇してから第1薬を漸減すべきで，急速な減量，中止はしない．有効治療濃度範囲はあくまでも目安であり，副作用の出現の有無，増量にて発作が増悪することもあり得ることを認識したうえで，投与量を調節し，その薬剤の効果を判定すべきである．血中濃度は半減期の5倍で定常状態となり，その後，投与時直前