Bayer, SA and J Altman (1991) NEOCORTICAL DEVELOPMENT Raven Press.

CHAPTER 17

Summary and Conclusions*

17.1 SUCCESSIVE TRANSFORMATIONS OF THE CORTICAL GERMINAL MATRIX

The analyses of [^{3}H]thymidine autoradiograms (Chapter 4) indicate that successive transformations of the cortical germinal matrix can be linked to three epochs of neurogenesis. The experimental data derived from exposing the developing cortex to low-level x-irradiation (Chapter 10) show that time-dependent changes in radiosensitivity of the neuroepithelium can also be linked to the [^{3}H]thymidine autoradiographic labeling patterns and epochs of neurogenesis. When taken as a whole, these data establish that, in spite of their homogeneous appearance in Nissl preparations, the cells in the neuroepithelium are heterogeneous. Figure 17–1, an expanded version of the diagram that appears in Fig. 4–14, summarizes the characteristics of the cortical germinal matrix at early, middle, and late stages of cortical development. Figure 17–2 shows the bands of heavily labeled cells (*black bars*) that appear in the neuroepithelium 24 hours after an injection of [^{3}H]thymidine on E14 through E21.

During the early stage (E13–E15, left column, Fig. 17–1), the neuroepithelium is the sole component of the cortical germinal matrix. Most of the mitotic cells divide in a periventricular position at the lumen of the ventricle, but by E15 some also are seen in a paraventricular position. The labeling pattern 2 hours after injection with [^{3}H]thymidine shows that the cell nuclei in the synthetic phase of the cell cycle cluster like bunches of grapes strung on a line in the external two-thirds of the neuroepithelium (the synthetic zone) while unlabeled nuclei and many unlabeled mitotic cells cluster in its internal one-third (the mitotic zone). The segregation between the synthetic and mitotic zones is interpreted to indicate that most cells are undergoing interkinetic nuclear migration during the cell cycle. One day after injection of [^{3}H]thymidine (Fig. 17–2A,B), heavily labeled cells form a band in the external part of the neuroepithelium (upper heavy), and lightly labeled cells form a band near the ventricle (lower light). There are noticeable clumps of heavily labeled cells in the external half of the neuroepithelium that we interpret to be postmitotic neurons that are sequestered there before leaving (sSP, Figs. 17–2A,B). Exposure to low-level x-ray (200 R) produces approximately 50% cell loss on E13 and total devastation on E14 and E15. Because the periventricular cells are all killed, the ventricular wall is destroyed, and pyknotic debris from the brain parenchyma is shed into the lumen. The products of the neuroepithelium at this early stage are the neurons destined to reside in layer I and the subplate (layer VII). The neuroepithelium is also a source of a variety of other products at this stage: namely, proliferating cells that will later set up a secondary germinal matrix in the subventricular zone, many late-generated neuronal precursors, and some glial precursors.

In the middle stage (E16–E17, center column, Fig. 17–1), the cortical germinal matrix is divisible into a large neuroepithelium and a small subventricular zone

* References in this chapter have been omitted since they appear elsewhere in the text.

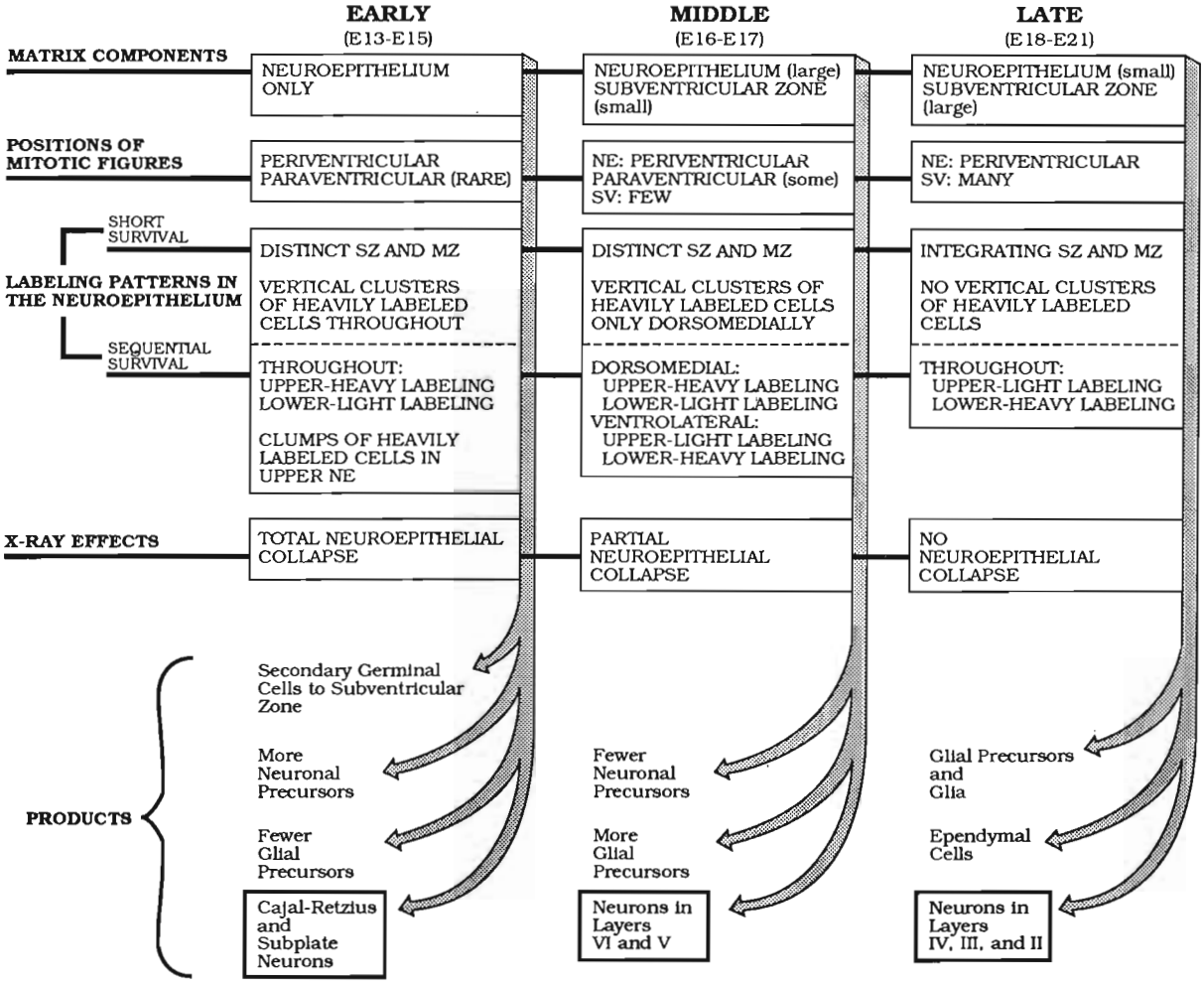

FIG. 17–1. The successive transformations of the cortical germinal matrix during development are presented in a diagrammatic table summarizing the observations presented in Chapters 4 and 10. These findings establish that heterogeneity exists in the neuroepithelium, and successive transformations from early (*left column*) to middle (*center column*) to late (*right column*) stages can be related to the major epochs of cortical neurogenesis.

above it. In the neuroepithelium, most mitotic cells are in a periventricular position, but some are also seen in a paraventricular position. The subventricular zone has only a sparse scattering of mitotic cells. The labeling patterns in the neuroepithelium 2 hours after injection with [^{3}H]thymidine show that nuclei in the synthetic phase of the cell cycle are still situated externally, while unlabeled nuclei and mitotic cells are situated internally. This indicates that most neuroepithelial cells are still undergoing interkinetic nuclear migration. However, the grape-like cell clusters in the synthetic zone are seen only dorsomedially. One day after injection with [^{3}H]thymidine (Fig. 17–2C), the stratified labeling pattern in the neuroepithelium undergoes a reversal from the early (up,h and lo,l) to the late (up,l and lo,h) pattern, starting ventrolaterally and spreading dorsomedially. Since bands of heavily labeled cells (presumptive postmitotic neurons) appear outside of the neuroepithelium just where the pattern has become reversed, the reversal indicates that postmitotic neurons are no longer sequestered in the external part of the neuroepithelium. Exposure to low-level x-ray is still effective in killing cells, but clumps of surviving cells are also seen in the neuroepithelium. Because some periventricular cells are still killed, the pyknotic debris falls into the ventricular lumen in between the surviving cell patches. The products of the germinal matrix at this stage are mainly neurons that will reside in layers VI and V throughout the entire cortex. Some neuronal precursors are still added to the population in the germinal matrix, but fewer than before because declining numbers of neurons will be produced in the subsequent, late stage. In contrast, glial precursors are probably on the rise because glia will be produced in massive numbers as neurogenesis declines.

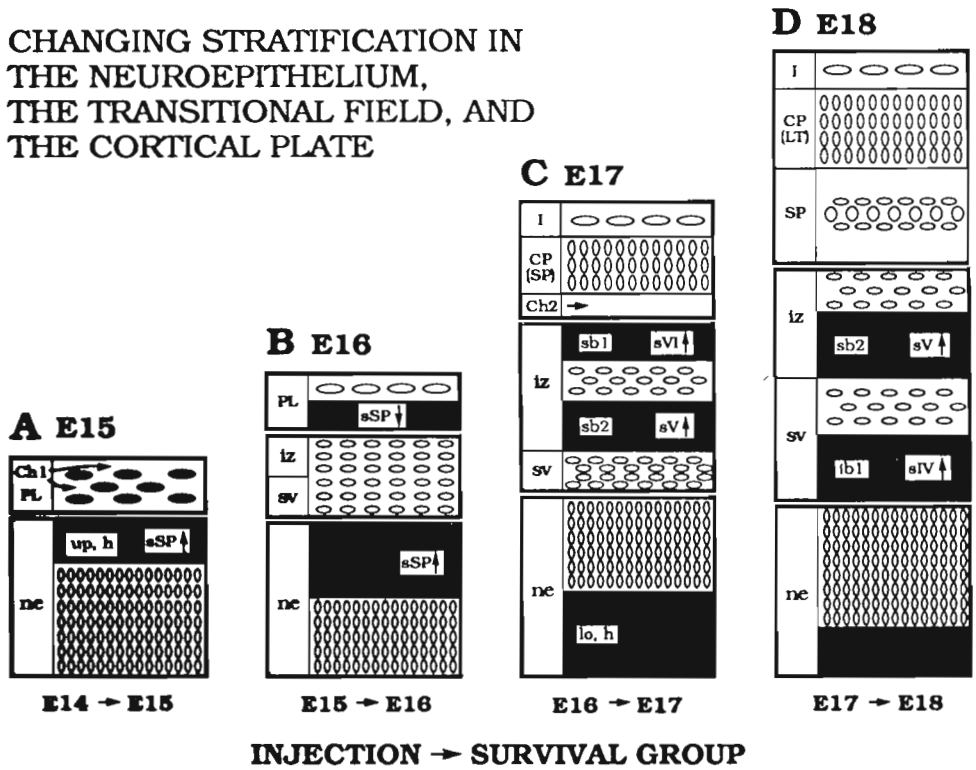

FIG. 17–2. Summary diagram of the location (ne, sv, and iz), the assigned name (sb1, sb2, etc.), and the presumed fate (sVI, sV, etc.) of the different sojourning bands of heavily labeled cells (*opaque bands or ellipses*) in embryos that received [^{3}H]thymidine 24 hours prior to sacrifice on the following days: E15 **(A)**, E16 **(B)**, E17 **(C)**, E18 **(D)**, E19 **(E)**, E20 **(F)**, E21 **(G)**, and E22 **(H)**. Separate rectangles represent three components (when present) of the developing cortex: the neuroepithelium (ne, *lower rectangle*); the transitional cortical field comprised of the subventricular zone and the intermediate zone (sv and iz; *middle rectangle*); and the developing cortical gray matter consisting of the primordial plexiform layer and the cortical plate (I, PL, SP, and CP; *upper rectangle*). The fine lines in the upper intermediate zone (izu) represent coronally oriented fibers and the fine dots in the subplate (SP) sagittally oriented fibers. Horizontal arrows suggest the horizontal dispersion of glial cells (gl) through the formative white matter. The downward pointing arrow in the subplate indicates the putative descent of subplate neurons from the primordial cortical plate to the subplate (as described in Chapter 5); the upward pointing arrows suggest the ascent of young neurons from the sojourning zones to the cortical plate. The letter *s* refers to the putative sequestered neurons in the neuroepithelium or sojourning neurons in the transitional field; mn designates the presumed migrating neurons through the upper intermediate zone (izu) after leaving the sojourn zones.

In the late stage (E18–E21, right column, Fig. 17–1), the cortical germinal matrix is divisable into a shrinking neuroepithelium and an expanding subventricular zone. In the neuroepithelium, most mitotic figures are seen in a periventricular position, and the subventricular zone is full of proliferating cells, especially on E19 and E20. The labeling patterns in the neuroepithelium 2 hours after injection with [^{3}H]thymidine show that there are no grape-like clusters in the external part, and nuclei in the synthetic phase of the cell cycle are closer to the ventricle; by E21, the synthetic and mitotic zones completely overlap. Our interpretation is that, by now, fewer and fewer neuroepithelial cells undergo interkinetic nuclear migration. One day after injection with [^{3}H]thymidine (Fig. 17–2D–G), the stratified labeling pattern in the neuroepithelium has reversed to the late pattern (up,l and lo,h) throughout the cortex, and bands of heavily labeled cells are always seen outside of the neuroepithelium in the transitional field. Exposure to low-level x-ray is becoming ineffective in killing cells in the neuroepithelium. Since most of the periventricular cells survive, the ventricular wall no longer ruptures, and pyknotic debris is confined to the brain parenchyma. The increased cell survival indicates that fewer radiosensitive neurons are being produced in favor of more radioresistant glia and ependymal cells that keep the ventricular wall intact. The neurons produced during the late stage are destined to settle in the superficial layers IV–II.

These two different methods, [^{3}H]thymidine auto-

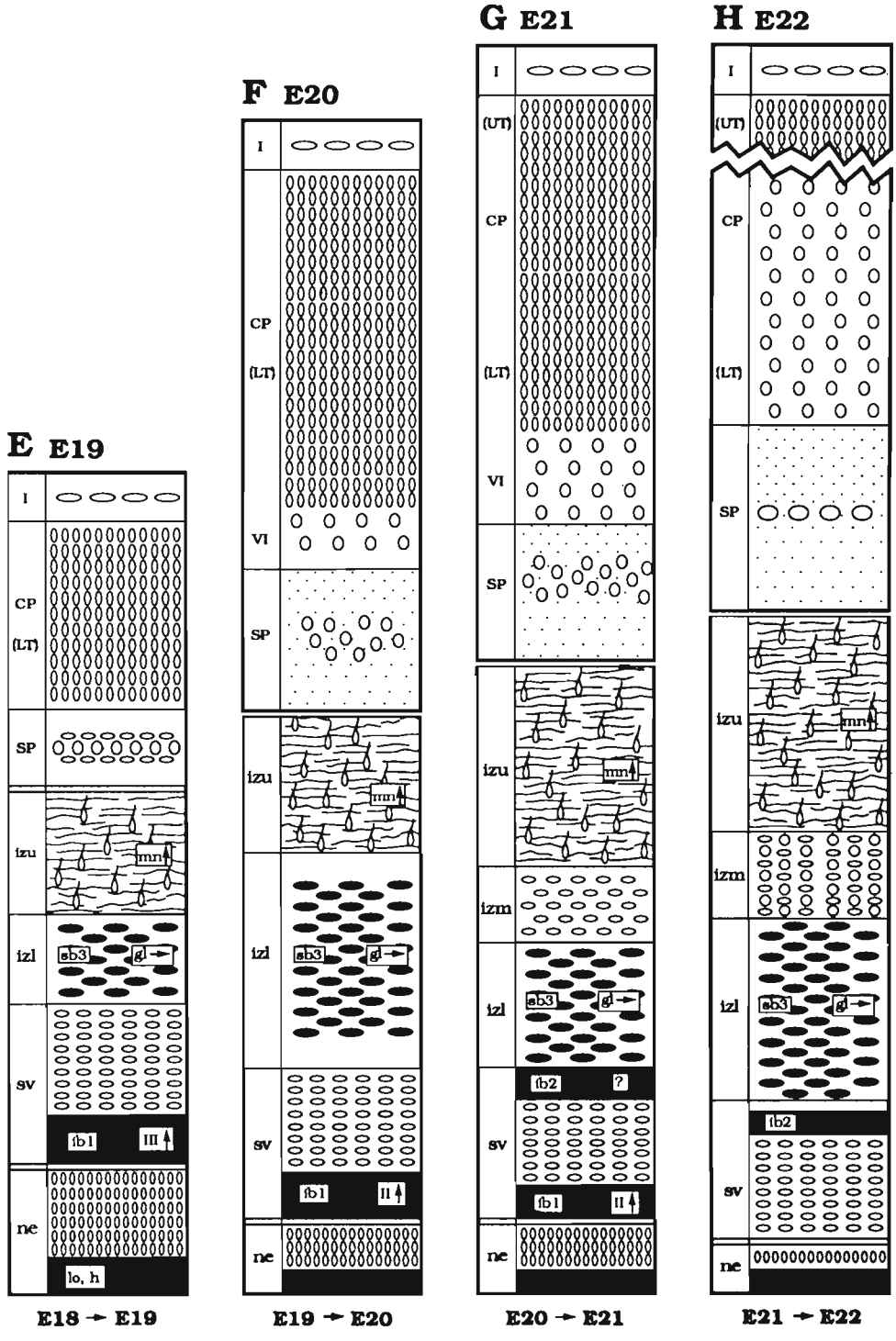

FIG. 17–2 (*Continued*)

radiography and exposure to x-irradiation, establish cellular heterogeneity in the cortical neuroepithelium. Although these techniques cannot directly distinguish cell types, we believe that glial precursors can be distinguished from neuronal precursors by two indirect lines of evidence: (1) The continual decrease in the proportion of cells undergoing interkinetic nuclear migration can be linked to the steady decline in the production of neurons from the middle to the late stages of cortical development. By the process of elimination,

we presume that the proliferating cells that do not undergo interkinetic nuclear migration are producing glia and ependymal cells (Chapter 16). (2) The early total devastation of the neuroepithelium after exposure to x-ray can be linked to the time when more neurons than glia are being produced. Conversely, the increase in radioresistance during the late stage is linked to the production of more glia and ependymal cells than neurons.

17.2 DEVELOPMENTAL EVENTS IN THE TRANSITIONAL FIELD

In Chapters 7, 8, and 9 we described several new observations regarding cellular interactions in the transitional field (the combined subventricular and intermediate zones). Autoradiograms of the embryonic neocortex (Chapter 7) show that bands of heavily labeled cells appear at different levels in the transitional field 1 day after an injection of [^{3}H]thymidine. These bands are interpreted to be cell-specific sojourn zones, some for neurons destined to reside in layers VI–II and others for glia. Quantitative data from normal embryos (Chapter 8) indicate that a majority of the cells is horizontally oriented in the subventricular and intermediate zones. Data gathered using a variety of methods (Chapter 9) indicate that, although some cells are migrating radially into the dorsal cortex, many other cells are migrating laterally from their generation sites in the dorsomedial neocortical neuroepithelium to settling sites in the lateral and ventrolateral parts of the neocortex, and even to points outside of the neocortex. When taken as a whole, the observations in these chapters suggest that the transitional field is a major staging area for different classes of neocortical neurons.

17.2.1 Cell Sorting In Sojourn Zones

Using observations in normal methacrylate-embedded embryos and in those killed 1 day after injection with [^{3}H]thymidine, we summarize laminar development in the neocortex in a series of drawings from E15 to E22 (Fig. 17–2). In the neuroepithelium, the subventricular zone, and the intermediate zone, black bars represent dense bands of heavily labeled cells and black ellipses represent dispersed heavily labeled cells. Subsequent to the formation of the primordial plexiform layer on E15 and E16 (Fig. 17–2A,B), the neurons destined to settle in the cortical plate first pause (sojourn) in different bands in the transitional field from E17 (Fig. 17–2C) to E21 (Fig. 17–2G). By correlating the sequential appearance of the bands with the timetables of neurogenesis, we associated neurons destined to settle in different cortical layers with different bands. Putative layer VI neurons sojourn on E17 in the most superficial part of the intermediate zone, the first superior band (sb1, Fig. 17–2C), which appears in the far ventrolateral part of the developing cortex on E16 (not shown in Fig. 17–2B). Putative layer V neurons sojourn on E17 and E18 in the second superior band (sV and sb2, Fig. 17–2C,D). That band appears in the lateral and ventrolateral neocortex at the junction between the subventricular and intermediate zones on E17, and is seen throughout the neocortex in the upper intermediate zone by E18. The first inferior band (ib1, Fig. 17–2D) appears adjacent to the neuroepithelium in the lower subventricular zone on E18 (Fig. 17–2D), presumably containing neurons for layer IV (ib1 and sIV). The first inferior band persists up to E21 and is postulated to contain successive waves of neurons destined to reside in the superficial layers of the neocortex, mainly layer III neurons on E19 (ib1 and sIII, Fig. 17–2E), and layer II neurons on E20 and E21 (ib1 and sII, Fig. 17–2F,G). The dissolution of the first inferior band on E22 (Fig. 17–2H) is correlated in time with the cessation of cortical neurogenesis.

Two sojourn zones persist after the cessation of neurogenesis. The third superior band is first seen in the lower intermediate zone on E19 (sb3, izl, and gl, Fig. 17–2E) and remains in the same position until the end of the embryonic period (Fig. 17–2H). Because the band occupied by sb3 becomes the white matter at the base of the cortex, we postulate that it contains dispersing glial cells. The second inferior band is first seen in the upper subventricular zone on E20 (ib2, Fig. 17–2G) and persists in that location on E21 (ib2, Fig. 17–2H). We do not currently have any hypotheses about the identity of cells in ib2 except that they are not neurons.

When the locations of the three bands postulated to contain neurons (sb1, sb2, and ib1) are considered, the following relationship is noted: older neurons destined to form the lower tier of the cortical plate (layers VI–V) sojourn in bands closer to the cortical plate, while the younger neurons destined to form the upper tier of the cortical plate (layers IV–II) sojourn farther from the cortical plate. For instance, the putative layer VI neurons that sojourn in sb1 on E17 are just beneath the cortical plate (Fig. 17–2C), while the putative layer II neurons that sojourn in ib1 on E20 and E21 are just outside the neuroepithelium (Fig. 17–2G,H). The outside-in transient cytogenetic gradient between the sojourn zones (older cells superficial, younger cells deep, Chapter 7, Fig. 7–10) in the transitional field is the mirror image of the inside-out permanent cytogenetic gradient between layers in the cortical plate (older cells deep, younger cells superficial, Chapter 6, Fig. 6–9).

Our hypothesis that the second superior band (sb2) contains neurons that are destined to settle in layer V is supported by the finding of regional differences in

its thickness. This band is prominent in the anterior motor cortex where layer V cells are numerous, but it is barely recognizable in the most posterior visual cortex where layer V neurons (particularly large pyramidal cells) are sparse. These differences may be due to an intrinsic gradient in the neocortical neuroepithelium, a topic that was discussed in Chapter 16. Paradoxically, there are no regional differences in the appearance of the first inferior band (ib1), the putative sojourn zone of neurons destined to settle in layers IV–II, even though cytoarchitectonic differences in the distribution of superficial neurons exist between motor and sensory areas of the cortex. That paradox is resolved by the finding that the neocortical ventricular zone is progressively shrinking in the dorsomedial direction as the basal ganglia grow into the lateral telencephalic wall. As we will summarize in the next section, many of the layer IV–II neurons that sojourn in ib1 in the anterior and middle parts of the developing neocortex will migrate laterally into the sensory areas, thereby reducing the number of these neurons settling dorsomedially.

17.2.2 Somatic Orientation, Cell Migration, and Time of Arrival of Cells in the Cortical Plate

Chapter 8 presents evidence that a majority of the cells in the subventricular and lower intermediate zones have a flattened elliptical shape with their long axes oriented horizontally, parallel to the coronal plane and perpendicular to the sagittal plane (Fig. 8–9). Sequential-survival [^{3}H]thymidine autoradiographic observations (Chapter 9) trace the horizontally oriented cells from the intermediate and subventricular zones of the anterior and middle dorsal neocortex to a prominent migratory pathway, the lateral cortical stream, that skirts around the basal ganglia. Finding laterally migrating cells in the neocortex is not surprising because computer-generated three-dimensional reconstructions (Color Figs. 2–7) show dramatic spatial changes between the span of the neocortical neuroepithelium and the span of the cortical plate. As early as E16, the lateral ventricle begins to shrink in the dorsomedial direction as growth of the basal ganglia takes up more room along its lateral wall, and the shrinkage continues throughout the rest of embryonic development. That situation deprives progressively more of the ventrolateral and lateral cortical plate in anterior and middle parts of the neocortex from an underlying neuroepithelium. Since most of the neurons in layers IV–II of the lateral and ventrolateral neocortex are generated after the neocortical neuroepithelium has been displaced dorsomedially, these neurons must migrate laterally to reach their settling sites. However, the shrinking cortical neuroepithelium must also be the source of neurons destined to reside in the overlying dorsal cortical plate. The sequential-survival [^{3}H]thymidine autoradiograms in Chapter 9 show that neurons generated in the dorsomedial neocortical neuroepithelium take at least two different migratory routes and have several different destinations (Fig. 9–12). Some migrate only radially for approximately 1 day and settle in the dorsal cortical plate. Others migrate varying distances for 1–2 days in the lateral cortical stream to settle in the lateral and ventrolateral parts of the cortical plate. Still others migrate farther ventrally for 3 or more days in the lateral cortical stream and settle outside of the neocortex in the piriform cortex and possibly in the basal telencephalon.

Because neocortical neurons that migrate laterally have a longer route, their time of arrival in the cortical plate is delayed when compared to those that migrate only radially. For example, neurons generated on E17 arrive in the lateral and ventrolateral parts of the cortical plate 1 day later than those in the dorsal-cortical plate (Chapter 9, Fig. 9–1). Because most neurons within a given neocortical layer are generated in a transverse gradient (lateral cells are older than medial cells), the earlier time of origin of laterally settling neurons is counterbalanced by their later time of arrival in the cortical plate. For example, many lateral layer IV neurons are generated on E17 (Chapters 12 and 13), and they arrive in the cortical plate on E20 (Figs. 9–1C and 9–4A). Even though many medial layer IV neurons are not generated until E18 (Chapter 14), they also arrive in the cortical plate on E20 (Figs. 9–7 and 9–8A) because they spend less time migrating in the subventricular and intermediate zones. The delayed time of arrival of neurons in the superficial layers of the lateral neocortex can be correlated with the mismatch between the ages of thalamic source cells and their cortical target cells, as was explained in Chapter 16.

17.3 THE FORMATION OF THE PRIMORDIAL PLEXIFORM LAYER AND THE CORTICAL PLATE

In Chapters 5 and 6 we offered some new interpretations about the ontogeny of the primordial plexiform layer and its relationship to the cortical plate. The first wave of neurons that migrate to the surface of the cortex form what Marin-Padilla called the primordial plexiform layer (pl, Fig. 17–2A,B). That layer actually consists of two successively forming separate layers, layer I (the marginal layer) and the subplate (layer VII). Layer I contains not only the earliest-generated Cajal-Retzius cells but also an extensive extracellular matrix (channel 1) of unknown significance. Horizontally oriented Cajal-Retzius cells can be seen beneath the pia as early as E14, and neurons labeled by an E14

[^{3}H]thymidine injection become abundant by E15 (Fig. 17–2A). The principal neuronal constituents of the subplate (layer VII) are the polymorph cells. Although the generation of subplate neurons occurs mainly on E14 and E15, a morphological subplate (implying a distinct layer of neurons situated beneath the cortical plate) is not recognizable until after the cortical plate has begun to form. The subplate neurons generated on E14 are sequestered in the upper part of the neuroepithelium on E15 (sSP, Fig. 17–2A). Those generated on E15 accumulate just beneath the Cajal-Retzius cells on E16 (sSP, Fig. 17–2B) and in the primitive cortical plate in the ventrolateral cortex. A second extracellular matrix (channel 2) develops beneath the cortical plate on E17 (Fig. 17–2C). As more neurons accumulate in the cortical plate, the subplate neurons descend into channel 2 on E18 (Fig. 17–2D) to form a distinct layer. On subsequent days, the channel 2 extracellular matrix becomes filled with fibers (*fine dots,* Fig. 17–2F–H). As development progresses and the cortical plate expands, the spatial separation between the two components of the primordial plexiform layer, layer I and the subplate, progressively increases.

The embryonic forerunner of layers II–VI in the adult cortex is the cortical plate. Early during cortical development, the growth of the cortical plate is marked by the progressive accumulation of densely packed radially oriented cells (Chapters 6 and 8, Fig. 17–2C). It is now well established that the cortical plate consists of older neurons at the base and younger neurons that migrate past them toward the surface. Autoradiographic observations (Chapter 6) and quantitative data (Chapters 11–14) suggest that the cortical plate is built in two tiers (Chapter 6, Fig. 6–9). Many cells in layers VI and V are cogenerated on E16 and E17 and accumulate in the lower tier (LT) of the cortical plate between E18 and E20 (Fig. 17–2D–F). Within a radial slab of the neocortex, there is less overlap in the generation of layer V and layer IV neurons than the overlaps between the other layers. In dorsomedial parts, neurons in layers IV–II are cogenerated on E18 through E20 and accumulate in the upper tier (UT) on E21 and E22 (Fig. 17–2G,H) and during the first few days of postnatal life. By P5, most of the neurons in the upper tier are in place (Chapter 3). The overall inside-out gradient in the settling of neurons is followed by a similar gradient in the differentiation of neurons. The decreasing packing density of neurons in the lower part of the cortical plate signals the onset of more advanced dendritic differentiation of neurons that will form the lower tier (Fig. 17–2F,H). The dendritic differentiation of the upper tier neurons takes place in the rat cortex postnatally.

Neurons in the primordial plexiform layer display different developmental characteristics from those in the cortical plate. First, the Cajal-Retzius and subplate neurons rapidly accumulate in the primordial plexiform layer without sojourning in the intermediate or subventricular zones. In contrast, the neurons that settle permanently in the cortical plate (layers VI–II) sojourn in cell-specific bands (sb1, sb2, and ib1) for 1–2 days after their generation before continuing their migration to the cortical plate. Second, the primordial plexiform layer is an early differentiating and prominent component of the embryonic cortex, in contrast to the delayed maturation of the cortical plate, suggesting that this system plays some important role in the early morphogenesis of the cortical gray. Since both the Cajal-Retzius and subplate neurons are much less conspicuous in the adult cortex, they may have a lesser functional significance in the operation of the mature cortex.

17.4 CORTICAL NEUROGENETIC GRADIENTS

Neurons in layers VI–II are generated in three spatiotemporal gradients throughout the developing neocortex (Chapters 3 and 11–14). (1) The radial gradient: older neurons are situated in the depth of the cortex, closer to the white matter, while younger neurons are situated more superficially, closer to layer I. (2) The transverse gradient: neurons situated ventrolaterally, closer to the rhinal sulcus, tend to be older than neurons situated dorsomedially, closer to the cingulate cortex. (3) The longitudinal gradient: neurons situated anteriorly, closer to the frontal pole, tend to be older than neurons situated posteriorly, closer to the occipital pole.

The transverse and longitudinal gradients are diagrammatically summarized in Fig. 17–3. In the lower tier of the neocortex (*left,* Fig. 17–3), the longitudinal (*darkly stippled arrow*) and transverse (*lightly stippled arrows*) gradients sweep across the cortex without evidence of modifications brought about by areal subdivisions. However in the upper tier of the neocortex (*right,* Fig. 17–3), the longitudinal and transverse gradients (*empty arrows*) are modified somewhat within and between some of the cortical areas. For example, both global neurogenetic gradients persist within the primary somatosensory cortex (Chapter 13). Only the transverse gradient persists within the primary visual cortex (Chapter 11), and there is neither a transverse nor a longitudinal gradient in layer IV/II in the primary auditory cortex (Chapter 12) or in the motor cortex (Chapter 14).

One pattern that emerges in the neurogenetic gradients of the superficial layers is that primary sensory areas (*outlined with dashed lines,* Fig. 17–3) always contain younger neurons than their respective secondary sensory areas (*solid arrows,* Fig. 17–3). In the auditory cortex, that is to be expected because the sec-

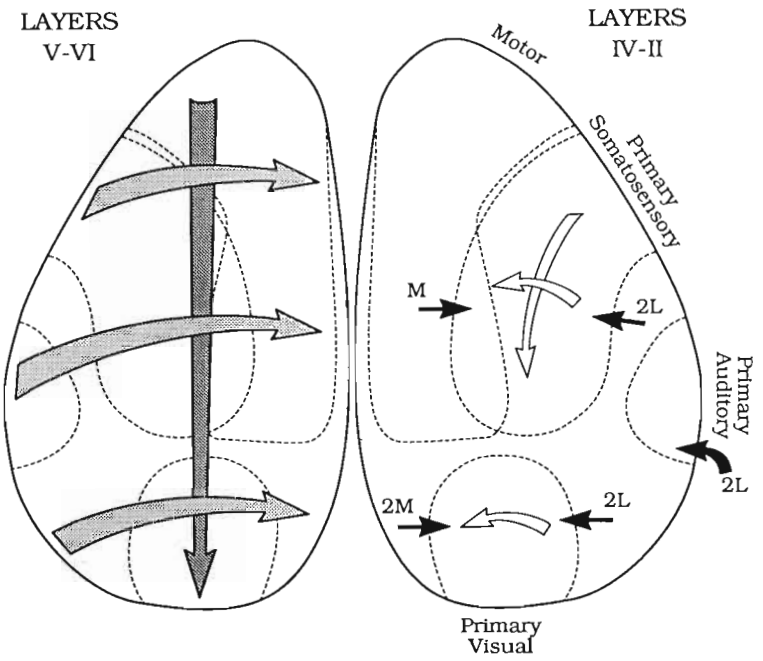

FIG. 17–3. A summary of the transverse and longitudinal neurogenetic gradients (*arrows*) on drawings of the dorsal and upper lateral surface of the neocortex. Dashed lines indicate the various cortical areas. On the left, the arrows represent the prominent neurogenetic gradients that are found between cells in layers V and VI. On the right, the arrows represent the neurogenetic gradients found between cells in layers IV–II. In both the deep and superficial layers, older cells are anterior and lateral, while younger cells are posterior and medial. However, the deep layers generally show these gradients more strongly than the superficial layers. In the superficial layers, there are reversals of the transverse (older lateral to younger medial) gradient at the medial borders of the somatosensory and visual cortex (*solid arrows* pointing away from the midline). That is the only evidence of temporal heterogeneity between areas in the neocortex. It is striking that so much homogeneity exists in development when there is a great deal of functional heterogeneity in the adult.

ondary areas (TE2 and TE3, Chapter 12) are located ventrolateral to the primary area (*solid arrow* pointing upward from the ventrolateral wall). Likewise, the secondary somatosensory area (PAR2) and secondary visual area (OC2L) are older than their respective medial primary sensory areas (*solid arrows* labeled 2L, Fig. 17–3). However, the global transverse neurogenetic gradient is violated in two instances (*solid arrows* labeled M and 2M, Fig. 17–3). First, younger neurons in layers III/II of the primary visual cortex (OC1M and OC1B) are located lateral to older neurons in the same layers of the medial secondary visual cortex (OC2M, Chapter 11, Fig. 11–5). Second, younger neurons in layers III/II of the somato-motor cortex (areas FL and HL) are located lateral to older neurons in the same layers of the motor cortex (areas FR1 and FR2, Chapter 14, Fig. 14–5B). It is important to note that the two exceptions to the global transverse gradient occur only during the generation of the youngest neurons in layers II and III of the primary somatosensory and visual areas, mainly on days E20 and E21, when cortical neurogenesis is nearly complete. When taken as a whole, the majority of neurons in the neocortex are generated either in accordance with the global neurogenetic gradients or generated so as not to violate them.

The limbic cortex surrounds the neocortex. Although there is the same stacking of older to younger cells in the radial dimension, the medial limbic cortex reverses the neocortical transverse gradient (Chapters 3 and 15) and the lateral limbic cortex has a different longitudinal gradient than the one in the neocortex (Chapter 15). These findings indicate that the limbic and neocortical parts of the cerebrum have different phylogenetic roots, a topic that was discussed in Chapter 16.