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Chapter Eighteen

Prenatal Development and Risk

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Introduction

As is the case throughout infancy, normal fetal development demands constant and complex interactions between genes, environment, and the emerging organism. Although certain developmental pathways are more highly canalized than others, that is, resistant to perturbations, the opportunities for altering trajectories are infinite. Adverse effects range from abnormal morphological and physiological growth to risks for adult-onset disease. Maternal stress, nutrition, and exposure to toxins are some of the agents that can play a role in causing changes in fetal development, which have implications for long-term health and functioning.

Fuller appreciation now exists regarding the long-term implications of the prenatal laying down of brain–behavior relationships. Up until recently, much of the child development literature that has considered the fetal stage has primarily emphasized physical development and/or malformations, with a focus on teratological risk factors. However, the intensely dynamic nature of the developing, fetal brain–behavior relationships and the relevance of this process for future functioning are becoming more and more evident. These dynamic processes reflect continuous fetal adaptation to a changing uterine environment.

This perspective suggests a paradigm shift in the examination of influences on child development. Although it is common to consider the postnatal environment, from socioeconomic status to parenting characteristics, as greatly affecting the child's trajectory, fetal research points to the striking relevance of the prenatal environment for fetal as well as child development. The impact of the prenatal environment occurs on multiple levels, from biochemical factors influencing gene expression in the fetus's neuronal circuitry to characteristics of the mother's lifestyle affecting the fetal milieu.

More specifically, cells acquire identities, axons are guided from the periphery to target, synaptic connections are induced and reinforced, and other cells are programmed to die based on and shaped by exquisitely timed, complex interactions between the genes and environmental input. At another level, sensory development too is shaped by the prenatal environment. For example, what the mother ingests will affect not only the biochemical supply for fetal neuronal growth but the future child's eating habits as well. Flavors and smells, as well as protein and vitamins, are passed on to the fetus. Therefore, in addition to receiving the required nutrients, the future baby is learning food preferences too. Another way by which the maternal environment shapes the fetal environment is via maternal mood. For example, exposure to life stress affects maternal physiology and appears to be associated with long-term changes in their offsprings' future behavior and stress reactivity. These data suggest that mood-based alterations in maternal physiology amount to a changed environment affecting the fetus, although the precise mechanisms of such influence have yet to be established.

In what follows, we describe fetal neurobehavioral development throughout gestation and, in particular, focus on the role of the *in utero* environment in facilitating – and altering – fetal growth and behavior. Until recently, the richness and complexity of both fetal behavior and the *in utero* environment were inaccessible or largely ignored. The dynamic and complex nature of these fetal–environment interactions demands multiple perspectives as well as interdisciplinary research. Today, investigations from diverse disciplines such as epidemiology, obstetrics, neurobiology, genetics, neonatology, and psychobiology provide novel methods, perspectives, and results in the search for the fetal roots of human behavior.

The First Trimester

The Developing Embryo

The window of opportunity for environmental shaping of infant development actually opens prior to conception. For example, both male and female fertility is affected by nutrition and stress (Negro-Vilar, 1993; Wynn & Wynn, 1994), smoking (Adlerete, Eskenazi, & Sholtz, 1995; Fraga, Motchnik, Wyrobek, Rempel, & Ames, 1996) and alcohol consumption (Grodstein, Goldman, & Cramer, 1994). Once the sperm and egg unite, the genetic material from the mother and father combine to make a blueprint for infant development, but ample opportunity will arise for environmental input. Once the egg has been fertilized, it begins moving slowly through the fallopian tube to the uterus. The timing of its arrival is critical in order for the pregnancy to be sustained. The uterine lining is being made ready, under the influence of progesterone produced by the corpus luteum. It has been suggested that dieting can reduce the size of the corpus luteum, causing insufficient hormone levels to sustain pregnancy (Wynn & Wynn, 1994). Once the blastocyst reaches the uterus, it floats around for about three days, dividing continually. For conception to be successful, the ball of cells has now to implant in the wall of the uterus. Once the implantation has been successful, the embryo starts to secrete chemicals which enable signals eliciting a series of adaptations to the state of pregnancy. For example, the mucus in the cervix thickens to become a dense plug, which prevents any infection from entering the uterus and disrupting the pregnancy, and the immune system is modified so that the tiny embryo is not attacked (Roth et al., 1996). When the blastocyst implants in the uterine lining, the outer layer of cells, called the trophoblast, multiplies rapidly. These cells perform many important functions in forming various protective and support systems for the fetus. Some cells have already differentiated to form the amniotic sac, which will contain the amniotic fluid in which the fetus will develop, and the yolk sac, which is the early blood cell factory for the fetus. Some trophoblast cells fuse to form a protective cushion around the amniotic sac (the chorion), while others aggregate to form columns which stick to and then invade the uterine lining (chorionic villi). Recent research has shown that the formation of these columns is an essential part of first trimester placental growth, and that maternal smoking can actually decrease the number of columns that are formed (Genbacev, Bass, Joslin, & Fisher, 1995). Recreational exercise, on the other hand, is thought to have a beneficial effect and may even promote placental growth (Clapp & Rizk, 1992). Placental growth is largely dependent on the growth of these villi, which gradually lengthen and then the tiny blood vessels within them expand (Jackson, Mayhew, & Boyd, 1992).

The fetus is attached to the chorion via a short stem, which develops into the umbilical cord by 14 weeks of pregnancy. It is at the very tip of the thread-like capillaries within the chorionic villi that the exchange of oxygen and nutrients from the mother's blood vessels occurs. The blood of the fetus and mother do not intermingle (this is why mother and child can have different blood types): Instead, substances (both beneficial and harmful) diffuse through the thin membranes separating the maternal and fetal bloodstreams. Thus, the walls of the blood vessels act as a filter. The growth of the placenta is influenced both by hormonal control and by metabolism, and recent scientific evidence suggests that even some of the growth hormones may be under the influence of nutrients (Robinson et al., 1995). Not surprisingly, placental growth affects fetal growth and, as will be discussed later, research also suggests that babies who are disproportionately small at birth are at higher risk for coronary heart disease and hypertension in later life. It has been suggested that these diseases are "programmed" by inadequate nutrition to the developing fetus (Godfrey & Baker, 1995). (See subsequent section on Nutrition.)

Nervous System Development

During the first few months of gestation, a hierarchy of control systems emerges within the nervous system that largely determines what the fetus is doing and when. The hierarchical structure becomes more complex as the fetus develops. The more functions in the fetus's repertoire, the greater the need for organization by the nervous system. Initially, the fetus's behaviors are of a reflexive nature, and the circuitry controlling them may consist only of a few sensory cells directly connected to some motor cells, which may even be found in the spinal cord and work independently of the brain (Hofer, 1981). The spinal cord is made up of nerves that carry messages back and forth from the trunk and limbs to the brain. The types of behavior mediated by the spinal cord are likely to be the early movements seen starting around 7–8 weeks of the pregnancy.

The emergence of the senses follows a predetermined pattern of development that is similar in all mammals. The first sensory system to develop is touch. By about 9 weeks, if the area around the lips is touched, the fetus will respond by moving. By 12 weeks the fetus will begin to make grasping movements when the fingers are touched. The sense of taste and smell becomes functional next, then the vestibular system, which gives a sense of balance and position at 14 weeks. The auditory system begins to function at about 21 weeks, and finally vision at 26 weeks. It is fascinating that in the development of all of these senses, the systems work *in some basic way*, even before they are anatomically complete (Hofer, 1981). In terms of memory, language and thought, the control and integration of movement and the senses, the primary part of the brain responsible is the cerebral cortex, the outer crust of the hemispheres. For the first two or three months of pregnancy there is relatively little development in this "crust." It is not surprising, therefore, that behaviors emerging before this time, for example, early fetal movements, are largely reflexive and are controlled via simpler circuits that arise in the midbrain (Flower, 1985).

The cerebral hemispheres develop from the forebrain at about 9 weeks and rapidly increase in size, expanding to form different regions that will later become highly specialized. By mid-pregnancy, the cerebral hemispheres have expanded so much that they cover the rest of the brain. By the fourth month of pregnancy, the cells in the cerebral hemispheres begin to proliferate and migrate (Lou, 1982). As these higher centers of the brain develop, and more neural inputs become active, increasingly sophisticated messages can be sent from the brain. Particularly important at this time is that the process of inhibition becomes functional. This means when the fetus's brain sends a nerve impulse to the muscles, instead of only being able to cause movement, it can now begin to modify it. Consequently, this eventually leads to better control and refinement of movement. A by-product of this process is that at about 15 weeks there is a bit of a lull in activity. This is followed by a period of reorganization of behaviors: reflexive circuits are still in place, but these are now "controlled" by more sophisticated nerve cells in the new "higher" brain centers.

Emerging Behavioral Repertoire

One of the earliest movements the child will make is a startle, where the fetus's arms and legs shoot outwards in abrupt fashion. These occur at about 8 weeks of pregnancy. Within a week following this, the child will make graceful general movements of the head, trunk, and limbs. A stretch is usually seen for the first time at about 10 weeks: the fetus's head moves back, the trunk arches, and the arms are lifted into the air. Yawning usually begins a week later (DeVries, 1992).

Why does the fetus move so much? In a sense, it is because she is unable to stop. The neural circuits that control movement are very rudimentary at this time. Early in development, the circuit may be confined to the spinal cord, which is made up of nerve fibers carrying messages back and forth to the trunk and limbs. As the child develops, so these pathways become more sophisticated, and connect in the midbrain. This is the most significant center of neural activity in the brain up until mid-pregnancy

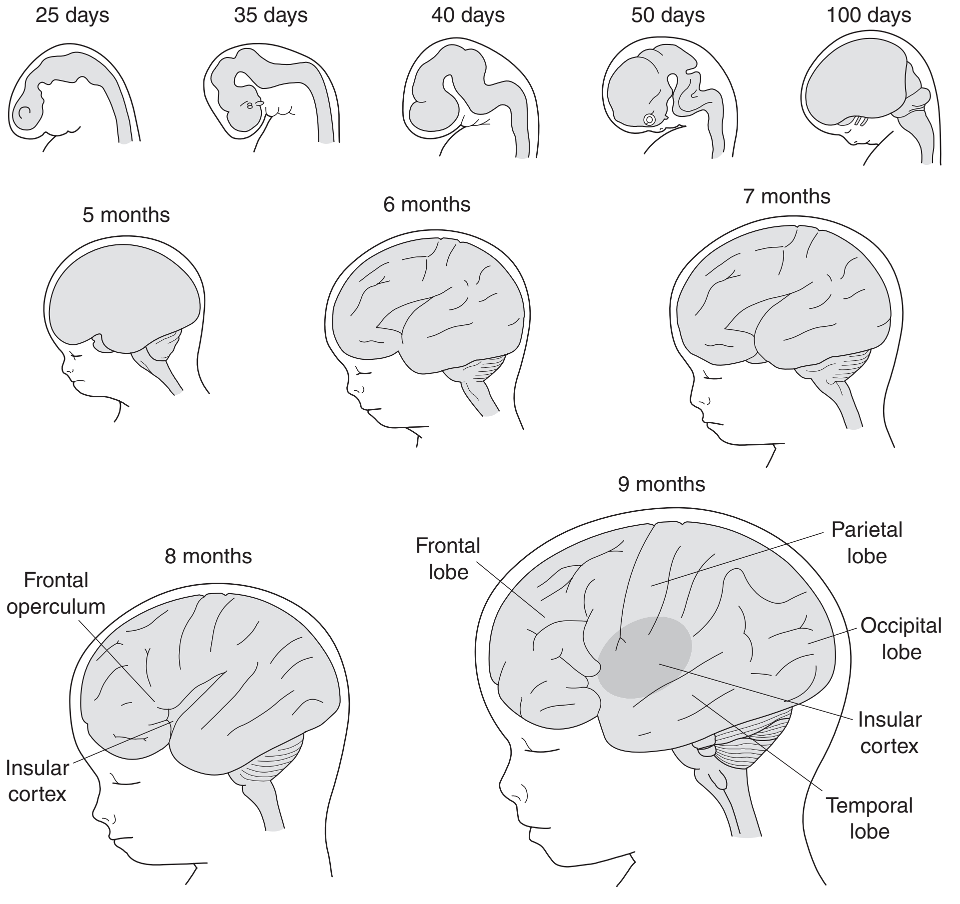

Figure 18.1 Brain centers.

(Flower, 1985). Once these early nerve cells start firing, the fetus starts moving. It is not until the birth of nerve cells which inhibit behavior and which can modify the action of these primitive circuits that the fetus has longer periods of rest (Hofer, 1981). Many more neurons than are needed develop between the limbs and the brain, and once the full range of co-coordinated movement is established in the fetus, some of these cells die off. It appears that fetal movement is necessary in order for the physical systems to develop normally and stimulates further development of muscles, tendons, and ligaments (DeVries, 1992). If muscles are immobilized during development, then joints can fuse and make future movement an impossibility (Pittman & Oppenheim, 1979). Additionally, frequent changes in position, head rotations followed by rump rotations, alternating extensions of the legs and bending the head backwards may promote better circulation and help to prevent skin from sticking together and forming adhesions (DeVries, 1992).

These motor behaviors result in the movement of amniotic fluid through the fetal body. Originally it was thought that a major role of this fluid was a protective one, since it cushions the fetus when the mother moves around. However, it now

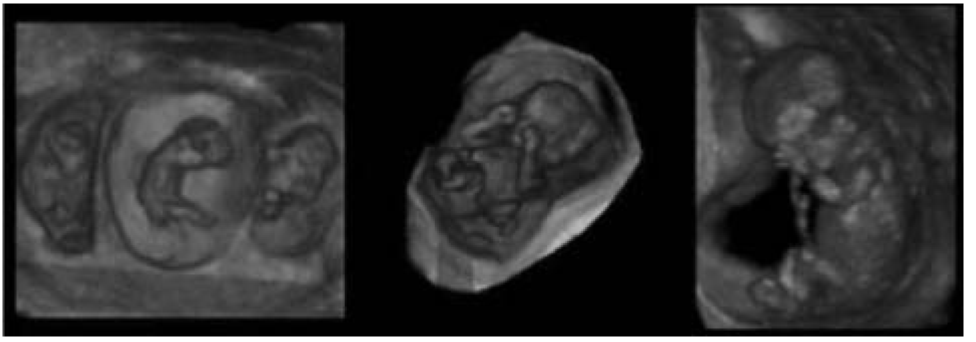

Figure 18.2 From left to right, photos are images of first trimester fetuses captured by noninvasive 3D ultrasound. Photo 1 is 11-week-old triplet fetuses, photo 2 is a 12-week-old fetus with arms brought to face, and photo 3 is a 13-week-old singleton fetus. (Photos courtesy of (1) Dr. Martin Metzenbauer, Austria; (2) Dr. Armin Breinl, Austria; (3) Dr. Leonardo Mandujano, Chile)

appears that the movement of amniotic fluid through the fetal body is extremely important for normal structural growth of the fetus, particularly in relation to lung and gut development (DeVries, 1992). It is likely that movement alone, when amniotic fluid passes through the fetal body, provides physical stimulation for the development of certain structures, such as the mouth, jaw, and palate. Jaw opening can be seen in the fetus toward the end of the first trimester. The emergence of sucking follows closely behind (DeVries, 1992). When the fetus sucks, her jaw opens and closes rhythmically at a rate of about once a second. When her mouth opens, her tongue is pushed against the roof of her mouth, creating suction and causing the amniotic fluid to move in and out. This pressure is probably responsible for the positional change of the bones in the palate at this time, and the prevention of cleft palate formation. It seems likely that early sucking could serve as "preparatory exercise" for nursing once the fetus is born (Prechtl, 1984). In addition to its later nutritive role, sucking may provide comfort to the newborn and perhaps even the fetus. Amniotic fluid surrounds the fetus and is contained within a membrane called the amniotic sac. This fluid is thought to be produced initially by the amniotic membrane itself. Later on, the fetus's lungs and kidneys are also important contributors to amniotic fluid. The vessels of the umbilical cord also may be involved in amniotic fluid production (Gebrane-Younes, Hoang, & Orcel, 1986). The exact composition of amniotic fluid varies throughout pregnancy, and a major constituent is fetal urine (Seeds, 1980). This fluid contains a high percentage of water, but its constituents are also thought to play a minor role in fetal nutrition. It has been suggested that amniotic fluid may provide 10 to 14 percent of the nutritional requirements of the fetus, but also contains some important growth-stimulating factors for the gastrointestinal tract (Mulvihill et al., 1985).

Once the child is born, breathing is of course necessary for the exchange of blood gases. In the fetus, breathing movements are thought to be vital for lung development, even though they do not cause any exchange of blood gases. These movements are usually seen for the first time around the end of the first trimester (DeVries, 1992). Sometimes just one breathing movement is made, often resembling a sigh, whereas at other times there may be short periods of regular or irregular breathing movements. Although fetal breathing does not cause amniotic fluid to move in and out of the lungs themselves, they do cause large changes in tracheal pressure and to-and-fro flow within the bronchial tree. The lungs are liquid-filled throughout fetal life. The lung liquid is produced by the lungs themselves and leaves by the trachea, where then it is either swallowed or exits the mouth into the amniotic fluid. This liquid keeps the lungs distended, which is necessary for them to develop properly. The volume of lung liquid is regulated by the resistance provided by the upper airways. During breathing movements, the larynx is dilated and resistance to the lung liquid is reduced; however, contractions of the diaphragm retard liquid loss during breathing movements (Hooper & Harding, 1995). Since neural control is operating at a very basic level at this stage in development, hiccups are seen more frequently than breathing movements, although both result in the movement of the diaphragm. This is probably because hiccups represent a reflexive type of behavior, whereas breathing reflects the development of more advanced motor patterns which currently are immature (Stark & Myers, 1995).

The Earliest Sensations

At the same time that the fetus is beginning to move, she is also developing a sense of touch. By about the ninth week of pregnancy, the fetus responds when her lips or the area around the mouth is touched. Initially the fetus moves her head and neck away from the source of touch, often with her mouth open: Later in pregnancy, the fetus will move toward the "touch." This is the precursor of the "rooting reflex," which helps the baby to find the nipple for nursing. Similarly, a little later in development, if the palm of the fetus's hand is stroked then her fingers will close for a moment and the toes curl if the sole of the foot is touched (Hepper, 1992). Once the fetus starts to move around she will be touching the uterine wall, the umbilical cord, and also herself. The fetus will touch her own face more frequently than any other body part. So the fetus is provided with a wide breadth of physical sensations which probably help to promote further development of the physical sensation of touch.

The Second Trimester

The Visual System

By the fourth month of pregnancy, the gross structures of the eyes are almost completely formed. The muscles of the eyes are not yet fully formed, but the eyes are already beginning to make movements. The fetus's eyes will sometimes make slow rolling movements, or faster movements that may be smooth or jerky in nature. These movements are probably important for further muscle development. Behind the lens, the neural part of the eye and its supportive network of tissues are developing. As yet, the light-sensitive cells – the rods and cones – are only present in the central area of the retina. However, the nerve cells that will connect with these light receptors have already grown long fibers or axons that have already reached the thalamus. This is considered to be the first relay station for visual information, which is then sent to higher centers of the brain. The lower visual pathways are now considered to be complete. In about the fifth month of pregnancy the cells within the thalamus become specialized to deal with various aspects of visual information, such as color, fine detail, and so on. Even though the connections may be present between the thalamus and the cortex, there is fairly little differentiation within the visual cortex at this stage in development.

The Chemosensory System

Chemosensory development encompasses both the gustatory and olfactory senses, but it is difficult to say exactly what the fetus can smell and taste. Both flavors and smells from the mother's diet can pass into her bloodstream and then into both the amniotic fluid and fetal blood. There are three possible sites where "chemosensation" can occur during development: the nose, the mouth, and via the bloodstream itself (Schaal, Orgeur, & Rognon, 1995). The fetus swallows amniotic fluid regularly throughout the day. This fluid passes into the stomach, where it will then be broken down further and sent to other organs, the brain, liver, and kidneys, before it is expelled from the bladder back into the amniotic fluid again. During the fourth month, the plugs of tissue that were previously blocking the nostrils have gone, and when the fetus "inhales," amniotic fluid also passes through the nose. The fetus actually inhales twice as much fluid as she swallows (Duenholter & Pritchard, 1976), so the sensory receptors within the nose are continuously being bathed in amniotic fluid. During the second half of pregnancy, the constitution of amniotic fluid becomes increasingly dependent on fetal urination. This may be particularly important for stimulation of the chemosensory system, since it contains large amounts of ammonia-smelling urea.

Flavors and smells from the food consumed will also pass into the bloodstream after digestion. These will then pass via the placenta into the fetal circulation blood. Unlike the amniotic fluid, the smells and tastes within the blood have not been broken down or metabolized and are relatively undiluted, and consequently more intense. The blood will flow in tiny capillaries through the fetal nose and mouth and therefore have ample opportunity to diffuse into the sensory apparatuses that detect smell and taste. It appears that nearly all babies show a preference for sweet substances over bitter. If the amniotic fluid tastes sweet then the fetus will swallow more regularly than if it contains bitter substances (Hepper, 1992). Not surprisingly, after a meal and when glucose levels rise within the maternal bloodstream and the amniotic fluid, there is more breathing and swallowing. The amniotic fluid probably tastes sweeter as a result of the additional glucose. Swallowing by the fetus will also regulate the volume of the amniotic fluid. While some of the fetus's ability to detect and prefer certain flavors over others may be genetically determined, other preferences may be learned *in utero*. Exposure to alcohol while in the womb has been shown to increase fetal swallowing and may cause preferences for alcohol later in life (Molina, Chotro, & Dominguez, 1995). It appears that preferences for smells may be more individually tailored for individual babies, depending on what flavors and smells they have been exposed to during life in the womb. Research with newborns has shown that babies can recognize the smell of their mother's breastmilk, and it has been suggested that this arises through the early learning about their mother's diet that took place in the womb. This has been particularly supported by studies that have shown that if a mother dramatically changes her diet after her pregnancy, her baby may have a more difficult time learning to suckle (Hepper, 1988).

The Vestibular System

As described above, the fetus does a lot of moving around *in utero*, constantly changing position within the warm amniotic fluid that cushions her from the outside world. Additionally, since the mother is moving about for much of the day, the fetus is also subjected to constant passive motion and will experience positional changes relative to gravity, depending on whether the mother is standing up, sitting, or lying down. This information is sensed by the vestibular apparatus consisting of three semicircular canals, set at right angles to each other within the fetus's inner ear. These canals are fluid-filled and when the fetus moves (or is moved) the fluid within at least one of the canals will move, stimulating tiny hairs within the canal lining. Depending on the direction and plane of movement, one semicircular canal may be stimulated more than another. This information is then sent to the brain to be processed and information about motion and position extracted.

Although it is difficult to elicit responses to vestibular stimulation in babies *in utero* (Hepper, 1992), this does not mean that this system is not functioning. By 25 weeks, the fetus will show a righting reflex (Hooker, 1952), and it is possible that the vestibular system is in some way responsible for most babies lying head down prior to delivery. We do not know exactly how much information about position and motion the fetus is actually processing at this time. We do know that the system is actively being stimulated, and that this stimulation is very important for many aspects of normal fetal growth and development. Vestibular stimulation plays an important role in changing arousal states, and this will become more apparent as time goes on. Initially, during the pregnancy, the fetus is often quiet when the mother is moving about a lot and causing a lot of vestibular stimulation. In contrast, when the mother is lying down at night, the fetus is receiving minimal vestibular stimulation and is often at her most active. Once the fetus is born, the parent will probably instinctively rock the fetus when she is fussy or to put her to sleep. Again, the vestibular system is being stimulated and may play a role in eliciting changes in the arousal state of the child. The level of vestibular stimulation received by the fetus during the pregnancy is particularly high. The activity alone provides a level of stimulation to the vestibular system that will probably not be matched until the baby starts to independently walk (Hofer, 1981). Studies of preterm infants (who are deprived of the vestibular stimulation that would have been provided by their mother's movement) have detected lags in neurobehavioral development which may in part be due to a lack of vestibular stimulation. Weight gain, visual responsiveness, and even later expressive language development have been shown to be improved if the incubator is gently rocked

(Masi, 1979). Along the same lines, if preterm babies are put on waterbeds instead of mattresses, the rocking movement of the water may compensate for the vestibular stimulation that they missed out on *in utero* and may result in better sleep organization (Korner, Schneider, & Forrest, 1983).

Brain Development

Month five is a time of considerable growth and reorganization within the fetus's brain. Much of the basic circuitry that controls reflexive acts is already in place in the spinal cord and the brain stem, the swelling at the top of the spinal cord. These areas of the brain will control many of the basic functions that the fetus will need to survive, such as breathing and temperature regulation. Other more sophisticated actions need more "processing" by the brain, and it is the cerebral cortex within the cerebral hemispheres that is responsible for this. This is a particularly important time for development within the cerebral hemispheres, which have now grown so much that they cover the rest of the brain (Cowan, 1979). They develop fairly late in relation to other brain structures and have a much longer developmental time course, not reaching full maturation until nearly adulthood. Maturation of the cerebral hemispheres is marked by three main events: First, the generation of nerve cells from the initially thin walls; second, the migration of cells to specific areas of the brain; and third, differentiation of the cells to become specialized to perform specific tasks (Kandel et al., 2000). Developmental neurobiologists have begun to discover the intricate intracellur processes, including complex gene–environment interactions, leading to cell birth, differentiation, and survival as well as the pathways by which axons reach their target neurons and how synapses are formed and elaborated.

Neural cells are rapidly generated in the walls of the cerebral hemispheres, starting around the third month of pregnancy. This process is still continuing at a rate of thousands of cells per second. Consequently, many more brain cells than ever will be needed by the fetus are created, and a normal part of further brain maturation is the pruning of some of these cells, often after the fetus is born. It may be that the excess of nerve cells is created as a safety measure. If some brain cells are nonfunctional or become damaged during development, others may be able to take over (Kandel, 2000).

As the cells are generated, so the process of migration begins. Each cerebral hemisphere is divided into four lobes, frontal, temporal, parietal, and occipital. Each of these lobes is thought to deal with specific functions. The frontal lobe is generally thought to be associated with movement. The parietal lobe is concerned with sensation of touch, pain, and limb position. The temporal lobe is important for hearing, memory, and a sense of self and time. The occipital lobe is the visual center of the brain. How do the newly generated brain cells know which area of the brain they have to migrate to, and how do they get there? It is likely that the actual vicinity where the brain cell was generated will in part determine its final location. However, there are probably other factors, such as the time or order in which the cells are programmed to migrate, that enter into the equation (Rakic, Stensas, Sayre, & Sidman, 1974; Sidman & Rakic, 1973). In addition to the nerve cells themselves, a network of supporting glial cells is growing; these provide support both structurally and functionally to the nerve cells. The glial cells form a supportive scaffolding for the nerve cells to migrate along to the surface of the cerebral hemispheres (Rakic et al., 1974). This migration causes the outer layer of the cerebral hemispheres to become densely packed with cells, and the outer surface takes on a grayish appearance, hence the name gray matter. Below this, many fibers from other deeper and earlier-formed nerve cells are invading the cerebral cortex, forming a whitish zone (white matter). Once formed, the nerve cells in the cerebral hemispheres will also send out nerve fibers to other nerve cells throughout the brain and the rest of the body. These too will pass through the white matter. Once the nerve cells have reached their target area in the cortex, they tend to form into distinctive layers.

It is likely that the generation of nerve cells has stopped in the cerebral cortex. However, the fetus's brain is continuing to grow in size and complexity. The bodies of the nerve cells themselves increase in size and, even more strikingly, the wiring between nerve cells has increased enormously. In order to contain all this nervous tissue within the relatively tight quarters of the fetus's skull, the brain surface begins to crumple up, forming grooves and humps (Cowan, 1979). The nerve cells themselves have to form many connections. This phase of neural development is progressing rapidly at this time. Messages from a nerve cell are sent via axonal processes. The axons usually travel long distances to connect with cells in specific areas of the brain or the rest of the body. For instance, a nerve cell in the motor cortex might have to make a connection with a muscle in the fetus's leg. A growth cone forms, which sends out tiny tubes that attach and then retract, pulling the growth cone forwards. It appears that the growth cone knows where it is going and with which structures it should make connections. The tube makes contact with many structures and "feels" the surface of the cell membranes, ensuring that connections only occur with those that are specific to the nerve cell and its axon (Lund, 1978).

In addition to brain development resulting from nerve–axon connections, nerve cells also make important links with other nerve cells via dendrites. When a nerve impulse travels along the axon and reaches the gap that separates it from the dendrites of the nerve cell, it causes the release of chemical substances into the gap which then act on the dendritic spine, causing the impulse to be transmitted to the connecting cell across the synapse. Cells that do not have many connections will be eliminated later in development. Connections are strengthened by experience; this is probably why fetal behavior and the *in utero* environmental factors that can impact on emerging fetal behavior are so important for normal development. A good example of this is seen with the fetus's early movements. Every time the fetus moves, nerve impulses are sent back and forth from the brain to the limbs, strengthening the connections between the synapses and ensuring that these movements continue to mature. It is known that early in development, one nerve cell may activate many muscle cells in a limb. However, as more nerve cells form connections, something closer to a 1 : 1 relationship develops between nerve cells and muscle cells, and the earlier connections from just one nerve cell become eliminated. This in turn allows for more sophisticated types of movement to develop (Hofer, 1981). Fetal breathing – which is dependent on nerve communication between the brain and abdomen, lungs, and thorax – is seen less frequently in fetuses of women who smoke and, as a consequence, these babies often have lung-related problems at birth (Milner, Marsh, Ingram, Fox, & Susiva, 1999).

In the sixth month of the pregnancy, axons begin to be myelinated. The myelin acts as an insulator for the nerves and prevents the leakage of the nerve impulses. This leads to an increase in speed in travel for the nerve impulses, which then results in a more fluent and rapidly responding system. Although myelination begins around the sixth month of pregnancy, this is really limited to the lower centers of the brain and by birth much of the baby's brain will still be unmyelinated. It is likely that the first area of cerebral cortex that undergoes myelination is the primary motor cortex, the area of the brain that controls the fetus's movements. The first nerve cells that become functional are those which control the trunk and arms, and these also become myelinated well before those governing leg movement. This is why babies will have relatively well coordinated arm and hand movements long before they begin to walk (Kolb & Wishaw, 1985). The primary sensory areas of the cortex concerned with processing information from the sense organs also mature after birth. Those fibers that are responsible for touch become myelinated first, followed by the primary visual system and then the auditory system. Among the last nerve fibers to become myelinated are those that belong to the corpus callosum, the bundle of fibers that connect one side of the brain to the other. Higher brain centers that integrate information are not completely myelinated until puberty. Although systems can still function in the absence of myelin, its formation leads to better neuronal stability and to a large increase in the speed at which messages between the nerves can travel (Hasegawa et al., 1992). It is estimated that the speed of transmission probably triples to over 60 ft per second once the nerves become myelinated (Purpura, 1975). The myelin coating is not of a uniform thickness, but becomes constricted at regular intervals. These constrictions in the myelin are called the Nodes of Ranvier, and the nerve impulses are thought to jump from node to node. The thickness of the myelin determines the speed of the transmission, and thickness continues to increase over a long period, for example, for about two years in the visual system (Magoon & Robb, 1981). The formation of myelin can be affected by multiple factors; prenatal exposure to lead may lead to problems with myelination, as can insufficient fat and fatty acids in the young infant's diet (Lampert & Schochet, 1968).

Expanding Behavioral Repertoire

Pregnant women may be just becoming aware of a faint fluttering sensation associated with fetal movements and a dramatic behavioral shift in activity reflecting major reorganizational changes within the brain. The neural circuits that can turn off or modify body movements (inhibitory pathways) are beginning to be in place, enabling distinct periods of rest instead of the almost continuous activity that occurs during the first trimester (Hofer, 1981). The repertoire of body movements remains the same as those seen in the first trimester, but what has changed is the frequency of the various movements (Nijhuis, 1995). There are now fewer startles, stretches, and general body movements. In the first trimester hiccups were one of the most frequently observed body movements, but now these occur much less often. However, breathing, another activity that also results in diaphragm movement, is becoming more frequent, increasing from an incidence of about 5 percent of the time to about 30 percent of the time (Visser, 1992). During these intervals breaths occur about once every second. Since breathing movements require a lot of energy, more breathing movements occur after a meal, since glucose levels are higher and more energy is available (Mulder, 1992). As described previously, although breathing movements do not result in any exchange of amniotic fluid, these prenatal movements are thought to be important for lung development. In addition to increased breathing, there is also an increase in the number of eye movements. Organized bursts of activity emerge followed by gradually lengthening periods of rest, with periods of total inactivity lasting up to 20 minutes.

The Auditory System

By the beginning of the sixth month, the auditory system ear is sufficiently developed to respond to sound. However, neither the ear nor the brain areas serving hearing are completely formed at this stage. One major immaturity can be seen within the sensors of the ear itself, i.e., the tiny hair cells within the cochlea, which vibrate when stimulated by sound and convert these vibrations into electrical messages that are then sent to the brain. Another immaturity is apparent within the nerve fibers which carry these messages. Consequently, the fetus's ability to hear different sounds is somewhat limited by these factors. However, almost all frequencies can be heard, although lower frequencies will be heard better than higher-pitched sounds (Abrams, Gerhardt, & Peters, 1995). The sounds that the fetus hears have to pass through various maternal tissues, which effectively cut out the higher frequencies; consequently, those sounds entering the fetus's ears are predominantly low-frequency ones. However, even though the auditory environment of the fetus is largely limited to lower-frequency sounds, it is quite varied. These include the background noises of mother's pulsing heartbeat, which changes constantly as both mother and fetus move and when maternal pulse and blood pressure change. Borborygmi are the gastrointestinal sounds associated with digestion, and these are part of the fetal sound experience. Mother's voice is by far the most frequently heard and loudest sound (Fifer & Moon, 1995). However, there is no unambiguous way of determining exactly what the fetus is hearing, since the mother is listening to sound traveling through air, whereas the fetus is listening to sound that has traveled through the amniotic fluid with no air spaces on either side of the eardrum. Furthermore, the rest of the auditory system is still immature, and so we do not know how well these sounds are converted into electrical signals by the sensors in the ear, or what the fetus's brain makes of these messages. However, we can learn something about what the fetus is hearing by looking at her response to sound (Hepper, 1992).

At this age, fetus's hearts beat faster in response to most sounds. Very loud sounds will result in a very fast heart rate. As the fetus gets older, her response will change based on the sound intensity, how deeply she is sleeping, and how familiar she is with the sounds (Lecanuet, Granier-Deferre, & Busnel, 1995). The fetus will also respond to some sounds by moving her limbs, or sometimes by stopping her movement in the middle of a high-activity period. One study has shown that fetuses will actually startle and empty their bladders following the loudest of sounds (Zimmer, Chao, Guy, Marks, & Fifer, 1993). Changes in brain electrical activity during sound stimulation have been measured

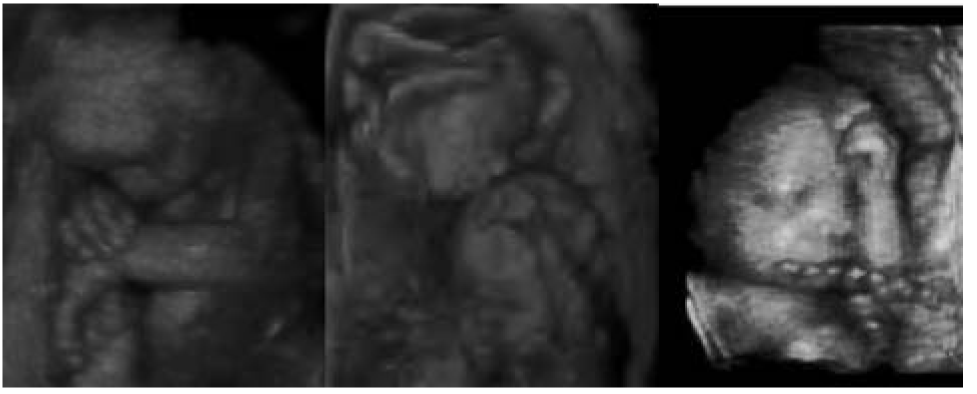

Figure 18.3 From left to right, photos are images of second trimester fetuses captured by noninvasive 3D ultrasound. Photo 1 is a 27-week-old fetus with limbs intertwined, photo 2 is 23-week-old twins, and photo 3 is a 23-week-old fetus showing face, arm, and umbilical cord. (Photos courtesy of (1) Dr. Armin Breinl, Austria; (2) Dr. Armand Vergnaud, France; (3) Dr. Juan Carlos Pons, Venezuela)

in prematurely born infants by 27 weeks gestational age. Sounds are thought to cause permanent changes in the developing auditory system which are probably required for normal brain maturation. Permanent changes are also reflected in newborn perceptual capacities and sound preferences as a newborn. Areas of the brain devoted to processing and remembering "multimodal" stimulation are probably also affected, since during some sound experiences several senses are activated at once. For example, when a mother speaks, her diaphragm moves, resulting in movement of the fetus; consequently those pathways that sense pressure, touch, and balance are also stimulated along with the auditory system.

The Third Trimester

The Visual System

By the seventh month of the pregnancy, the fetus's eyelids are no longer fused closed. The fetus will spend some time with her eyes open and will now be making blinking movements. Externally, the fetus's eyes will look fully formed. There are some still some minor immaturities in their gross structures, but the major source of immaturity in the fetus's visual system is within the neural structures of the eye, the retina, and the pathways to the brain. Nonetheless, if the fetus were born now, she would have some vision, even at this early age. Babies of this age can easily distinguish between light and dark (Taylor, Menzies, MacMillan, & Whyte, 1987) and have the ability to discriminate form to some extent (Dubowitz, Mushin, Morante, & Placzek, 1983). Certainly by 30 weeks of age, the premature newborn is able to see patterns of fairly large size provided that they are of sufficiently high contrast (e.g., black stripes on a white background) and fairly close to the baby's eyes (Grose & Harding, 1990). The fetus does have the basic "equipment" to be able to see, even though this ability is really not in use until birth. The lighting within the uterus is very poor. Only the very brightest of lights might provide a reddish glow but would not be sufficient even for an adult visual system to distinguish shapes clearly. The part of the brain associated with vision has a fairly protracted development, not surprising given the level of sophistication of the mature visual system. At this stage in development, the basic layered structure of the primary visual cortex is complete. The cells from the thalamus connect predominantly to the fourth layer of the visual cortex. The next important stage in visual development, the formation of many connections between the neurons in the visual cortex, is just beginning this month. These connections continue to develop postnatally, until the child is about 8 months of age (Huttenlocher & DeCourten, 1987). The most rapid period of connective development occurs after birth when the fetus's visual system is being stimulated by the external world. At this point in time the baby is probably relatively near-sighted. However, by the time she is due to be born, the relative growth of the cornea and eyeball will compensate for this (Weale, 1982). Even though the curvature of the cornea and the length of the eye are coordinated by the time the baby is born, immaturities within the lens or perhaps the muscles working the lens will result in the baby having a relatively short range of focus. This is perfect for the task in hand, looking at the faces of the people that are holding her. The ability to focus on objects across the room will soon develop in the first months of life.

Physical Growth

Up until the beginning of the third trimester, much of the energy provided by the mother's diet has been used in forming the fetus's body and internal organs. Pigmented fatty tissue, brown fat, is now laid down on the fetus's muscles and under the skin, and as time goes on, so the size of the cells in the fatty tissue increases, leading to a thickening of this layer. Although the fetus is currently protected in the warm environment of the amniotic fluid and has no need to regulate her own temperature, this layer of insulating fat is important since it will help the fetus to maintain a constant body temperature once outside the womb. In addition to preventing heat loss by providing a layer of insulation, brown fat cells are actually capable of producing heat themselves. By the time the fetus is full-term there will be large stores of these concentrated in her back and neck. Ensuring an adequate maternal diet and a healthy lifestyle will enhance this important "fattening up" of the fetus's body. This is a time during which the fetus's size increases rapidly, and in the final month of the pregnancy the fetus will be gaining as much as 1 oz per day. Adequate maternal nutrition has been shown to be important in the formation of adequate fat deposits, and fasting during the last three months of pregnancy can dramatically alter this process (Lumey, Stein, & Ravelli, 1995). A daily caloric intake of approximately 2700 calories is thought to be necessary to maintain a healthy pregnancy. Prenatal exposure to tobacco and alcohol have also been shown to have an inhibitory effect on fat deposition in fetuses. A failure to acquire adequate fat deposits will also contribute to lower birth weights in these babies (Haste, Brooke, Anderson, & Bland, 1991). Low-birthweight children are not just poor at temperature regulation; these infants are at greater risk for many developmental problems, as will be described below in more depth.

Behavioral Organization

The fetus's behavior is becoming progressively more organized as she approaches term. She is no longer the continually moving creature of five months ago; instead she has distinct patterns of rest and activity. In fact, two dominant patterns of behavior have now emerged. The fetus will spend most of her time either in active sleep or quiet sleep. By this stage, the fetus will only be spending about 20 to 30 percent of her time in a deep sleep state, where she will remain motionless, her heartbeat steady, and her breathing movements when they occur are rhythmic. Not surprisingly, this state is known as quiet sleep. For most of the rest of the time the fetus will not be awake but in a state similar to neonatal active sleep. The fetus initiates many different body movements in this sleep state and the eyes move rapidly back and forth and open periodically. Heart rate and breathing patterns will tend to be irregular and the fetus will be responsive to the sensory stimuli that she is naturally exposed to in her uterine environment. During periods of active sleep the fetus may be more reactive to sounds and touch. Consequently most of the time, the fetus's brain is "buzzing" with electrical activity as messages about her environment are constantly being sent from her sense organs to the brain, and other signals generated by the brain itself are sent all over her body. In this way, many muscles and organs are all being stimulated or "exercised." It is thought that this level of activity is probably necessary for adequate development and further maturation of the vital organs and the nervous system. This is borne out by studies of mothers who took certain types of medication (chiefly for hypertension and depression) during pregnancy. These drugs were shown to reduce the amount of active sleep their babies experienced and as a result these babies were shown to have smaller heads, brains, brain cells, and fewer brain connections (Mirmiran & Swaab, 1992). The putative advantage of being able to carry out all this activity in a state of active sleep rather than wakefulness is to conserve energy.

The fetus is making fewer general body movements now – these movements probably only occur about 15 percent of the time. The fetus is also making breathing movements fairly frequently (about 30 percent of the time) and there is a barely perceivable slowing in the rate at which she breathes in comparison to one month ago (still about once every second). It is also likely that the fetus will be making more breathing movements approximately one hour after the mother has eaten. This is thought to be because more energy is available and breathing movements are very energy-consuming (Visser, 1992). These breathing movements are important for lung development, which is undergoing a vital period of maturation at this time in readiness for birth.

In contrast to one month ago, the 9-month-old fetus no longer spends quite as much time in a state of active sleep. In active sleep, the fetus makes general body movements, some breathing movements, and her heart rate tends to be irregular, often with large accelerations. Her eyes will move rapidly back and forth and probably even open and close from time to time. However, since the fetus's brain has matured in the last month, more inhibitory pathways have now developed, thus reducing the amount of movement the fetus performs. Consequently, the fetus will have longer periods when she is resting quietly in a deep sleep. In fact, she will now spend about half the time in this state. During quiet sleep, the fetus is quiet and not moving and her heart rate is steady. The fetus may or may not be making breathing movements, but when she does, these tend to be rhythmic and steady in nature (Nijhuis, 1992). On the whole, the fetus's activity and rest periods alternate cyclically throughout the day. Already the length of one entire activity–rest cycle has lengthened from that seen one month ago, and now probably lasts about 80 to 100 minutes (Visser, 1992). However, superimposed on this cyclical rhythm are maternal physiological factors such as hormone levels, breathing, heart rate, and uterine activity (Mirmiran & Swaab, 1992). Variations in some or all of these factors are thought to influence the fetus's behavior over the course of the day. In general there is a peak in activity occurring when the mother is asleep, in the late evening, and a relative lull in activity in the early hours of the morning (Patrick, Campbell, Carmichael, Natale, R., & Richardson, 1982).

The reflex behaviors that the baby will demonstrate after she is born, notably, breathing, rooting, sucking, and swallowing, are in place now. Another protective reflex that the baby will demonstrate is an eye blink in response to a rapidly approaching object or bright lights. Like the breathing reflex, this remains in place throughout life. Other reflexes that have less obvious functional significance include the toe-curling reflex, the finger-grasping reflex, and the startle reflex. These reflexes all disappear within the first year of life. Another reflexive behavior that has received a good deal of attention is the stepping reflex. If resistance is provided to her feet the fetus will make stepping movements, placing one foot in front of the other. This reflex usually disappears in the first two months after birth. There is some argument as to whether this activity is a kicking motion (Thelen, 1986) or whether it is the precursor of early walking (Zelazo, 1983). It has also been suggested that this reflex may help in the birthing process itself (Kitzinger, 1990).

Sensory Development

Some senses, such as touch, begin development early in pregnancy and this sense is probably the most highly developed at this stage in the fetus's life. When the fetus moves around she will be touching the uterine wall, the umbilical cord, and also herself. The fetus will touch her own face more frequently than any other body part. So the fetus is provided with a wide breadth of physical sensations which probably help to promote further development of the physical sensation of touch. Although initially the fetus would have moved her head and neck away from the source of touch, now she moves toward it with her mouth open. This is the precursor of the "rooting reflex," which helps the baby to find the nipple for nursing. Now if the palm of the fetus's hand is stroked her fingers will close for a moment and the toes will curl if the sole of the foot is touched (Hepper, 1992).

As was noted previously, it is difficult to separate the sense of taste and smell when the fetus is in the womb. However, we do know that the flavors and odors from foods that the mother eats are transmitted into the placental blood and the amniotic fluid. The taste buds within the tongue and mouth are probably present and being stimulated. The mechanism underlying the sense of smell is perhaps less clear. It is not known whether most stimulation of the "smell receptors" occurs when the amniotic fluid washes in and out of the nose, or when a more concentrated source of odor – the bloodstream full of nutrients (and odors) from the placenta – passes very close to these receptors (Schaal et al., 1995). The fetus is capable of hearing now, as is evidenced by changes in heart rate and/or movement in response to externally presented sounds (Lecanuet & Schaal, 1996) and by electrophysiological studies of preterm infants. During the final trimester the fetus is exposed to a wide variety of sounds, particularly the sound of her mother's voice, heartbeat, and stomach sounds, but also to external noises (Abrams et al., 1995; Fifer & Moon, 1995; Lecanuet & Schaal, 1996). As already noted, although the fetus's eyelids are now open and the child can see in a rudimentary way, there is very little stimulation of the visual sense while in the womb. This is probably the least developed of all the senses at birth. The maturation of the sense of vision is very dependent upon adequate stimulation (Blakemore & Cooper, 1970), which can only occur once the child emerges from the dark environment of the womb. However, a premature infant as young as 28 weeks can distinguish light from dark (Taylor et al., 1987), coarse patterns of high contrast (Grose & Harding, 1990), and track a highly colored object (Dubowitz, Dubowitz, Morante, & Verbhote, 1980). At this stage of development the infant's acuity is poor and is therefore unable to resolve fine detail (Dubowitz et al., 1983).

Learning and Memory

The fetus does exhibit some very basic early memory at this point in time. It is not really known how long these memories last, but many examples of uterine learning are present at birth. The uterine environment provides a rich array of sensory stimuli, from touch, smell, taste, and sounds, and it has been conclusively demonstrated that newborn babies recognize and show a preference for many types of stimuli that they were exposed to in the womb. Probably the most striking example of this is the preference that newborn babies show for their own mother's voice. Studies have shown a neonatal ability to discriminate sounds heard *in utero*, either the mother's voice or the language heard *in utero* (Mehler et al., 1988; Ockleford, Vince, Layton, & Reader, 1988). Contingent sucking procedures have been used to detect preferences for mothers' versus strangers' voices, native versus non-native language phrases, and recordings of mothers' voices filtered to simulate intrauterine speech (reviewed in Moon & Fifer, 2000). Other studies have looked at how a newborn baby is able to recognize the smell of his or her own mother's breast milk (Makin & Porter, 1989), and this is thought to be attributable to some familiarization with the odors and tastes from the mother's diet while in the womb. In fact, it has been shown that babies of women who change their diets dramatically after their baby is born, typically to a less spicy one, are more likely to experience feeding difficulties (Hepper, 1992). Other research has concentrated on demonstrating how a baby in the womb actually modifies his or her behavior over time in response to a particular type of stimulation. Researchers have shown that babies will move in response to a loud sound occurring only a few feet from the womb. However, if this sound occurs repetitively, the fetus is capable of demonstrating an early learning and memory capability, habituation and dishabituation to novel sounds (Hepper, 1995; Leader, 1995; Lecanuet et al., 1995; van Heteren, Boekkooi, Jongsma, & Nijhuis, 2000).

Figure 18.4 From left to right, photos are images of third trimester fetuses captured by noninvasive 3D ultrasound. Photo 1 is a 37-week-old fetus in quiet sleep, photo 2 is a fetus sucking, and photo 3 is of a 30-week-old fetus with limbs extended. (Photos courtesy of (1) Dr. Armin Breinl, Austria; (2) Obgyn.net; (3) Dr. Saied Tohamy, Egypt)

Labor will provide the final context for environmental input to shape or elicit adaptive behavior, or in some cases, to convey risk. The sensory perceptual experience of the fetus during contractions may stimulate independent respiration (Ronca & Alberts, 1995). Stimulation of catecholamine release may aid in the transition to postnatal life by, for example, protecting against birth asphyxia and promoting neurologic adaptation (Lagercrantz & Slotkin, 1986; Otamiri, Berg, Ledin, Leijon, & Lagercrantz, 1991). Thus, the normal fetus should emerge after nine months with a full complement of skills required to meet the next challenge, i.e., adaptation to environment of the infant. However, there is a wide range of individual differences in the capacity to respond to the postnatal environment, and some infants will be more vulnerable than others to atypical or at-risk developmental trajectories.

Risks to Fetal Development

Perinatal complications can have their origins in parental preconception conditions as well as emerge from gene–environment interactions throughout embryogenesis and gestation. Atypical developmental trajectories range from congenital malformations to subtle variations with apparent minor clinical significance (Ashmead & Reed, 1997; Sweeney, 1998). Two to 3 percent of newborns are diagnosed with frank congenital abnormalities and another 2 to 3 percent of children are identified as having them before age 2. Although numbers vary somewhat, it is estimated that for 50 percent of the congenital abnormalities, the cause remains unknown. Genetic factors are thought to account for roughly 10–15 percent of congenital defects, while environmental agents acting alone – such as alcohol, excess quantities of vitamin A, and radiation – are thought to cause another 10 percent of them. The rest of the congenital anomalies are believed to be the result of multifactoral causation, that is, the result of genes and environment interacting together (Ashmead & Reed, 1997; Milunsky & Milunsky, 1998). Some sources estimate that research will eventually show that multifactoral causation actually may account for up to 75 percent of these anomalies (Ashmead & Reed, 1997). Abnormal developmental trajectories – ranging from subtle to significant – also can be associated with intrapartum risks such as those resulting from labor complications, for example, hypoxia during delivery, or those resulting from multiple births, which can result in an increased incidence of low birth weight and preterm delivery (Tough, Greene, Svenson, & Belik, 2000).

In this section of the chapter, we cover some of the common abnormal infant phenotypes with well-mapped-out genetic etiologies (e.g., Down's syndrome). We next discuss some of the environmental risks for fetal development, traditionally known as teratogens (from the Greek word for monster, *teratos*). However, our focus here is on research exploring the mechanisms by which even subtle alterations in the intrauterine environment can influence fetal neurobehavioral development and have an impact on the child's long-term health. The effects of alcohol and smoking on fetal development are discussed, in addition to the influence of minimal alcohol use and environmental smoke exposure. Well-established aspects of prenatal nutrition are covered, such as folic acid, as well as new research linking weight gain during pregnancy and protein intake to the child's risk for heart disease. Finally, new data are discussed indicating that women's mood during pregnancy, specifically stress and anxiety, may affect fetal development.

Chromosomal Disorders

The DNA forming the human genetic code is stored in the cell nucleus in structures called chromosomes. Human chromosomes consist of 22 pairs called autosomes and two sex chromosomes (XX, for females; or XY, for males). In chromosomal defects, whole chromosomes are missing or duplicated, or parts of them are missing or duplicated. The most common abnormalities are monosomies, in which there is only one copy of chromosome pair, or trisomy, in which there are three representatives of a chromosome pair. Most monosomies are not viable, except for Turner's syndrome, in which the individual has an X chromosome and no second sex chromosome. A person with Turner's syndrome is phenotypically female but sterile. Overall, chromosomal abnormalities are seen in 1/200 live births and in 50–70 percent of first trimester miscarriages (Ashmead & Reed, 1997; Robinson, Linden, & Bender, 1998).

There are three major trisomies of the sex chromosomes, all of which survive. In Klinefelter's syndrome, individuals have XXY trisomy and are phenotypically male, but infertile. Individuals with XYY trisomy also are phenotypically male and often exhibit impulsive and aggressive behavior. XXX individuals have a female phenotype and are often retarded (Robinson et al., 1998).

There are three major autosomal trisomies. The most common is Down's syndrome, with three copies of chromosome 21. Down's syndrome is characterized by varying degrees of mental retardation, anomalous facial features, and, for approximately a third of the cases, serious heart defects. Extra copies of chromosomes 13 (Patau syndrome) and 18

(Edward's syndrome) result in severe defects of the central nervous system and morphological malformations such as cleft lip (Ashmead & Reed, 1997).

Finally, some chromosomal abnormalities are the result of the translocation or rearrangement of chromosomal segments. Some affected individuals have no abnormalities, however they are at greater risk for producing gametes with chromosomal alterations in structure and/or number. New techniques have recently enabled researchers to identify chromosomal microdeletions, which only span a few contiguous genes (Sweeney, 1998; Wilson, 1992).

Abnormal numbers of chromosomes are usually caused by an error in the separation of chromosomes into appropriate daughter cells during meiotic division. For reasons still only partially understood, there is a dramatic increase in the risk of chromosomal anomalies with advancing maternal age. For example, risk of Down's syndrome at age 20 is 1/2000; at age 30 it is 1/1000; by age 37 it is 1/200 (Davidson & Zeesman, 1994; Hsu, 1998).

Single Gene Disorders

Disorders can result from a single gene abnormality or allele, dominant or recessive, on either an autosome or a sex chromosome. An allele is an alternative form of a particular gene. An autosomal recessive (AR) disorder will be expressed in a child when each parent (who is heterozygous) has one allele with the mutation, giving the child two of these alleles, one from each parent (making them homozygous). There is a 25 percent chance of heterozygous parents having an affected (homozygous) child. The risk of an affected individual having a child with the disorder depends on his or her partner's status with respect to the genetic mutation, and, therefore, on how rare the disease is. Research suggests that every individual is heterozygous for approximately 8–10 AR genes linked to disease. Examples of autosomal recessive genetic disorders are: sickle cell disease, cystic fibrosis, and Tay–Sachs disease. An autosomal dominant (AD) disorder will be expressed with just one abnormal allele present. A parent affected with an AD disorder has a 50 percent chance of passing this disease onto his or her child. Huntington's disease, Marfan syndrome, and polycystic kidney disease are examples of autosomal dominant disorders (Ashmead & Reed, 1997).

Sex-linked diseases or functional disorders are known as X-linked characteristics because in most cases there are no corresponding alleles on the Y chromosome. In X-linked inheritance, all daughters of an affected male are carriers and there is no male to male transmission. X-linked disorders can be recessive or dominant. Because males only have one X chromosome, an abnormal gene on an X chromosome results in disease in all affected males. For females to be affected by an X-linked disorder, they need either to be homozygous or to have most of their normal X chromosomes inactivated (called Lyonization). X-linked recessive disorders are: Duchenne muscular dystrophy and hemophilia.

X-linked dominant traits are expressed in females but most often lethal in males. Females survive the X-linked dominant disorders because of random inactivation of the abnormal X chromosome in half of females' cells, allowing for expression of the normal gene by the other normal X chromosome. Examples of X-linked dominant disorders include hypophosphatemic (vitamin D-resistant) rickets and Kennedy disease (spinal and bulbar muscular atrophy) (Ashmead & Reed, 1997). Certain ethnic groups are at greater risk for specific genetic disorders than others. For example, in Ashkenazi Jews (Jews of Eastern European descent), 1 in 30 is a carrier of Tay–Sachs disease, while approximately 8 in 100 African Americans from North America are carriers of the sickle cell gene (Davidson & Zeesman, 1994).

Environmental Influences

Alcohol

Heavy maternal alcohol consumption profoundly influences fetal and child development. The most severe effects are found in offspring of women alcoholics, who consume, on average, six standard drinks per day (one standard drink = 12 oz beer = 5 oz of wine = 1.5 oz of liquor or 15 g of absolute alcohol). For the children who survive, the effects include mild to severe physical anomalies and cognitive and behavioral impairments. However, other adverse fetal outcomes include increased risk for spontaneous abortion, stillbirth, premature placental separation, intrauterine growth restriction, and, some studies suggest, preterm birth – itself a risk factor for future health problems, poor development, and newborn mortality (Smigaj, 1997).

Children of women who abuse alcohol and who meet criteria for Fetal Alcohol Syndrome (FAS; approximately 1.97 per 1000 live births in the United States) have craniofacial dysmorphology, including smaller head circumference and a flattening of the nose area, other congenital anomalies, and long-term attention deficits as well as mental retardation. However, a subset of children do not meet the criteria for FAS but nonetheless show significant impairment related to their mothers' alcohol use during pregnancy. These children exhibit some of the behavioral and cognitive deficits associated with FAS and are referred to as having either prenatal exposure to alcohol (PEA), Fetal Alcohol Exposure (FAE), alcohol-related birth defects (ARBD), and alcohol-related neurodevelopmental disorders (ARND). The rates of babies born with these partial FAS syndromes are believed to be much higher than for frank FAS (Mattson & Riley, 1998; Roebuck, Mattson, & Riley, 1999). There are several possible pathways by which maternal alcohol use affects the developing fetus. Alcohol, which freely crosses the placenta, affects fetal cell activity. Specifically, alcohol increases cellular peroxidase activity, decreases DNA synthesis, disrupts protein synthesis, and impairs cell growth, differentiation, and neural cell migration. Alcohol also impedes placental transfer of amino acids and glucose, adversely affecting fetal growth, and alters the chemical makeup of maternal blood, causing maternal vasoconstriction and chronic fetal hypoxia (Hanningan, Saunders, & Treas, 1999; Smigaj, 1997).

The developmental timing and frequency of drinking episodes during pregnancy (e.g., maternal abstinence after the first trimester versus binge-drinking throughout pregnancy) can greatly alter the impact that maternal drinking will have on the fetus. In general, drinking during the first trimester results in craniofacial abnormalities, while exposure during the second and third trimesters coincides with the period of rapid brain development, influencing fetal central nervous system development. In particular, new research with animal models suggests that there may be an enhanced period of vulnerability to cerebellar cell loss in humans during the 24–32 weeks of pregnancy, when Purkinje cell dendritic growth is occurring (Goodlett & Johnson, 1999).

Recent studies based on autopsy reports and tools of modern neuroscience such as magnetic resonance imaging (MRI) have identified neuroanatomical variations in the brains of children with FAS. Autopsy reports indicate that the brains of FAS children are microencephalic (abnormally small). The MRI studies generally show reductions in the volumes of both the cerebral and cerebellar brain regions in FAS children. Follow-up reports of behavior and cognitive development indicate that significant *in utero* exposure to alcohol is associated with attentional deficits, mental retardation, and poor academic performance. Data from recent neuropsychological studies comparing FAS and PEA children to controls matched for age, gender, and ethnicity indicated that FAS and PEA children have lower overall IQ scores as well as lower scores on most subtests. Similar studies from the same laboratory suggest that FAS children perform less well on verbal measures of comprehension and naming ability, and have inferior fine-motor speed and coordination (Roebuck et al., 1999). These findings of cerebral cortex/cerebellum anomalies as well as cognitive and motor weaknesses in FAS/PEA children are consistent with current neuroscience research indicating the interrelatedness of cognitive and motor development (Diamond, 2000). It is clear that high levels of prenatal alcohol exposure have a dramatic and long-term impact on development, even when the strict criteria for FAS is not met. Because there is no known level of safe alcohol consumption during pregnancy and because the effects of lowered intake, although present, are likely to be subtle and hard to detect, complete abstinence during pregnancy is recommended (Smigaj, 1997).

Smoking

Despite major efforts to warn pregnant women of the dangers cigarette smoking poses for their fetus, smoking is still one of the most preventable risk factors for an unsuccessful pregnancy outcome (Bulletin, 1997). The adverse consequences of prenatal exposure to maternal smoking are well known; some of the newest research focuses on the effects of passive smoking or environmental tobacco smoke (ETS) during pregnancy on birth outcomes.

On average, babies born to smokers weigh 100–200 g less than those of nonsmokers and have twice the risk for fetal growth restriction (Horta, Victora, Menezes, Halpern, & Barros, 1997; Walsh, 1994). Furthermore, independent of the risks for lower birth weight, smoking is associated with risk for prematurity and perinatal complications, such as premature detachment of the placenta (Andres, 1996; Kyrklund-Blomberg & Cnattingius, 1998). Cigarette smoking also is associated with a two- to threefold increase for Sudden Infant Death Syndrome (SIDS) (Golding, 1997). Finally, more subtle effects of fetal exposure to maternal smoke have been found during childhood. Behavioral problems and cognitive weaknesses, including problems with attention and visuoperceptual processing, have been associated with smoking during pregnancy (Fried & Watkinson, 2000; Fried, Watkinson, & Gary, 1992; Wakschlag et al., 1997).

Maternal cigarette smoking adversely affects fetal development – often with long-term consequences for child health – by causing a chronic reduction in nutrient and oxygen delivery to the fetus as well as acute hypoxic injuries (Lambers & Clark, 1996). Nicotine and carbon monoxide are the two main agents of these effects. Nicotine induces vasoconstriction in the placental and fetal vascular beds, reducing oxygen and nutrient input to the fetus. Carbon monoxide, which binds to hemoglobin to form carboxyhemoglobin, reduces the oxygen-carrying capacity of blood. It also increases the affinity of hemoglobin for oxygen so that oxygen release to tissues is inhibited (Walsh, 1994). Because the fetus gains weight at a rapid rate during the third trimester, studies indicate that maternal smoking during this period has the greatest impact on fetal growth (Lieberman, Gremy, Lang, & Cohen, 1994). Smoking-induced reductions in oxygenation throughout pregnancy have far-reaching effects on cellular and tissue development in the fetus, influencing the development of the central nervous system and cardiorespiratory functioning, to name a few.

The strong effects that active smoking exerts on pregnancy outcomes has led researchers to investigate whether maternal exposure to environmental tobacco smoke (ETS) also has an influence on fetal development. New data indicate that even ETS poses risks for the fetus. Studies suggest that exposure to passive smoking during pregnancy is associated with reductions in fetal weight ranging from 25–40 g (Spitzer et al., 1990; Windham, Eaton, & Hopkins, 1999) as well as greater likelihood of a low-birthweight baby (Mainous & Hueston, 1994).

Nutrition

As described previously, in order to support the developing fetus, women must increase their caloric intake to reach between 2700–3000 calories per day. In addition, specific nutritional requirements must be met for healthy fetal development. For example, adequate amounts of calcium are needed for fetal bone, muscle, and transmitter production; sufficient supplies of iron are necessary for fetal red blood cell and tissue production (Judge, 1997). Recently, the central importance of folic acid to fetal development has emerged. Specifically, in the last ten years, research has shown that inadequate amounts of folic acid are linked to serious congenital abnormalities known as Neural Tube Defects (NTD). Consisting primarily of anencephaly ("brain absence") and meningomyelocele (a protrusion of the brain), these NTDs are induced in the first 28 days of pregnancy when the early foundation of the spinal cord, the neural tube, is forming (Sweeney, 1998). Folic acid plays roles in nucleic acid and protein synthesis as well as in neural and red cell development, all of which are underlying processes in neural tube development (Judge, 1997). Because the impact of folic acid deficiency on fetal development cannot be reversed, it is recommended that women increase their folic acid intake prior to conception. On the other hand, because more than half of the pregnancies in North America are unplanned and because women living in poverty intake below optimal levels of folic acid, primary prevention of NTD has yet to be accomplished (Koren, 1994).

Recent research from epidemiological and animal studies indicates that independent of gross congenital anomalies, women's food intake and/or weight gain during pregnancy may subtly affect fetal development in ways that have implications for the child's future medical and mental health. For example, in several large samples, low birth weight has been linked to increased risks for future cardiovascular disease (CVD), and for factors, such as high blood pressure, associated with CVD (Clark et al., 1998; Law et al., 1993; Moore, Cockington, Ryan, & Robinson, 1999; Rich-Edwards et al., 1997). To account for this association, researchers hypothesize that aspects of the fetus's cardiovascular functioning are "programmed" *in utero* by maternal nutritional and/or hormonal factors (Barker, 1995). One line of investigation suggests that reductions in maternal protein intake decreases the activity of a placental enzyme that protects the fetus from maternal stress hormones, thereby exposing the fetus to elevated levels of these stress hormones, which is associated with lower birth weight and higher blood pressure in the offspring. Although the emerging data with human pregnancy are not entirely consistent with this hypothesis, animal studies support this line of thinking (Langley-Evans, 2000; Langley-Evans, Welham, Sherman, & Jackson, 1996). Other possible mechanisms that might account for the association between maternal protein intake, low fetal weight, and increased risk for CVD include the possibility that low protein intake reduces the size of the pancreas and glucose tolerance, leading to low birth weight and alterations in metabolism (Charif, Ahn, Hoet, & Remacle, in press).

New research also indicates that women's nutrition during pregnancy and baby's birth weight also might be markers for physiological processes that place the infant at risk for future breast cancer (Michels, Trichopoulos, Adami, Hsieh, & Lan, 1996; I. Morgan, Damber, Tavelin, & Hogberg, 1999) and psychiatric illness (Susser, Brown, & Matte, 1999). Specifically, epidemiological studies suggest that higher birth weight is associated with an increased risk for breast cancer (I. Morgan et al., 1999). Other studies based on the offspring of Dutch women pregnant during the Nazi food embargo ("the Dutch Hunger Winter") suggest that extreme undernutrition (less than 1000 calories a day) during first and second trimesters (and thus occurring during rapid brain reorganization) is associated with the risk of becoming schizophrenic or having antisocial personality disorder (Neugebauer, Hoek, & Susser, 1999; Susser et al., 1999). Although the mechanisms underlying these associations are not yet known, it is likely that future research will clarify the impact of variations in maternal nutrition and newborn weight on the child's physical and mental health.

Psychosocial Stress

Psychosocial stress during pregnancy has long been linked to negative birth outcomes such as low birth weight and prematurity (Istvan, 1986; Lobel, 1994; Lobel, Dunkel-Schetter, & Scrimshaw, 1992; Stott & Latchford, 1976). Current findings are largely consistent in pointing to stress-induced maternal vasoconstriction as contributing to diminished fetal oxygen and nutrient intake, and consequently, reduced birth weight and stress-elicited surges in stress hormones as precipitating labor and, consequently, early delivery (Lobel, 1994; Lobel et al., 1992; Wadhwa, Dunkel-Schetter, Chicz-DeMet, Porto, & Sandman, 1996; Wadhwa, Porto, Garite, Chiez-DeMet, & Sandman, 1998). However, it is only relatively recently that animal studies and research on fetal development have discovered the influence of maternal stress on fetal neurobehavioral development.

In animal models, offspring whose mothers are exposed to acute stress during pregnancy (e.g., electric shock) versus controls exhibit long-term changes in behavior and the regulation of stress hormones. Prenatally stressed animals show inhibited, anxious, fearful behavior throughout the life span, hypothesized to result from their excessive level of endogenous arousal. Specifically, prenatally stressed rats suppress ultrasonic vocalization to separation from their mother (K. Morgan, Thayer, & Frye, 1999; Takahashi, Baker, & Kalin, 1990) and try more often to escape from novelty (Vallee et al., 1997). In tests with primates, prenatal stress is associated with poorer neuromotor maturity and distractibility (Schneider, 1992; Schneider & Coe, 1993; Schneider, Roughton, Koehler, & Lubach, 1999). The offspring of rats exposed to an acute stressor compared to controls also have elevated ACTH stress hormone responses as preweanlings (Takahashi & Kalin, 1991; Takahashi, Kalin, Barksdale, & Vanden Burtgt, 1988) and increased stress-induced corticosterone secretion as adults (Vallee et al., 1997). Because prenatally stressed animals are compared to genetically similar controls, the evidence from these studies suggests that physiological processes associated with stress during pregnancy may have an impact on developmental processes. Researchers now hypothesize that over the course of pregnancy, the frequency and magnitude of maternal stress may have a cumulative effect, shaping fetal and child central and peripheral nervous system development. There are two primary systems that likely mediate the possible influence of maternal psychiatric symptoms on the fetus: the maternal autonomic nervous system and the hypothalamic–pituitary–adrenocortical (HPA) axis.

Increased sympathetic activation

Stress is associated with elevated and/or chronic sympathetic activation and with the release of catecholamines and vasoconstriction. Vasoconstriction is believed to alter utero-placental blood flow, causing subsequent oxygen and calorie reduction to the fetus and thereby affecting fetal growth (Copper et al., 1996; McCubbin et al., 1996) and possibly influencing fetal central nervous system (CNS) development (Teixeira, Fisk, & Glover, 1999). Increased catecholamine levels may affect the fetus by sustaining maternal vasoconstriction and increased blood pressure (McCubbin et al., 1996; Shnider, Wright, & Levinson, 1979).

The HPA axis

The hypothalamic–pituitary–adrenocortical (HPA) system plays a major role in stress responses. Briefly, cortisol, a glucocorticoid stress hormone, is the primary by-product of the HPA axis in humans. Cortisol is regulated by the hypothalamus in the brain via its secretion of corticotrophin-releasing hormone (CRH) to the pituitary, signaling for it to secrete ACTH, which, in turn, causes cortisol to be secreted from the adrenal cortex. In response to experiences of threat or challenge, the hypothalamus, largely through contact with other brain centers, initiates a cortisol response. In turn, as part of a negative feedback loop, increasing levels of circulating ACTH and cortisol inhibit further release of CRH. Although there is controversy as to how much biologically active maternal cortisol crosses the placenta (Gitau, Cameron, Fisk, & Glover, 1998; Glover, Teixeira, Gitau, & Fisk, 1999), there is consensus that CRH and ACTH are synthesized by the placenta (Sandman, Wadhwa, Chicz-DeMet, Porto, & Garite, 1999). Some evidence suggests that in pregnancy, increased HPA-axis functioning is associated with elevated levels of psychosocial stress (Wadhwa et al., 1996). Although still exploratory, the data indicate that increases in maternal sympathetic and HPA-axis activity associated with stress may affect the fetus and are consistent with animal models that highlight the potential impact of altered maternal physiology on offspring development, particularly on the developing glucocorticoid system in the fetal brain.

Psychosocial stress during pregnancy has been associated with alterations in neurobehavioral development in the fetus as well. In a comprehensive examination of fetal ontogeny, DiPietro, Hodgson, Costigan, and Johnson (1996) assessed fetal variables in relation to maternal variables. Fetuses of pregnant women who reported greater life stress had reduced parasympathetic and/or increased sympathetic activation as measured by reduced fetal heart rate variability (HRV). Moreover, fetuses of mothers who reported greater stress and had faster baseline heart rate (HR) showed a delay in the maturation of the coupling of fetal HR and movement, hypothesized to be an index of impeded central nervous system development (DiPietro et al., 1996). Low socioeconomic status – often associated with increased social stress – is associated with higher and less variable fetal HR throughout the second and third trimesters (Pressman, DiPietro, Costigan, Shupe, & Johnson, 1998).

Anxiety during pregnancy also has been linked to alterations in pregnant women's physiology and fetal behavior. Pregnant women who have high concentrations of CRH, which is associated with increased anxiety and life stress, have fetuses with a diminished capacity to dishabituate, that is, to respond significantly to the presence of a novel stimulus after having habituated to a repeated series of stimuli (Sandman et al., 1999), indicative of an alteration in CNS development.

In a recent study from our laboratory examining the effects of acute maternal stress and anxiety on fetal development (Monk et al., 2000), pregnant women's anxiety was associated with differences in fetal HR activity. During a cognitive challenge to mothers in the final month of pregnancy, fetuses of women describing themselves as more anxious showed significant HR increases and the fetuses of less anxious women exhibited nonsignificant decreases during the mental stressor. The data indicate that over the course of gestation, maternal psychological variables such as stress and anxiety acting via alterations in maternal physiology may influence fetal neurobehavioral development.

Significantly, in children and adults, differences in cardiac functioning, such as increased HR and reduced HRV, are associated with mood disorders (e.g., Monk et al., in preparation; Sloan et al., 1994) and are believed to indicate weaknesses in an individual's competency to modulate emotional reactivity (Porges, Doussard-Roosevelt, & Maiti, 1994). Furthermore, although the research in this area is just emerging, studies indicate that there is continuity between fetal and infant development. For example, work from the Kagan laboratory indicates that low resting HR during the prenatal period predicts lower levels of crying and motoric responses to novelty at 4 months old (Snidman, Kagan, Riordan, & Shannon, 1995). Using sonographic visualization, Groome found that fetuses who move at certain rates during active sleep move at the same relative rate at 2 and 4 weeks postpartum (Groome et al., 1999). Other exploratory research suggests that a relatively greater number of weak body movements, as opposed to strong, full-body ones, was positively associated with the amount of crying during the first three months of life (St. James-Roberts & Menon-Johansson, 1999). The authors speculate that an inability to inhibit responsiveness is the common underlying characteristic linking increased fetal body movements and greater crying. In the most extensive study of fetal to newborn continuities, DiPietro et al. (1996) found that indices of fetal neurobehavior accounted for as much as 60 percent of the variance of infant temperament. In general, higher fetal activity resulted in increased fussiness and inconsistent behavior, while greater periodicity resulted in lower scores on these variables. Taken together, these findings indicate that the development of fetal phenotypes – vulnerable to mother's psychosocial stress – have implications for the child's future development.

Emerging Questions and the Future of Fetal Research

In this chapter, we have summarized normal stages of fetal development as well as recent approaches to the study of risks for abnormal outcomes. A key implication of this work is that what takes place prior to postnatal life is of central importance to the child's development. Hence, it is only a slight exaggeration to assert that the future success of developmental research rests, in part, on the attainment of an even better understanding of the prenatal period.

Two overarching hypotheses will guide the majority of future fetal research: (1) the premise that there is continuity between fetal and infant development; (2) the premise that the *in utero* environment – from maternal nutrition to maternal stress hormones – is significant to development just as the postnatal environment is. Furthermore, both of these research premises are consistent with the contemporary approach to developmental studies known as dynamic systems (DS) (Karmiloff-Smith, 1998; Lewis, 2000; see also chapter 3 in this volume). Briefly, DS theory emphasizes the dynamic, recursive interactions inherent in developmental processes such that prior interactions continually shape subsequent ones and new structures or properties of the organism come into existence (emerge) through ongoing processes intrinsic to the organism–environment system. Such an approach allows for the centrally directed, unfolding aspect of fetal development, in which the progress of fetal development is largely protected from the vagaries of environmental input, to the reality of immensely diverse outcomes resulting from the unique cascades of interacting genes and subtly different environments. With its emphasis on the inherently dynamic quality of development, DS theory provides an organizing perspective for studies characterizing how developmental processes – and future trajectories – are initiated long before birth.

As knowledge accumulates about the timing and mechanisms involved in the *in utero* construction of the brain and central nervous system, particularly during the second and third trimesters, future research endeavors will likely focus on the use of new technology to investigate fetal and infant neurobehavioral continuities as well as on measuring differences in babies exposed to alterations in the prenatal environment. Specific topics will likely include:

- Characterization of fetal CNS development and its relation to infant brain–behavior relationships as assessed by infant EEG and behavioral measures.
- Epidemiological, animal, and clinical investigations of how risk for adult diseases, such as hypertension, may be "programmed" *in utero* by inadequate nutrition.
- Advances in genetic research detailing the mechanisms of cell proliferation, migration, death, and connectivity during the fetal period, what factors influence these processes, and the resulting neurobiological alterations to development.
- The influence of exposure to high levels of ambient air pollution during pregnancy on fetal and newborn development using DNA and behavioral assays.
- The role of maternal stress as well as psychiatric conditions in the development of child neurobehavioral problems.
- The possibility that fetuses experience pain.

The roots of infant development are being uncovered by paying closer attention to the nature and timing of prenatal gene–environment interactions. The identification of fetal phenotypes, and the underlying brain–behavior relationships, are the sine qua non for these investigations into the origins of normal and abnormal developmental trajectories. Development begins before birth; increasingly, we are learning how to study it that way.

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