The concept of transient radial glial cells, based originally on observations made on the human fetal brain stained with the classical Golgi silver impregnation method, has been evolving with the application of advanced methods of anatomy, molecular biology and genetics. In addition to providing scaffolding for migration and placement of neurons, these specialized cells can generate neuronal cell lineage that either immediately, or following multiple divisions, migrate along the elongated radial process of the mother cell. Comparative analysis of the data on emergence, function and morphogenetic transformation of radial glial cells in the mouse, macaque and human embryonic cerebral wall reveals both similarities as well as species-specific differences in the timing, sequence, biochemical composition and level of phenotypic differentiation that provide insight into cortical development and evolution, as well as into pathogenesis of genetic and acquired cortical abnormalities.

Introduction
As the name implies, radial glial cells are a morphologically, biochemically and functionally distinct cell class characterized by cell soma situated near the ventricular surface, an elongated fiber shaft that, during development, transiently spans the entire width of the cerebral wall. Radial glial cells have been observed in most regions of the mammalian brain during specified developmental periods, suggesting their pivotal role in construction of the nervous system: first, by participating in generation of diverse brain cells, and second, by providing scaffolding for migrating neurons. It may not be coincidental that radial glial cells were initially discovered in the human fetal brain [reviewed in (Varon and Somjen, 1979; Rakic, 1995b, 2003; Bentivoglio and Mazzarello, 1999)]. Indeed, among the non-neuronal cells that may be found in the developing human brain, none are larger or more impressive than radial glial cells. Interest in radial glial cells recently increased with the realization of its role in both evolution and neuropathology of the cerebral cortex. Thus, the present article is focused on the emergence, differentiation, disappearance and role of radial glial cells in the developing mammalian forebrain, with particular emphasis on primate evolution.

After the initial description of radial glial cells with the classical Golgi method at the end of nineteenth century (Magini, 1888; Ramón y Cajal, 1890; Retzius, 1893), there was relatively little advancement in understanding their nature and function until the introduction of new methods that provided higher resolution and more discriminating identification of cell classes. Electron microscopy and immunohistochemistry in primate embryos not only confirmed a separate glial phenotype of radial cells, but also revealed their role in neuronal migration (Rakic, 1971a, 1972; Levitt and Rakic, 1980; Levitt et al., 1981; Gadisseux and Evrard, 1985; Kadhim et al., 1988; deAzevedo et al., 2003). Each radial glial cell has only one basal endfoot at the ventricular surface, whereas at the pial side the radial fibers, particularly during the later stages of development, often form several branches that terminate with multiple endfeet that form the outer cerebral surface (glia limitans) and are coated with a basement membrane (Rakic, 1972, 1995b). As the width of the cerebral wall expands, so does the length of radial glial fibers, some of which terminate on the capillaries which begin to invade the cerebral hemispheres (Schmechel and Rakic, 1979a). In most mammals, with some notable exceptions, the telencephalic radial glial cells are transient, and disappear or transform into astrocytes with the completion of cortical development (Schmechel and Rakic, 1979a,b; Levitt and Rakic, 1980). The term radial glia (RG), adopted to avoid connotations beyond what has been known about their function, while recognizing their morphological, ultrastructural and molecular characteristics as distinct cell lines (Rakic, 1971b, 1972, 1985), is now generally accepted and will be used throughout this article.

Species-specific Adaptations in Timing and Phenotypic Specification
In most mammalian species RG cells are morphologically and biochemically similar, but there are also some small but functionally and clinically significant differences. Since the size of a migratory neuron in the mouse and human embryo is approximately the same, the negotiation of the tortuous, several thousand micron long pathway in the large, convoluted primate brain poses a formidable navigational problem for postmitotic cells. Indeed, the peak of neuronal migration in humans occurs during the mid-gestational period, concomitant with the rapid increase in the width of the cerebral wall and emergence of its convolutions (Sidman and Rakic, 1973, 1982; Rakic, 1978). Unlike the straight and short migratory pathway in rodents, in the large gyrencephalic primate cerebrum, the migratory pathway became not only longer, but also increasingly curved (Fig. 2) (Rakic, 1978). Nevertheless, several generations of bipolar migratory neurons faithfully follow this curvilinear pathway rather than moving in a straight fashion to the closest site of the cortex (Rakic, 1978). In the past three decades RG guided migration has been observed in gyrencephalic cerebrum of a variety of large mammals, including the human (Sidman and Rakic, 1973; Kadhim et al., 1988; Misson et al., 1991; O’Rourke et al., 1992; deAzevedo et al., 2003). This glial scaffolding may be particularly important in the primate fetal cerebrum, where a large subventricular zone supplies a bulk of interneurons at the late developmental stages (Lentinic et al., 2002; Smart et al., 2002). The majority of these neurons migrate radially at the time when the cerebral wall is expanding (Lentinic et al., 2002; Rakic, 2003). In contrast, in rodents, most if not all cortical interneurons originate from the ganglionic eminence of the ventral telecephalon and migrate tangentially to the cortical plate [reviewed by Marin and Rubenstein (Marin and Rubenstein, 2003)].
Thus, in mice, as many as 25% of all cortical neurons migrate non-radially, whereas in human this percentage is <10% of the total (Letinic et al., 2002).

It is not possible to determine accurately the embryonic stage, when initially pluripotential neuroepithelial cells that span the thickness of the cerebral wall diverge into more restricted subtypes, without taking into consideration species-specific differences in brain size and shape, as well as ultrastructural and biochemical composition. For example, in the primate forebrain, including the human, where RG were initially discovered, electron microscopic and immunohistochemical visualization of glial acidic fibrillar protein (GFAP) confirmed that RG cells can already be identified as a distinct entity from the GFAP-negative cells at the onset of corticoneurogenesis (Levitt and Rakic, 1980; Levitt et al., 1981, 1983; Choi, 1986; deAzevedo et al., 2003). GFAP is present in the cytoplasm of glial cells in most vertebrate species and provides a useful marker for the astrocytic cell phenotype, including RG cells (Onsteniente et al., 1983; Dahl et al., 1985; Zupanc, 1999). The intermediate filament vimentin is also a helpful marker for the identification of RG as a separate cell line in primates, since the adjacent neuronal cells are vimentin-negative. In rodents, the phenotype of the primary RG cells can be characterized by immunoreactivity to RC1, RC2, vimentin, Rat 401 and Ran-2. However, it should be underscored that RG cells in rodents are GFAP-negative until the completion of corticoneurogenesis, and their antigenic properties are changed during the emergence of a secondary phenotype indicated by a substitution in the intermediate filament protein composition from vimentin to GFAP (Bovolenta et al., 1984; Pixley and De Vellis, 1984; Rickmann et al., 1987; Misson et al., 1988a,b; Voigt, 1989; Cameron and Rakic, 1991). The differentiation of RG cells during the stage of the most active neuronal migration is characterized in primates by abundant GFAP immunoreactivity and the presence of multiple lamelate expansions, which stands in contrast to the late differentiation in rodents, where GFAP immunoreactivity can be observed only after birth. Furthermore, many RG cells in primates stop mitotic activity while serving as scaffolding for migrating neurons (Schmechel and Rakic, 1979b). The phase of corticoneurogenesis in the macaque lasts 2 months (Rakic, 1974) and in the human ∼5 months, while the cerebrum undergoes rapid growth and dramatic morphogenetic changes (Sidman and Rakic, 1982).

It has been suggested that a differentiated and more durable glial scaffolding might be essential for migration and allocation of neurons in species with a larger and more convoluted primate cerebrum (Rakic, 1978, 1995a). For example, in the fetal human cerebral wall several generations of GFAP-negative migrating neurons can be aligned along a single GFAP-positive shaft, and the number of thus associated neurons increase with the gestational age (see below) (Rakic, 2003).

Recent studies showed that the uncommitted bipolar cells [primary RG phenotype of Cameron and Rakic (Cameron and Rakic, 1991)] can divide and give origin to neurons (Noctor et al., 2001; Tamamaki et al., 2001). This potential of RG cells has been observed both in vitro and in vivo in several laboratories (Malatesta et al., 2000; Hartfuss et al., 2001; Alvarez-Buylla and Garcia-Verdugo, 2002; Gaiano and Fishell, 2002; Noctor et al., 2002; Weissman et al., 2003). This finding suggests that the newly generated cells assume a bipolar shape and migrate along the radial fiber of the mother cell which remains attached to the ventricular surface (Noctor et al., 2001). Our own study, using a retrovirus carrying the GFP reporter gene as a marker, confirms that RG in mice can both generate as well as guide the migration of cortical neurons. When crossed with ROSA26R transgenic mice, embryos carrying both transgenes showed lacZ expression in radial glial cells, pyramidal neurons and astrocytes, indicating that both cortical neurons and astrocytes can be derived from radial glial cells (N. Sestan and P. Rakic, unpublished data). Thus, in a sense, the daughter cells are guided by the radial fibers of their mother’s cells to the appropriate location.

Figure 1. Schematic diagram of the evolving concepts of the relationship between RG cells and migrating neurons in the developing mammalian cerebral wall based on studies with increasingly more sophisticated methods applied on the embryonic forebrain of species ranging from the mouse and opossum pouch young to the human and non-human primates. See the text for further details.
Both of these two models support the radial unit hypothesis of cortical development and evolution. Another recent report has suggested an alternative assignment of cell fates following division in the ventricular zone (VZ), namely that the RG transforms into migrating neurons by translocating their nuclei to the cortex within the radial process, while the round cell budding from the RG cell remains as a stem cell within the VZ (Fig. 1E) (Miyata et al., 2001). This, as well as some older models based on the Golgi method (Berri and Rogers, 1965; Moster, 1970), assumes existence of a single common progenitor within the SV/SVZ which is in disagreement with the studies using various cell lineage markers (McCarthy et al., 2001; Malatesta et al., 2003). Furthermore, they are in mutual disagreement in regard to which of the two daughter cells becomes a neuron and which remains as a stem cell, as well as where the separation of the daughter cell from the mother cell actually occurs (Fig 1). Finally, these models do not apply to primates, where the EM and immuncytochemical evidence shows a clear difference between the GFAP-laden RG fibers and the GFAP-negative leading process of the migrating neurons (Rakic, 1972, 1978, 2003; Sidman and Rakic, 1973; Levitt and Rakic, 1980; deAzevedo et al., 2003).

The fundamental question is whether the cerebral proliferative centers of the forebrain (e.g. VZ, SVZ, GE), in addition to multipotent RG cells, also contain more restricted neuronal and glial cell progenitors. It should be emphasized that the "radial glial scaffolding" concept was derived from the analysis of advanced stages of primate cortical development when separate cell phenotypes are well differentiated (Rakic, 1972). However, during the early stages of corticogenesis migratory pathway postmitotic cells have a radial process that is sufficient in length to reach the marginal zone, as they do in rodents (Sidman and Rakic, 1973); in subsequent months, when the fetal cerebral wall expands in size, more differentiated and prominent RG scaffolding becomes readily apparent in both the macaque (Schmechel and Rakic, 1979a; Levitt and Rakic, 1980; Levitt et al., 1981, 1983) and the human (Sidman and Rakic, 1973; Kadhim et al., 1988; deAzevedo et al., 2003; Rakic, 2003). For example, the RG cells in the monkey cerebrum may be 3000–7000 mm long, while the leading process of bipolar migratory neurons of 50–200 mm in length (Rakic, 1972) is similar in length to those observed in rodents. This is the stage when separate glial and neuronal cell lines are easily identifiable by EM and immunocytochemical methods (Rakic et al., 1974, 2003; Levitt and Rakic, 1980; Levitt et al., 1981, 1983; Cameron and Rakic, 1991).

Several studies in humans (Carpenter et al., 2001; Letinic et al., 2002; deAzevedo et al., 2003) and non-human primates (Levitt and Rakic, 1980; Levitt et al., 1981, 1983) show the existence of at least two separate stem cell lines in the VZ and a highly expanded subventricular zone (SVZ): one glial and the other neuronal. Unlike in rodents, cells isolated from the human VZ/SVZ even at early stages of corticogenesis generate separate neuron restricted precursors and glia-restricted precursors (Carpenter et al., 2001). Retroviral gene transfer labeling of cell lineages in human embryonic slices shows that multiple divisions of neuronal stem cell progenitors occur in the VZ/SVZ before they begin radial migration to the neocortex (Letinic et al., 2003). Similarly, diversity of progenitors may also exist in rodents, but could be overlooked because of their smaller number or lack of the cell class-specific markers for their identification at early stages (McCarthy et al., 2001; Tan, 2002; Malatesta et al., 2003). Furthermore, even the neuron-restricted class is further specified. For example, more specialized stem cells of both glial and neuronal lineages that produce different classes of projection and local circuit neurons can be identified by retroviral labeling (Parnavelas et al., 1991; Kornack and Rakic, 1995; Reid et al., 1995; Tan et al., 1998). Likewise, heterochronous transplantation of VZ cells indicate that progenitors produce layer-specific neurons depending on the time when they are dissociated from the embryo (McConnell, 1988). The molecular heterogeneity of remnant stem cells in the fetal human cerebrum has also been demonstrated by molecular phenotyping of clonal neurospheres (Suslov et al., 2002).

In mammals, most of the RG cells disappear, only a vestige persisting in some specialized areas where they adapt to the local functional requirements and spatial conditions (e.g. the Bergmann glial cells of the cerebellum, tanyocytes of the hypertalamic or Müller cells of the retina). These specialized cells share basic morphological, immunological and biochemical features with RG (Bartlett et al., 1981; Evrard et al., 1990; Robinson and Drehcr, 1990) [reviews in (Fedoroff and Vernadasik, 1986; Rakic, 1995b)], and they can be considered morphologically and biochemically divergent forms of embryonic RG that continue to be maintained in the adult mammalian brain. In contrast, in some non-mammalian vertebrates, RG cells persist throughout the adult life span (Ramón y Cajal, 1909; King, 1966; Tramontin et al., 2003). Thus, the fate of the RG cells depends on the context and functional requirements, which differ between species. Analyses of transitional forms of RG cells in Golgi-stained and GFAP-immunolabeled sections of the monkey and human cerebra indicate that RG cells become transformed into fibillary astrocytes and/or protoplasmic astrocytes, as suggested by Ramon y Cajal (Rakic, 1978, 1995b; Choi, 1986; Schmechel and Rakic, 1979a; Levitt and Rakic, 1980; Rickmann et al., 1987). The timetable of the disappearance of RG cells in the primate neocortex, hippocampus and cerebellum correlates with the emergence of astrocytes in these regions (Rakic, 1971a, 1972; Schmechel and Rakic, 1979a; Eckenhoff and Rakic, 1984). In the primate, telencephalon RG cells that span the entire cerebral wall disappear shortly after birth (Rakic, 1972; Schmechel and Rakic, 1979a,b). The cellular or molecular events that underlie the observed morphological transformation of RG cells are not known. In primary cultures of astrocytes, neuronal cells have been shown to exert an inhibitory effect on glial cell proliferation and, additionally, appear to regulate changes in astroglial cell shape from epithelial-like to radial or stellate (Sobue and Pleasure, 1984; Hatten, 1985; Arde and Bunge, 1988; Culican et al., 1990). The morphological transformation of GFAP-positive RG cells into classical astrocytic cell forms, as well as alternative RG forms, appears to coincide with the loss of RC1, RC2 and Rat-401 antigens, which are not expressed in adulthood (Hockfield and Mckay, 1985; Misson et al., 1988a,b; Evrard et al., 1990). A comparative analysis of antigenic and morphologic transformation in vivo (Misson et al., 1991) and in vitro (Culican et al., 1990) demonstrates that the morphological transformation of radial glial cells occurs concomitantly with a gradual acquisition of GFAP immunoreactivity and with a corresponding loss of RC1 immunoreactivity.

The primordial fetal RG cell have been considered as a progenitor that gives rise directly or indirectly to all major classes of astrocytes, but are also capable of generating neuronal cell lines (Cameron and Rakic, 1991). However, in selective areas such as the olfactory and hippocampal systems, modified RG persist in the adult CNS (Reichenbach, 1989; Rakic, 1995b) and may serve as multipotent stem cells (Doetsch et al., 1999; Chanas-Sacre et al., 2000; Rakic, 2002; Tramontin et al., 2003).
Recent studies using the gain of function approach has suggested that Notch activity may be involved in promoting glial differentiation at the expense of neurogenesis (Gaiano and Fishell, 2002; Sestan and Rakic, 2002), but both cell–cell interactions and cell lineages are likely to determine the fate of RG cells (Doetsch et al., 1999; Laywell et al., 1999; Gage, 2002; Kukekov et al., 2002). Thus, while during development RG cells contribute to brain construction, their remnants in some structures contribute to function in both health and disease during adulthood.

Role as Transient Radial Glial Scaffolding

What would be the role of the transient RG scaffolding in the fetal cerebrum? The use of a combination of Golgi impregnation and reconstruction from EM serial sections in the early 1970s revealed that during late stages of corticogenesis in the fetal macaque and human cerebrum, cohorts of postmitotic cells originating in the proliferative mosaic of the VZ follow a radial pathway consisting of single or, more often, multiple RG fibers, which span the expanding and increasingly more convoluted cerebral wall (Fig 2) (Rakic, 1972; Sidman and Rakic, 1973). The regularity of the migratory streams consisting of a multitude of individual GFAP-negative bipolar neurons which follow the GFAP-positive glial guides, suggests both the stability of the RG cells and the existence of selective adhesion between two cell types. Since the postmitotic neurons in the human cerebrum during the mid-trimester of gestation need several weeks to reach their final destination, one can observe as many as 30 generations of GFAP-negative neurons aligned along the single GFAP-positive GR guide (Rakic, 2003).

Figure 2. (A) Schematic three-dimensional reconstruction of the portion of the medial cerebral wall at the level of the insipient calcarine fissure (CF) in the 80-day-old monkey fetus. The reconstruction illustrates how the corresponding points in the ventricular zone (VZ) are connected by the array of elongated RG fibers which span the full thickness of the cerebral wall to the increasingly distant cortical plate (CP) situated below the convoluted pial surface [from Rakic (Rakic, 1978)]. (B) Three-dimensional reconstruction of migrating neurons, based on electron micrographs of semi-serial sections of the occipital lobe of the monkey fetus. The reconstruction was made at the mid-level of the 2.50 µm wide intermediate zone. The lower portion of the diagram contains uniform, parallel axons of the optic radiation (OR) while the irregularly disposed fiber systems occupying the upper part of the diagram are deleted to expose the radial fibers (striped vertical shafts RF1–6) and their relations to the migrating neurons A, B and C, and other vertical processes. The soma of migrating cell A, with its nucleus (N) and leading process (LP), is situated within the reconstructed space, except for the terminal part of the attenuated trailing process and the tip of the vertical ascending pseudopodium. The perikaryon of cell B is cut off at the top of the reconstructed space, whereas the leading process of cell C is shown just penetrating between fibers of the optic radiation (OR) on its way across the intermediate zone. LE indicates lamellate expansions; PS indicates pseudopodia [from Rakic (Rakic, 1978)].
Postmitotic bipolar neurons in the human fetal cerebrum can be observed migrating both radially and tangentially (Sidman and Rakic, 1973). While moving across the widening intermediate zone, the neurons originating in the VZ/SVZ may be in contact with a myriad of axonal and dendritic processes, but nevertheless the majority remains selectively attached to the adjacent surface of radial glial fibers, suggesting the existence of differential binding affinity mediated by heterotypic, ‘gliophilic’ adhesion molecules present on apposing neuronal and RG cell surfaces (Rakic, 1985, 1990; Rakic et al., 1994). In contrast, migrating cells which did not obey glial constraints and move tangentially, perpendicular to the RG fibers, aligned along axonal tracts were considered ‘neuropilic’ (Rakic, 1985, 1990). In the past decade, several classes of molecules have been found to be expressed selectively and transiently in the leading process of postmitotic neurons and at the surface adjacent to the RG fibers (Schachner et al., 1985; Fishell and Hatten, 1991; Komuro and Rakic, 1993, 1998; Cameron and Rakic, 1994; Rakic et al., 1994; Anton et al., 1996, 1997, 1999) (V. Gongidi et al., submitted for publication). Over time it has become evident that separate sets of molecular classes may be involved in the recognition, selective adhesion and maintenance of neuron-glial interactions. Among the candidate molecules are neuregulins, which binds to the glial surface via ErbB2 and 4 (Anton et al., 1997; Rio et al., 1997; Schmid et al., 2005), and integrins, which provide the optimal level of basic neuron-glial adhesion needed to maintain neuronal migration on RG (Anton et al., 1999). However, a gliophilic to neuropilic switch in the preference of adhesive interactions of developing cortical neurons occurs in the absence of functional α3 integrins (Anton et al., 1999).

When examined in vitro, neurons can often be observed as migrating bi-directionally (Hatten and Mason, 1990; Nadarajah et al., 2003) (E.S.B.C. Ang et al., submitted for publication). However, in vitro studies using [3H]thymidine and bromodeoxyuridine labeling indicate that virtually all postmitotic neurons eventually attain their proper areal and laminar positions in a remarkably precise and reproducible fashion (Rakic, 1974, 2002). What is dictating their one-way journey, from the place of their origin to their permanent residence? There is some evidence that postmitotic cells are being attracted and repelled by diffusible molecules emanating from the target tissues (Wu et al., 1999). Although the activity of several repelling molecules has been demonstrated, this developmental strategy alone is insufficient to place cortical neurons in their exact final position, since proper placement also requires surface-mediated interactions with RG cells. However, these two separate cellular mechanisms may cooperate in allocating particular classes of neurons and preventing their dispersion into inappropriate locations (Rakic, 1999).

Nuclear translocation has been considered as an essential component of neuronal migration (Ramon y Cajal, 1909; Berri and Rogers, 1965; Moster, 1970), but cellular and molecular mechanisms were not known. It was evident from the early EM studies that active movement of cells to their distant locations requires not only directed and selective growth of the leading process, but also the displacement of the entire cell soma with its nucleus to the new location (Rakic, 1971a, 1972; Sidman and Rakic, 1973), and this mechanism has been supported by the observation using in vitro (Nadarajah et al., 2003) and in vitro time-lapse cinematography (E.S.B.C. Ang et al., submitted for publication). After the last cell division, the leading process develops and preferentially extends radially along adjacent glial shafts. The content of the cytoplasmic organelles and membrane structure of the leading process of migrating neurons are more similar to the growing dendrites than to axonal growth cones (García-Segura and Rakic, 1985), the distinction also indicated by their morphology (Ramon y Cajal, 1909). However, the most significant difference is that during axonal extension the nucleus remains stationary, while during migration it translocates within the cytoplasm of the leading process (Rakic, 1972, 1981). The initial ultrastructural observations suggested that the mechanism of neuronal migration must involve translocation of the nucleus and surrounding cytoplasm within the growing leading processes of migrating cells (Rakic 1971a,b, 1972). The subsequent time-lapse imaging of migrating neurons in slice preparations showed that the leading process extends more slowly and steadily, whereas the nucleus moves in an intermittent, stepwise manner (Komuro and Rakic, 1995) (E.S.B.C. Ang et al., submitted for publication). This nuclear translocation is evident in early stages of corticogeneogenesis in rodents (Nadarajah et al., 2003), as well as in human when migratory pathways are still relatively short and the leading processes span the full thickness of the cerebral wall (Sidman and Rakic, 1973). However, even at the later stages, when the length of the leading process is only a small fraction of the total migratory pathway, the nucleus nevertheless moves intermittently within the leading process (Rakic, 1981, 2003). Therefore nuclear translocation is assumed in each model of neuronal migration diagramed in Figure 1; the issue is whether and when stem cell lines diverge.

The cytological and molecular mechanism of the physical displacement or translocation of postmitotic neurons only began to be explored by advanced experimental methods (Rakic and Komuro, 1995; Rivas et al., 1995; Komuro and Rakic, 1998; Behar et al., 1999; Hirai et al., 1999; Hatten, 2002). It became apparent that translocation of the nucleus and surrounding cytoplasm within the membrane envelope of the growing leading process needed to be orchestrated by rearrangement of the cytoskeletal scaffolding (Rakic et al., 1996). The nucleus can be translocated without changing the total length of the microtubules, by coordinating depolymerization of microtubule sheets at their positive negative ends (Rakic et al., 1996), as has been shown in non-neuronal cells (Kirshner and Mitchison, 1986; Barkalow and Hartwig, 1998). This hypothesis is consistent with the observation that the leading process of migrating neurons precedes the phase of more rapid nuclear displacement (Hatten and Mason, 1990; Komuro and Rakic, 1995, 1998) (E.S.B.C. Ang et al., submitted for publication). The rate of assembling the microtubule polymer in the leading process depends on the concentration of cytosolic calcium ions regulated by specific voltage and ligand-gated channels (Komuro and Rakic, 1993, 1995). Many of the agents that affect neuronal migration act by inducing changes in the cytoskeleton (Rakic et al., 1996), and it is, therefore, not surprising that many of the migratory defects involve abnormalities of the microtubule assembly (Gleeson and Walsh, 2000; Wynshaw-Boris and Gambello, 2001).

**Evolutionary and Biomedical Significance**

The fundamental principles of cortical development in all mammals are basically similar. However, it is unlikely that the most advanced part of the human brain has not changed during over 100 million years of mammalian evolution (Preuss, 2000). Indeed, there are numerous evolutionary modifications of developmental events that produce not only quantitative changes (e.g. the number of neurons and columns or timing and sequence of cellular events) but also qualitative ones (e.g. the elaboration of new neuronal types, addition of specialized...
cytoarchitectonic areas and formation of new connections). Most of the modifications of cortical development, as in other structures of the organisms, can often be traced to the action of phylogenetically conserved genes that act on the progenitor cells at or prior to their exit from their mitotic cycle generating a different outcome, depending on the evolutionary context and functional demands (Bang and Goulding, 1996; Shirasaki and Pfaff, 2002). These differences are of not only theoretical, but also clinical significance, as many of these new traits may be particularly vulnerable to genetic and environmental factors (Steward et al., 1999; Gurwitz and Weizman, 2001). In this article I have focused only on the adaptations of telencephalic RG based on our parallel analyses of developmental events in mouse, monkey and human embryos.

Why has natural selection elaborated transient scaffolding of non-neuronal cells in order to build the cerebral cortex? The answer may be related to the fact that during evolution the cerebral neocortex expands predominantly in surface area rather than in thickness, and as a result cerebral hemispheres become increasingly more convoluted (Rakic, 1995a). There has to be a cellular mechanism for building the ubiquitous, crystal-like laminar and radial architecture of the cerebral cortex, even in gyrencephalic brains, so consistently. A comparative embryological analysis of telencephalic development led to the proposal of the radial unit hypothesis of the ontogenetic and phylogenetic expansion of the cerebral neocortex at the cellular level (Rakic, 1988a). According to this hypothesis, the expansion of the surface of the cerebral cortex is accompanied not only by the proportional increase in the number and length of RG cells, but also by the earlier onset of their differentiation, as well as an increase in duration of the G1 phase of the cell cycle and their longevity during individual embryonic development (Kornack and Rakic, 1998). Thus, the mitotically active ventricular zone, situated at the surface of the cerebral ventricle, is depicted as a two-dimensional mosaic of proliferative units which constitutes the rough primordial ‘protomap’ of the prospective species-specific cytoarchitectonic areas (Rakic, 1988a). This enables several clones of neurons sharing a common site of origin in the VZ to use a common migratory pathway along the RG fascicle, across the growing intermediate and subplate zones, to settle within the same column in the cortical plate, so that the positional information of their origin is preserved. It has also been observed that neuronal precursors that form such cohorts of migrating neurons are coupled with gap junctions; and importantly, that prospective pyramidal neurons are clustered into vertical columns which are also gap junction coupled (LoTurco and Kriegstein, 1991; Peinado et al., 1993).

According to the radial unit hypothesis, RG cells play a prominent role in enormous cortical expansion during evolution, since the size of the cortical mantle depends on the number of contributing radial units, while the thickness of the cortex depends on the magnitude of cell production destined for each unit (Rakic, 1995a,b). The initial number of radial units in a given species is likely to be set up during the early stages of embryogenesis by the regulatory genes, while the organization and the final size of cytoarchitectonic areas are established through interactions with appropriate affere- rants from other structures and areas (Rakic, 1988a; Rakic et al., 1991). Thus, the enlargement of cerebral cortex during evolution could initially occur in the VZ through a heterochronous process that includes a modification of the rate and mode of cell division (Caviness et al., 1995; Rakic, 1995a; Haydar et al., 2003). Recent experiments on embryonic brains in which the number of founder cells is manipulated by either the reduction of programmed cell death (Kuida et al., 1996; Haydar et al., 1999) or an increase in cell proliferation (Chenn and Walsh, 2002, 2003) support this hypothesis. In both cases the number of founder cells in the early VZ increases, resulting in a larger number of proliferative units that generate a corresponding number of radial minicolumns that enlarge the cortex in surface and create convolutions in the normally smooth (lissencephalic) mouse brain. Thus, an increase in the number of founder cells leading to the larger number of radial units in the neocortex is clearly correlated with the evolution of RG scaffolding.

The malformations attributed directly or indirectly to damage of the RG scaffolding have been observed in some neurologically mutant mice (Rakic and Sidman, 1973; Caviness and Rakic, 1978; Nowakowski, 1984; Reiner et al., 1993; Gleeson and Walsh, 2000), as well as in response to various external agents (Schull et al., 1986; Sherman et al., 1987; Super et al., 2000; Gieddalski and Juliano, 2003). However, abnormalities of neuronal migration are particularly frequent in humans (Rakic, 1988b; Volpe, 2001), and range from gross malformations such as lissencephalia and polymicrogyria to the subtle heterotopia observed in the cerebral wall of patients with developmental dyslexia and childhood epilepsy (Gadisseux and Evrard, 1985; Rakic, 1988b; Buxhoeveden and Casanova, 2002; Casanova et al., 2002). A species-specific difference was discovered in the effect of the deletion of doublecortin (Dbx) mutation, which was found to have a profound effect on neuronal migration in the human telencephalon but does not affect formation and neurogenetic gradients of the mouse cerebral cortex (Corbo et al., 2002). Such species-specific differences may in part be related to the fact that, unlike that in rodents, the SVZ in the human contributes the majority of interneurons to the neocortex which need guidance for reaching their distant locations (Letinic et al., 2002). Thus, the modifications in the expression pattern of transcription factors in the forebrain may underlie species-specific programs for the generation of distinct lineages of cortical interneurons that may be differentially affected in genetic and acquired disorders related to neuronal migration (Rakic, 1988b; Jones, 1997; Gleeson and Walsh, 2000; Lewis, 2000). We have only just begun to understand the role of RG cells in these defects. One scenario may be that various agents which interfere with neuron-glia interaction, and thus indirectly impair neuronal proliferation and their path finding or motility, can, even with very little or no injury to neurons, prevent their normal placement. In most cases it is difficult to detect this condition in post-mortem human material and only functional deficits indicate the existence of cortical abnormality. Thus, radial glial cells play an important role not only in evolution and development, but also in the pathology of the cerebral neocortex.

Notes
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