Preface

Approximately 2 percent to 3 percent of the population of the United States has been diagnosed with severe neurological disabilities (e.g., mental retardation, cerebral palsy, autism, chronic severe mental illness). A far greater percentage (10 percent to 20 percent) has less severe disabilities (e.g. learning disabilities, disorders of attention, episodic mental illness). These neurologically based afflictions result in enormous human suffering and social cost, placing a significant burden on even the most affluent countries in the world. For more than 100 years scientists in a wide range of disciplines (e.g., sociology, psychology, medicine, developmental biology) have attempted to determine the causes of these disabilities. Many factors have been isolated including genetics, nutrition, pollutants, inadequate caretaking and social factors linked to poverty.

It is the belief of the authors of this book that one set of factors, those that alter the neurological development of the child during the fetal period, has not been given the attention that it deserves. The prenatal period of development is particularly sensitive to disruption because it encompasses a precisely timed period when organ systems are formed and rapid growth of neurological structures occurs. During no other period in the life course is the well-being of the individual so dependent on precisely timed biochemical events. As a result, an adverse prenatal exposure can impart immutable damage because of the sensitivity of the developing central nervous system during the prenatal period.

A growing number of specialists are making important discoveries regarding the types of factors that perturb fetal neurological development. These researchers have, in some cases, documented long-term psychological, behavioral and educational sequelae. However, this research is scattered throughout research literatures of a variety of professions (medicine, epidemiology, developmental psychopathology, reproductive biology), is technically challenging for non-specialists and is not readily available to many that do not have access to research libraries or specialized computerized retrieval mechanisms. Thus, it is the purpose of this book to summarize the most important findings regarding prenatal exposures that have been associated with learning and behavior problems of children and adolescents.

This volume is organized into five sections. The first introduces the main themes of the book and, in a separate chapter, presents an introduction to fetal development. This chapter was designed to set the stage for the understanding of how many

different types of perturbations result in long-term central nervous system damage that has a continued effect as the child matures. The second section is devoted to low birth weight, preterm birth and asphyxia. These are among the most widely researched markers or indicators that prenatal perturbations have occurred. The remaining three sections are devoted to detailed discussions of the research linking maternal illness, maternal drug use and maternal exposure to pollutants to long-term negative effects on child and adolescent development. We are particularly pleased to be able to summarize many recent findings in the area of air, water and household chemical pollutants as this volume is one of the first to include detailed reviews of this burgeoning area of scientific activity.

It is our hope that having this body of knowledge–compiled for the first time in one volume– will aid researchers, practitioners and policy makers in elevating prenatal events to a more central position in the understanding of learning and behavioral pathologies of children and adolescents. A nuanced understanding of the role of prenatal events is particularly important in today's world, as the number of children with developmental anomalies is increasing, largely due to improved medical care. This book stands to fill a cross-disciplinary conceptual gap and serve as an important resource to the psychological, medical and educational community, setting the context for appropriate prevention and intervention activities that have the potential to foster the developmental well-being of children.

November 2007   Roy Martin and Stefan Dombrowski
                                                      Athens, GA   Cherry Hill, NJ

Chapter 2
Prenatal Central Nervous System Development

This chapter provides an overview of the major stages of prenatal central nervous system (CNS) development. CNS development plays the central role in the primary argument of this book. That argument is that the prenatal CNS is particularly vulnerable to environmental perturbations because it is rapidly developing during that time period. Further, we argue that many of the learning and behavioral problems that occur in childhood and adolescence have their origins in these prenatal perturbations of CNS development.

This chapter sets the stage for exploring the relationship between prenatal exposures and later behavioral and/or psychological pathology by elucidating the normal course of prenatal brain development.

Prenatal CNS Development

To help conceptualize fetal CNS development, Nowakowski and Hayes (1999) metaphorically link the development of the CNS to the construction of a house. In the same way that a blueprint guides house construction, an individual's genome serves as a blueprint for the brain. Some of the DNA in the genome creates proteins that build structures, while others are 'timing genes' that manage the sequencing of the building process. Neurons and glial cells function as the foundational materials of bricks, wood and cement. Axons, dendrites and synaptic connections among neurons serve as the wiring for electricity and the telephone.

The construction of this elaborate communication structure we call the brain is complex, but there are some general principles that guide the process. First, while genes provide the blueprint, CNS development is a complex process that results from the interplay of genetically governed biological processes and a number of experiential/environmental factors (Capone 1996; Hynd and Willis 1989). Second, despite this complex genetic and environmental interaction, the formation of brain regions occurs according to a precisely sequenced schedule with more phylogenetically primitive regions (e.g., limbic system, forebrain) developing before more complex structures (e.g., cerebral cortex). Third, within these regions, brain development is

most vulnerable to insult during periods of most rapid growth and development (Dobbing and Sands 1979). Thus, the timing of an insult may be more important than the dose or nature of the insult in influencing the pattern of malformation. The fourth guiding principle is that of all organs in the body, the brain is most vulnerable to teratogenic disruption because of the extended amount of time it requires for development (Capone 1996). Fifth, although this chapter discusses prenatal brain development, birth does not mark a particular milestone in the development of the brain. The brain continues to develop throughout the lifespan (Bayer, Yackel and Puri 1982), although the most significant development occurs early in development during the fetal period and the first years of life (Aylward 1997; Nowakowski and Hayes 1999). With these general principles in mind, the following discussion highlights the most important developmental processes occurring in the CNS.

First Trimester Development

Following fertilization of the ovum and subsequent rapid cell division, the embryonic disc emerges. The embryonic disc comprises three layers of cells: the ectoderm, mesoderm and endoderm. The inner layer (endoderm) will transform into the internal organs (e.g., digestive and respiratory systems) of the body while the middle layer (mesoderm) will form the musculature and skeletal systems. The outer layer (ectoderm) evolves into a variety of structures including the Central Nervous System (CNS). The central process through which the ectoderm forms the initial structure of the CNS is neurulation. Neurulation commences toward the end
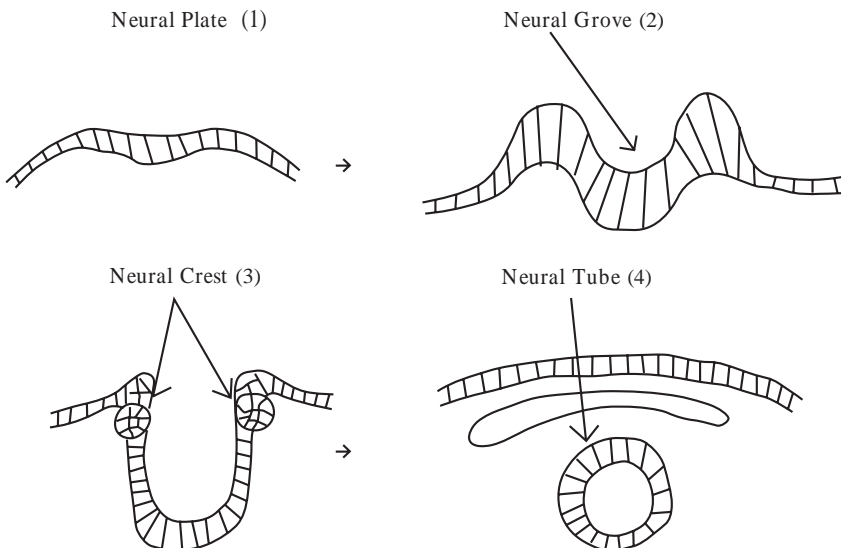

Fig. 2.1 Folding of Neural Tube
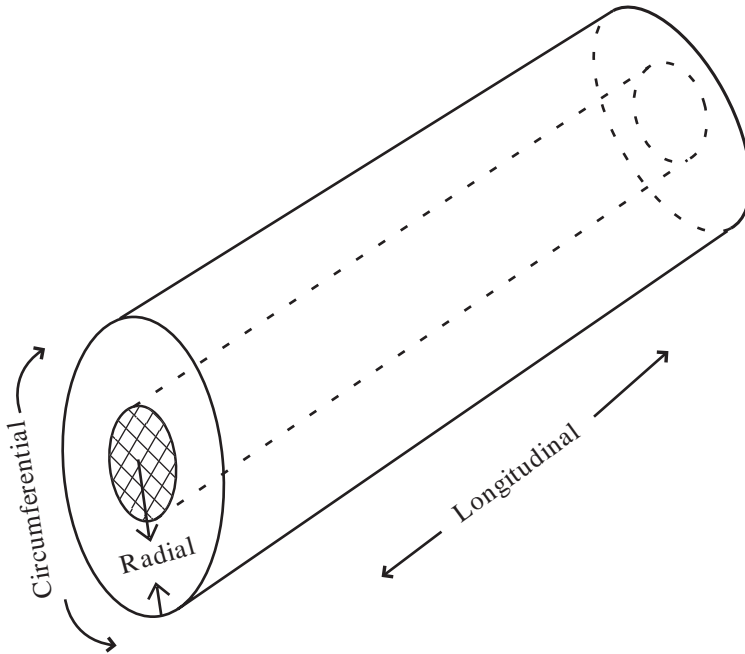
Fig. 2.2 Three Dimensional Neural Tube Development

of the third week of gestation when the outer layer of the embryo (the ectoderm) begins to fold upon itself to form the neural tube (see Figure 2.1).

The neural tube has a cylindrical (e.g., pipe-like) shape and develops along the three dimensions (longitudinal, circumferential and radial) that are typically used to describe a cylinder. Differentiation along these three dimensions determines the major structural aspects of the nervous system. Aylward (1997) and Nowakowski and Hayes (1999) provide a synopsis of this development. The head portion of the neural tube becomes the brain while the middle portion becomes the brain stem. The head or cephalic portion further differentiates into the forebrain, midbrain and hindbrain. In turn, these structures differentiate such that the rudiments of the adult brain are recognizable by the fifth week of gestation. For instance, by about the fifth week, the neural tube differentiates into the three primary structural units of the brain: the proencephalon (forebrain), the mesencephalon (midbrain) and the rhombencephalon (hindbrain). By the seventh week two additional structures are formed, creating the five primary units that will become the mature brain (Crossman and Neary 2000). The two additional structures are created when the prosencephalon and the rhombencephalon divide in two. The prosencephalon divides into the telencephalon and the diencephalon, while the rhombencephalon divides into the metencephalon and the myelencephalon. This developmental progression is illustrated in Fig. 2.3. Table 2.1 indicates the mature structures that develop for each of these five basic units of the CNS.
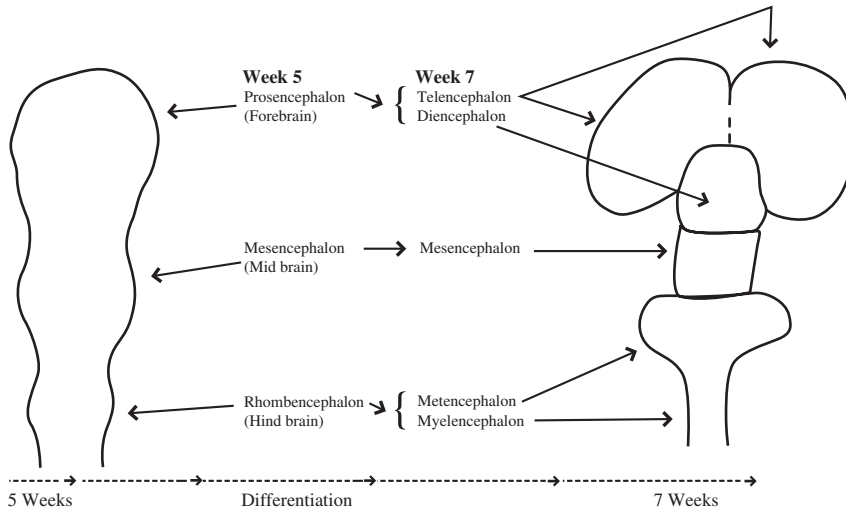
Fig. 2.3 Three & Five vesicle stages of brain development reference

Table 2.1 Sequence of CNS Development

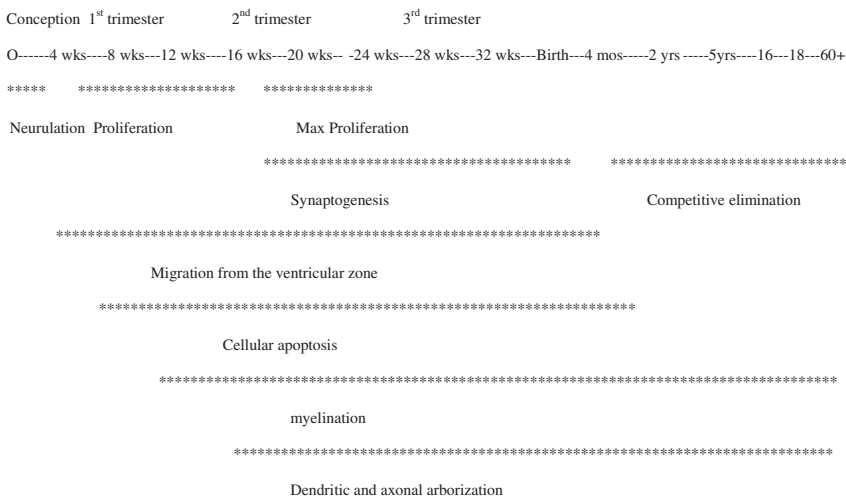| Three-Vesicle Stage (Primary Brain Vesicles)	Five-Vesicle Stage (Secondary Brain Vesicles)	Mature Structure
Forebrain (Prosencephalon)	Telencephalon	Cerebral cortex, basal ganglia, hippocampus, amygdala, olfactory bulbs
	Diencephalon	Thalamus, hypothalamus, optical tracts, retinae
Midbrain (Mesencephalon)	Mesencephalon	Midbrain
Hindbrain (Rhombencephalon)	Metencephalon	Pons, cerebellum
	Myelencephalon	Medulla oblongata
Caudal part of neural tube	Same	Spinal cord

From: Crossman and Neary (2000). *Neuroanatomy: An illustrated color text*. New York: Churchill Livingstone.

Disruption to neural tube development during the first few weeks often produces severely teratogenic outcomes. These typically involve structural anomalies of the CNS, such as a complete failure to develop major structural elements (e.g., anencephaly), to more minor structural flaws (e.g., myelomeningocele, encephalocele). Structural failures produced at this early stage of development frequently have catastrophic functional outcomes ranging from fetal death to serious mental and motor dysfunctions (Layde, Edmonds and Erickson 1980; Lynberg, Khoury, Lu and Cocian 1994; Milunsky, et al. 1992; Shiota 1982).
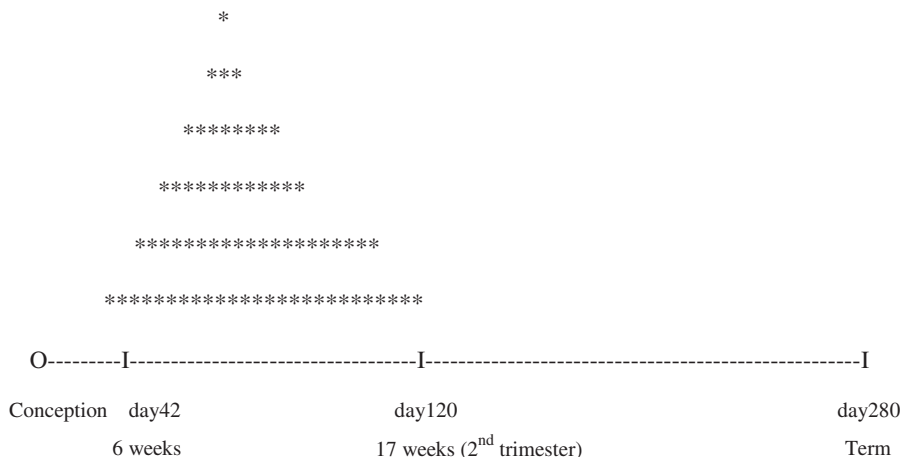
Although the rudimentary brain structures appear very early in life via differentiation of the neural tube along the longitudinal and circumferential dimensions, significant development along the radial dimension continues to occur throughout the prenatal period. Development along the radial dimension involves the processes of cell proliferation, migration and differentiation. Fig. 2.4 illustrates the timing of these processes.

Cell Proliferation

Cell proliferation is the molecular process by which the two types of cells (e.g., neurons and glia) that comprise the nervous system are created. Cell proliferation begins within the germinal matrix following closure (or "zipping") of the neural tube. The germinal matrix is comprised of ventricular and subventricular proliferative zones of cells that are, in turn, responsible for creating all the remaining structural and functional cells of the nervous system (Rakic 1992). Cell proliferation begins around the 40th embryonic day and is almost complete by the sixth month of gestation (Sidman and Rakic 1973), although cell proliferation continues in a few areas (cerebellar and hippocampal areas) even after birth (Bayer, Altman, Russo and Zhang 1993). Nonetheless, most of the neurons of the adult CNS are produced during the middle third of gestation (Nowakowski 1987). In the cerebral cortex, for instance, cell proliferation ends by about day 120 of gestation (week 17 of a 40 week gestation; see Fig. 2.5) (Rakic and Singer 1988).

Conception 1st trimester   2nd trimester   3rd trimester

O------4 wks----8 wks---12 wks----16 wks---20 wks-- -24 wks---28 wks---32 wks---Birth---4 mos-----2 yrs -----5yrs----16---18---60+

*****   ********************   **************

Neurulation Proliferation   Max Proliferation

                             ************************************* ******************************

                 Synaptogenesis   Competitive elimination

       ****

          Migration from the ventricular zone

       ****

       Cellular apoptosis

     ****

          myelination

       ****

     Dendritic and axonal arborization

Fig. 2.4 Timing of CNS Cellular Development. From: Giedd, J. N. (1997). Normal Development. *Child and Adolescent Psychiatric Clinics of North America*, *6*(2), 265-282

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Conception   day42   day120   day280
             6 weeks   17 weeks (2nd trimester)   Term

Fig. 2.5 Cell Proliferation in the Cerebral Cortex

All parts of the developing CNS have a ventricular zone. In some parts of the developing CNS there is an additional proliferative zone called the subventricular zone. This zone differs in several ways from the ventricular zone. Most of this difference is associated with the behavior of proliferating cells and the type of cells ultimately produced. Within the ventricular zone, for instance, there is substantial movement of the nuclei to and from the ventricular surface to the border of the ventricular zone with the subventricular zone and back again (Caviness, et al. 2003). This movement is depicted in Fig. 2.6.

On the other hand, proliferating subventricular zone cells do not move (See Nowakowski and Hayes 1999 for a more in-depth discussion of the cell cycle within the ventricular zone). Based in part on such behavior, it is thought that the subventricular zone primarily produces glial rather than neuronal cells (Nowakowski and Rakic 1981; Takahashi, Nowakowski and Cavines 1995). It has also been speculated that the subventricular zone is an evolutionarily newer cortical structure, compared to the ventricular zone (Sidman and Rakic 1973). Research typically posits that all of the neurons of the major subdivisions of the hippocampus (areas CA1, CA2 and CA3), an evolutionarily old cortical structure, are derived from the ventricular zone (Nowakowski and Rakic 1981). In contrast, the subventricular zone is believed to contribute large numbers of cells to the neocortex, the evolutionarily youngest structure in the brain (Sidman and Rakic 1982).

Cell Migration

Cells migrate from the two ventricular zones to their final positions. The timing of these events and ultimate destination of these neurons appears to be genetically
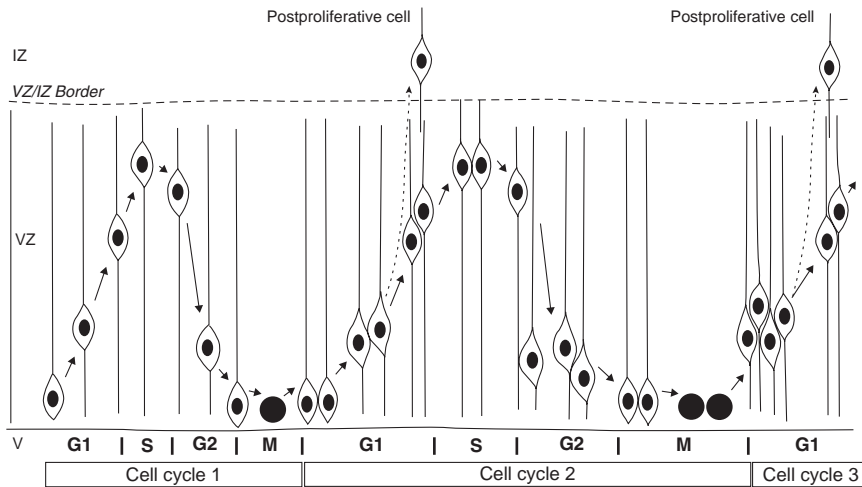
Fig. 2.6 Discussion of the Cell Cycle in the Ventricular Zone This diagram illustrates the up-and-down movement of the nuclei of the cells comprising the proliferative ventricular epithelium of the ventricular zone (VZ). With each pass through the cell cycle the nucleus of a single cell moves from its starting position at the ventricular surface at the beginning of G1 to the border of the VZ where it enters S. During G2, the nucleus again moves down the ventricular surface, where it enters M and divides to form two cells. With each pass through the cell cycle some postmitotic neurons are produced. The postmitotic neurons migrate away from the VZ to produce the structures of the adult brain (in this case the cerebral neocortex). (Copied with permission of Cambridge University Press from Nowakowski and Hayes 1999)

predetermined. The primary migrational activity occurs during weeks eight to 16 of gestation, with lesser activity continuing until week 25 (Kuzniecky 1994). There appear to be two forms of neuronal migration: passive and active (Hattan 1999; Hatten and Mason 1990; Nowakowski and Hayes 1999). Passive migration (cell displacement) occurs when cells are simply pushed away from where they originated by more recently generated cells (see Figure 2.7). In turn, these older cells are passively moved outward away from the proliferative zone. The result is that the oldest cells are located farthest from the proliferative zone. Passive migration is thought to lead to midline structures like the thalamus, dentate gyrus and regions of the brain stem (Altman and Bayer 1980; Bayer, Yackel and Puri 1982; Nowakowski and Rakic 1981).

Active migration requires that cells play a much more active role in reaching their final position. In contrast to passive migration, active migration occurs when younger cells move past older cells to the external regions of the brain, including the cerebral cortex (Rakic 1972; Sidman and Rakic 1973). Thus, the newly generated cells are located farthest from the proliferative zone, resulting in an inside-to-outside spatiotemporal gradient (see Fig. 2.8). Active migration is a big
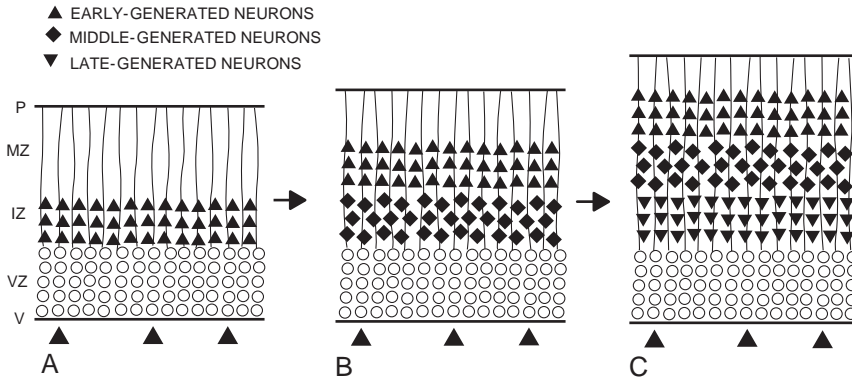
Fig. 2.7 Discussion of Passive Migration Some cells migrate only a short distance from the outer edge of the proliferative zone. When new cells are produced, the older ones are displaced outward away from the proliferative zone by the newly produced cells. (A through C) This sequence of events is illustrated as follows: (A) The first neurons to leave the ventricular zone are shown as triangles. (B) The next neurons to form (shown as diamonds) move away from the ventricular zone, displacing the earlier generated ones outward. (C) Finally, the last neurons to form (shown as inverted triangles) move away from the ventricular zone and displace both populations of earlier generated neurons. This sequence of events results in a specific distribution of neurons generally known as an outside-to-inside spatiotemporal gradient. V = Ventricular surface; VZ = ventricular zone; IZ = intermediate zone; CP = cortical plate; MZ = marginal zone; P = pial surface (Copied with permission of Cambridge University press from Nowakowski and Hayes 1999)

contributor to the development of the structures of the cortex, with different layers containing neurons with different migrational timetables (Nowakowski and Hayes 1999; Nowakowski, Cavines, Takahashi and Hayes 2002; Takahashi, Nowakowski and Cavines 1995). Migration is ultimately responsible for transforming the four fundamental layers of the telencephalic wall into the six-layered adult cerebral cortex. During the fifth gestational month, cerebral convolutions (e.g., sulci and gyri) appear. By the seventh month of gestation, all gyri appear and secondary and tertiary sulci become evident.

With an understanding of the mechanics of passive and active migration in mind, one understands that the final position of a neuron is linked to its time of origin. Researchers do not agree upon the actual mechanism by which cells "know" the location to which they should migrate. One of the more widely accepted theories suggests that radiating glial fibers direct migration to genetically predetermined regions of the brain in a complicated process that consists of at least three phases (Rakic 1978). At the beginning of a cell migratory phase a young neuron starts migrating by linking to a radial glial fiber. During the second or locomotor phase of migration the neuron moves along the surface of the radial glial cell. In the last phase of migration the neuron arrives at its final destination, detaches from the radial glial cell and is now ready for the process of differentiation. Recent research has focused attention on how

▲ EARLY-GENERATED NEURONS
◆ MIDDLE-GENERATED NEURONS
▼ LATE-GENERATED NEURONS
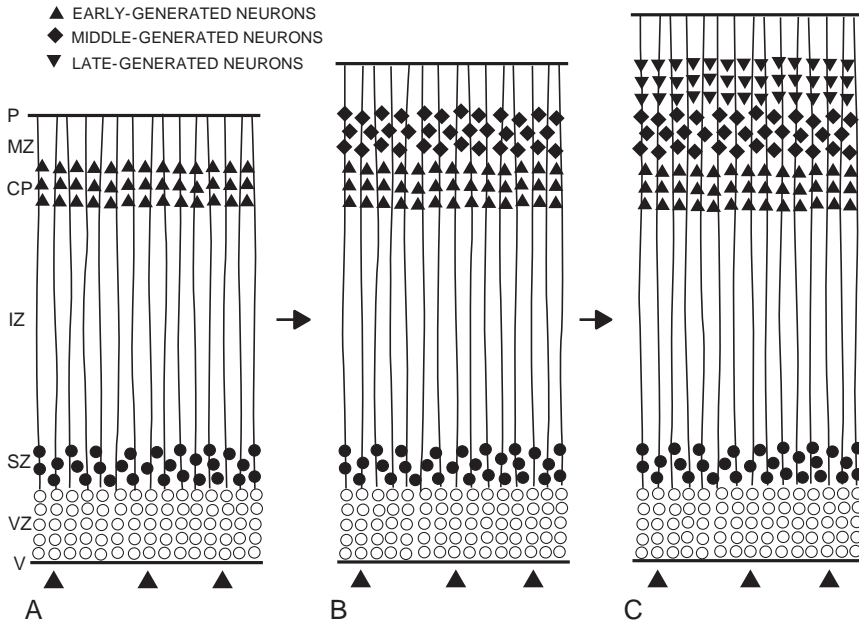
Fig. 2.8 Discussion of Active Migration Some cells may migrate a considerable distance from the proliferative zone. For example, in the cerebral cortex the later-generated cells bypass the earlier-generated cells and assume a position even farther from the proliferative zone. This is illustrated as follows: (A) The first neurons to leave the proliferative zones are shown as triangles. These cells form a cortical plate between the intermediate and the marginal zones. (B) The next neurons to form (shown as diamonds) leave the proliferative zones and migrate across the intermediate zone and past the previously generated cells to the top of the cortical plate. (C) The final neurons to reach the cortical plate are shown as vertical triangles. These cells have also migrated across the intermediate zone and past the previously generated cells to the top of the cortical plate. This sequence of events results in a specific distribution of neurons generally known as the inside-to-outside spatiotemporal gradient. V = Ventricular surface; VZ = ventricular zone; SZ = subventricular zone; IZ = intermediate zone; CP = cortical plate; MZ = marginal zone; P = pial surface. (Copied with permission from Cambridge University press from Nowakowski and Hayes, 1999)

reelin, a cell surface molecule, aides in directing neurons to their final position (Fatemi, et al. 1999; Nowakowski 1987). Additional research at the cellular and molecular levels is required to more precisely elucidate the mechanism of migration.

Cell Differentiation

Once neuronal and glial cells have migrated to their final positions these cells begin the process of differentiation. This starts by about the 25th month of gestation and does not finish until adolescence (Sidman and Rakic 1982). During the differentiation

stage axonal and dendritic properties become fine-tuned as cells transform into committed members of specialized systems. As a result relevant connections among neurons become established and begin to function. Axons involve presynaptic functioning while dendrites involve postsynaptic activity. Dendrites grow out and form an arborization (e.g., tree-like) pattern depending upon cell class. Dendritic growth begins after the completion of the migration phase (25 to 30 weeks), and continues at a relatively slow rate through adolescence. Synapses are over-produced up until about three years of age; thereafter, synapses are eliminated such that by adolescence, synaptic density is only about 60 percent of the maximum density that was achieved at age two (Aylward 1997).

Axonal development progresses via pioneer axons. Pioneer axons establish a chemical marker by which other axons recognize and produce selective contact with specific neurons and systems. These chemical markers are thought to be present only at selective periods during fetal development and guide the development and differentiation of the axon to its ultimate site. Although axon growth seems to occur primarily prenatally, axon development has been observed to occur postnatally in certain brain structures such as the corpus collosum, at least into early childhood (Nowakowski and Hayes 1999). There is some debate within the neuroscience community regarding the growth and evolution of axons. Some researchers suggest that axonal growth is genetically programmed while others indicate that environmental and experiential factors influence the connections that are formed and eliminated (Schore 2001). For instance, lack of environmental stimulation significantly disrupts dendritic growth (Kolb and Fantie 1989; Kolb and Gibb 1999).

Neuronal differentiation is also important for a number of formative processes, including the later formation of neurotransmitters and specific receptor cells at postsynaptic sites. Each differentiating neuron must distinguish which neurotransmitters it will ultimately use. Similarly, postsynaptic sites must express the receptors they will need to receive input from presynaptic sites.

Myelination

During neuronal differentiation the axonal myelination process begins (around six months gestation), but will not be completed until adolescence. Myelination refers to the process of covering the axon with a fatty substance (myeline) that serves the function of insulating axons. Myelination promotes rapid and efficient transmission of nerve impulses, like the insulation on an electrical wire enhances the transmission of electricity in your home. Prior to myelination the communication between neurons is approximately 50 to 100 times slower than what it is after myelination.

Alyward (1997) discusses several general rules by which axons myelinate. First, proximal pathways myelinate before distal pathways. Second, sensory pathways myelinate prior to motor pathways. Third, projection pathways experience myelination prior to association pathways. As an example, corticovisual pathways necessary for the visual-smile response experience myelination by the third postnatal month,

while motor cortex axons are myelinated by the first year of life. Fine motor development, as well as the maturation of the frontal lobes, is intimately linked to the myelination process.

Around the sixth month of gestation glial cells also begin the process of differentiating into oligodendrocytes and astrocytes. Oligodendrocytes are important for the genesis of myelin, while astrocytes have diverse functioning within the CNS, including repair of damaged tissue and removal of waste (Montgomery 1994). In the brain glial cells vastly outnumber neurons (10 to 50 times more).

Cell Death (Apoptosis)

During proliferation the number of cells created exceeds that which is needed within the mature CNS (Rakic, Bourgeois, Eckenhoff, Zecevic and Goldman-Rakic 1986). Some cells must be removed. This process has two distinct mechanisms: axonal retraction and neuronal pruning (Nowakowski and Hayes 1999). Axonal retraction involves recession of the collaterals of a neuron's axon or by a shrinking of the terminal arborization of the axon. Other connections are removed through selective cell death in which neurons die as a result of failing to establish appropriate connections (Hynd and Willis 1988). The retraction of axons and the death of cells are critically important to fetal brain and CNS development. Abnormalities in each process, selective cell death in particular, have been shown to lead to severe developmental abnormalities in experimental animals (Kuida, et al. 1996). Some research indicates that certain areas of the brain may experience up to 50 percent cell death (Oppenheim 1991). It is suggested, therefore, that neurons without appropriate connections become redundant and are eliminated according to a "use it or lose it" phenomenon. Cell death (apoptosis) is critically important for appropriate brain development (Zaidi, et al. 2001).

Summary

Within this chapter, we presented an overview of prenatal CNS development, emphasizing the processes occurring during the second and third trimester of pregnancy. The most important of these are cell proliferation, cell migration, cell differentiation, myelination and cell death. This discussion sets the stage for understanding the mechanisms by which the fetal brain may become perturbed, resulting in psychological and behavioral outcomes. Within each of the next chapters we discuss the mechanisms by which various factors such as smoking, illness, stress or infection can disrupt the developing fetal CNS.