Wnt families of secreted morphogens and their receptors (Figure 48–18). They are present at specific subsets of synapses and play distinct roles. For example, similar to neuroligin1 and neuroligin2, FGF22 and FGF7 are localized to and promote differentiation of excitatory and inhibitory synapses, respectively. Some of these organizing proteins may act in parallel with neurexins, while others may act as initial organizers, with neuroligins and neurexins consolidating the synapses at a later time and specifying their particular properties.

Together, these results suggest that central synapses are not patterned by master organizers akin to agrin, MuSK, LRP4, and laminins. Indeed, loss of no single central organizer studied to date is lethal in the manner observed for agrin, MuSK, LRP4, and laminin mutants. Instead, the enormous variety of neuronal and synaptic types in the central nervous system and their wide range of functional properties arise from a multitude of organizers that act combinatorially and in cell type–specific ways. Consistent with this view, genetic variation in many central organizers and synaptic recognition molecules, including neurexins, neuroligins, cadherins, and contactins, has been associated with behavioral perturbations in experimental animals and with behavioral disorders, including autism, in humans (Chapter 62).

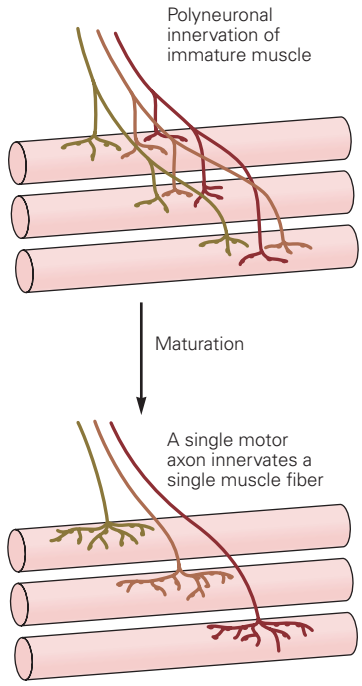

Figure 48–19 Some neuromuscular synapses are eliminated after birth. Early in the development of the neuromuscular junction, each muscle fiber is innervated by several motor axons. After birth, all motor axons but one withdraw from each fiber, and the surviving axon becomes more elaborate. Synapse elimination occurs without any overall loss of axons—axons that "lose" at some muscle fibers "win" at others. Central synapses are also subject to elimination.

Some Synapses Are Eliminated After Birth

In adult mammals, each muscle fiber bears only a single synapse. However, this is not the case in the embryo. At intermediate stages of development, several axons converge on each myotube and form synapses at a common site. Soon after birth, all inputs but one are eliminated.

The process of synapse elimination is not a manifestation of neuronal death. Indeed, it generally occurs long after the period of naturally occurring cell death (Chapter 46). Each motor axon withdraws branches from some muscle fibers but strengthens its connections with others, thus focusing its increasing capacity for transmitter release on a decreasing number of targets. Moreover, axonal elimination is not targeted to defective synapses; all inputs to a neonatal myotube are morphologically and electrically similar, and each can activate the postsynaptic cell (Figure 48–19).

What is the purpose of the transient stage of polyneuronal innervation? One possibility is that it ensures that each muscle fiber is innervated. A second is that it allows all axons to capture an appropriate set of target cells. A third, intriguing idea is that synapse elimination provides a means by which activity can change the strength of specific synaptic connections. We will explore this idea in Chapter 49.

Like synapse formation, synapse elimination results from intercellular interactions. Every muscle fiber ends up with exactly one input: None have zero, and very few have more than one. It is difficult to imagine how this could occur without feedback from the muscle cell. Moreover, the axons that remain after partial denervation at birth have a larger number of synapses than they did initially. Thus, synapse elimination appears to be a competitive process.

What drives the competition, and what is the reward? There is good evidence that neural activity plays a role: Paralysis of muscle reduces synapse elimination, whereas direct stimulation enhances it. These findings showed that activity was involved but did not reveal how the outcome was determined, because all axons were stimulated or paralyzed together. Because the essence of the competitive process is that some synapses gain territory at the expense of others, differential activity among axons may be a determinant

of axon winners and losers. Changing the activity of only a subset of axons in a living animal has been a technical challenge, but genetic approaches have made this possible in mice. In fact, when the activity of one of the inputs to a muscle fiber is decreased, that axon is highly likely to withdraw.

If the more active axon wins the competition, there is a new problem. Because all synapses made by an axon have the same activity pattern, one might predict that the least active axon in the muscle would eventually lose all of its synapses and the most active would retain all of its synapses. Yet this does not happen. Instead, all axons win at some sites and lose at others, so that every axon ends up innervating a substantial number of muscle fibers.

One possible resolution to this paradox is that the outcome of competition may not depend on the number of synaptic potentials from the winning axon at a synapse but rather on the total amount of synaptic input that the axon provides to the muscle—a product of the number of impulses and the amount of transmitter released per impulse. In this case, an axon that loses at several synapses might redistribute its resources (eg, synaptic vesicles) so that the remaining terminals would be strengthened and more likely to win at their synapses. Conversely, an axon that wins many competitions might find itself with insufficient vesicles to generate large synaptic potentials and thus would eventually lose to competitors at some synapses. Accordingly, the number of muscle fibers innervated by individual axons would vary much more among axons than is actually observed.

If activity drives the competition, what is the object of the competition? One idea is that the mechanisms are similar to those that determine whether neurons live or die. The muscle might produce limited amounts of a trophic substance for which the axons compete. As the winner grows, it either deprives the loser of its sustenance or gains enough strength to mount an attack that results in removal of its competitor. Alternatively, the muscle might release a toxic or punitive factor. In these scenarios, although the muscle does contribute a factor in the competition, the outcome is entirely dependent on differences between axons. These differences could be related to activity. The more active axon might be better able to take up trophic factor or resist a toxin. Such positive and negative competitive interactions have been demonstrated at nerve-muscle synapses in culture, although not in vivo.

Nevertheless, the muscle could play a selective role in synapse elimination rather than just providing a broadly distributed signal. For example, the more active axon might trigger a signal from the muscle fiber that strengthens its adhesive interactions with the synaptic cleft, whereas the less active axon might elicit a signal that weakens those interactions.

The complexity of the brain makes direct demonstration of synapse elimination problematic, but electrophysiological evidence from many parts of the central nervous system indicates that synapse elimination is widespread. In autonomic ganglia and cerebellar Purkinje cells, synapse elimination has been documented directly and its rules seem similar to those found at neuromuscular junctions. Individual axons withdraw from some postsynaptic cells while simultaneously increasing the size of the synapses they form with other neurons.

Glial Cells Regulate Both Formation and Elimination of Synapses

Classical studies of synapse formation and maturation focused, logically enough, on the pre- and postsynaptic partners. More recently, however, there has been a growing appreciation of the role played by a third type of cell: the glial cells that cap nerve terminals. Schwann cells are the glia at neuromuscular junctions, and astrocytes are the glia at central synapses. Both have been implicated in synapse formation and maturation.

The most penetrating analyses were performed by the late Ben Barres and his colleagues. They devised methods to culture neurons in defined media and in the complete absence of nonneuronal cells. Using this system, they found that neurons formed few synapses when cultured in isolation but many when astrocytes were present (Figure 48–20). The astrocytes provide multiple signals to neurons. Some, such as thrombospondin, promote postsynaptic maturation, whereas others, such as cholesterol, promote presynaptic maturation.

Another glial type, the microglial cell, also plays critical roles. Microglia are relatives of macrophages and monocytes in other tissues, sharing their ability to eliminate dead cells or debris. Initially thought to be primarily involved in the brain's response to damage, they have now been found to phagocytose synaptic terminals during the period of synapse elimination. True to their phagocytic origins, they use the complex system of complement factors, initially studied in the context of immunity, to target terminals; the targeting is activity dependent, providing a possible mechanism for the activity dependence of synapse elimination (Figure 48–21). An intriguing possibility is that dysregulation of microglial pruning contributes to synaptic loss in neurodegenerative diseases such as Alzheimer disease and schizophrenia (see Chapters 60 and 64).

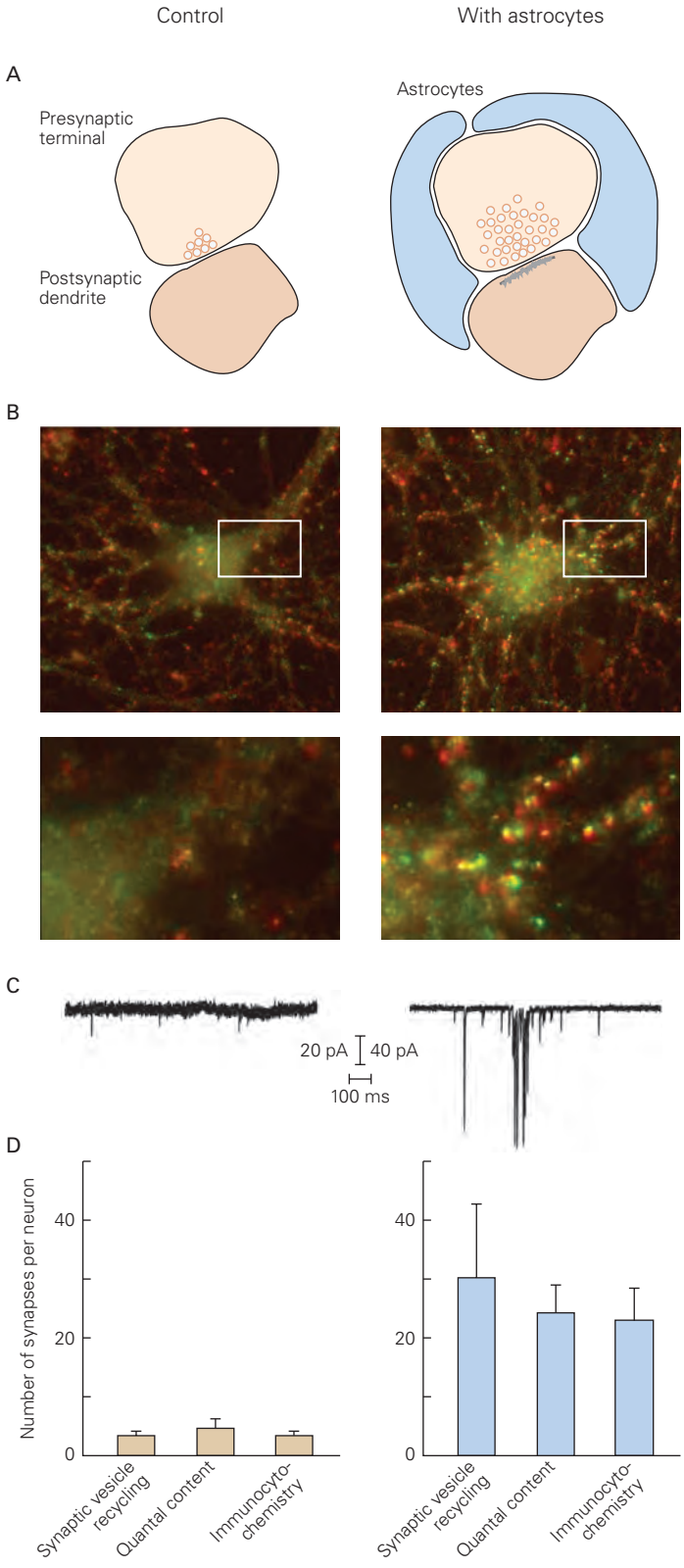

Figure 48–20 Signals from astrocytes promote synapse formation.

A. Astrocytes promote the maturation of both pre- and postsynaptic elements of the synapse.

B. Neurons cultured with astrocytes form more synapses, as assessed by expression of synaptic proteins (**yellow dots**). (Reproduced, with permission, from Ben A. Barres.)

C. Retinal neurons cultured with astrocytes form a greater number of synapses, as shown by increased transmitter release.

D. Synapse formation is enhanced in the presence of astrocytes by three measures.

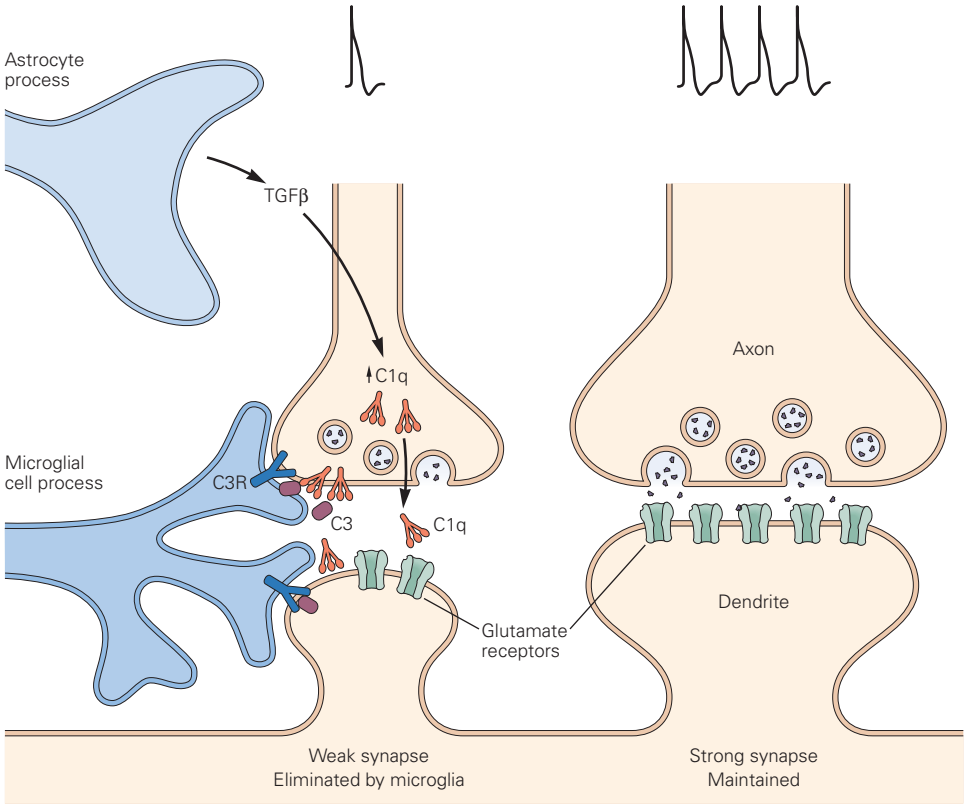

Figure 48–21 Microglia prune synapses, contributing to synapse elimination. Microglia engulf weak synapses. The engulfment is stimulated by complement components such as C1q, which tags the inactive terminal and marks it for removal by a process involving interaction of C3 with the complement receptor C3R on the microglia. Astrocytes play a role by secreting transforming growth factor β (TGFβ), which promotes production of C1q. (Adapted, with permission, from Allen 2014. Permission conveyed through Copyright Clearance Center, Inc.)

The roles of glia in synaptic development are only beginning to be worked out, and the assignments of astrocytes and microglia to synapse formation and elimination are clearly oversimplifications. Both glial types are involved in both processes, and Schwann cells may play both roles at the neuromuscular junction. Moreover, a complex set of signals passes between astrocytes and microglia, and between neurons and glia, all of which contribute to development and are at risk of going awry in brain disorders.

Highlights

1. Elaborate guidance mechanisms bring axons to appropriate target areas, but within those areas they still need to choose synaptic partners, often from among many neuronal types. Multiple mechanisms guide these choices.
2. Matching cell-surface recognition molecules on pre- and postsynaptic partners provide one prevalent mechanism for synaptic specificity. They include members of the cadherin, immunoglobulin, and leucine-rich repeat protein superfamilies. Individual members are selectively expressed by subsets of neurons and exhibit selective binding. Often, the binding is homophilic, biasing connectivity in favor of partners expressing the same molecule.
3. Other mechanisms promoting specificity include selective interactions among axons, the ability of some axons to convert their targets to the appropriate types, and selective elimination of inappropriate contacts.
4. At present, it remains unknown how many molecular species are required to wire up neural circuits in the mammalian brain. At one time, it seemed that molecular complexity might need to approach the complexity of circuits, but it is more likely that a few hundred recognition molecules will suffice, given their combinatorial use, as well as deployment of the same gene at multiple times and in multiple regions.

5. Spatial constraints that enhance specificity include restriction of axons and dendrites to particular laminae within a target region—thereby restricting their choice of partners—and restriction of synapses of particular types to defined domains on the target cell surface.
6. Some specificity mechanisms do not require the partners to be electrically active, but in many cases, activity-dependent mechanisms sharpen specificity. Activity can be spontaneous, early in development, or driven by experience at later stages.
7. The skeletal neuromuscular junction, at which the axon of a motor neuron synapses on a muscle fiber, has been a favored preparation for working out principles of synaptic development. A key finding is that multiple interactions between the synaptic partners are required for the formation, maturation, and maintenance of the synapse.
8. Motor neurons and muscle fibers can express genes encoding pre- and postsynaptic components, respectively, in each other's absence, but they exert profound influences on the levels and distribution of these components in their partners. Thus, signals between synaptic partners are best viewed as organizers rather than inducers.
9. At the neuromuscular junction, a layer of basal lamina occupies the synaptic cleft between the motor nerve terminal and the postsynaptic membrane. Nerve and muscle secrete signaling molecules into the cleft, where they become stabilized and organize differentiation.
10. A key nerve-derived organizer of postsynaptic differentiation is agrin. It acts through the receptors MuSK and LRP4 to cluster acetylcholine receptors and other postsynaptic components beneath the nerve terminal. Nerve-evoked activity also affects postsynaptic differentiation by modulating expression of postsynaptic components. Key muscle-derived organizers of presynaptic differentiation include members of the laminin and fibroblast growth factor families.
11. Central synapses develop in ways similar to those discovered at the neuromuscular junction. Many central synaptic organizers have now been discovered, including neuroligins, neurexins, protein tyrosine phosphatases, leucine-rich repeat proteins, and numerous others.
12. Many of the synapses that form initially in both the peripheral and central nervous systems are subsequently eliminated, generally by competitive, activity-dependent mechanisms. The consequence is that as circuits mature, the number of inputs a neuron receives may decrease dramatically, but the size and strength of the remaining inputs increase even more dramatically.
13. Along with pre- and postsynaptic partners, glial cells play key roles at the synapse. In particular, both astrocytes and microglial cells receive signals from and send signals to developing synaptic partners, with these signals contributing to synapse formation, maturation, maintenance, and elimination.

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Experience and the Refinement of Synaptic Connections

The human nervous system is functional at birth—newborn babies can see, hear, breathe, and suckle. However, the capabilities of human infants are quite rudimentary compared to those of other species. Wildebeest calves can stand and run within minutes of birth, and many birds can fly shortly after they hatch from their eggs. In contrast, a human baby cannot lift its head until it is 2 months old, cannot bring food to its mouth until it is 6 months old, and cannot survive without parental care for a decade.

What accounts for the delayed maturation of our motor, perceptual, and cognitive abilities? One main factor is that the embryonic connectivity of the nervous system, discussed in Chapters 45 through 48, is only a "rough draft" of the neural circuits that exist in our adult selves. Embryonic circuits are refined by sensory stimulation—our experiences. This two-part sequence—genetically determined connectivity followed by experience-dependent reorganization—is a common feature of mammalian neural development, but in humans, the second phase is especially prolonged.

At first glance, this delay in human neural development might seem dysfunctional. It does exact a toll,

but it also provides an advantage. Because our mental abilities are shaped largely by experience, we gain the ability to custom fit our nervous systems to our individual bodies and unique environments. It has been argued that it is not just the large size of the human brain but also its experience-dependent maturation that makes our mental capabilities superior to those of other species.

The plasticity of the nervous system in response to experience endures throughout life. Nevertheless, periods of heightened susceptibility to modification, known as *sensitive periods*, occur at particular times in development. In some cases, the adverse effects of deprivation or atypical experience during circumscribed periods in early life cannot easily be reversed by providing appropriate experience at a later age. Such periods are referred to as *critical periods*. As we shall see, new discoveries are blurring the distinction between sensitive and critical periods, so we will use the term "critical periods" to refer to both.

Behavioral observations have helped us appreciate critical periods. Imprinting, a form of learning in birds, is one of the most striking illustrations of a lifelong behavior established during a critical period. Just after hatching, birds become indelibly attached, or imprinted, to a prominent moving object in their environment and follow it around. This is typically their mother, but it could be an experimenter who is near the newborn chick. The process of imprinting is important for the protection of the hatchling. Although the attachment is acquired rapidly and persists, imprinting can only occur during a critical period soon after hatching—in some species, only a few hours.

In humans, critical periods are evident in the ways children acquire the capacities to perceive the world around them, learn a language, or form social relationships. A 5-year-old child can quickly and effortlessly learn a second language, whereas a 15-year-old adolescent may become fluent but is likely to speak with an accent, even if he lives to be 90 years old. Likewise, deaf children fitted with a cochlear implant during the first 3 to 4 years of life generally acquire and understand spoken language well, whereas neither production nor understanding may ever be normal following implantation at later ages. Such critical periods demonstrate that experience-dependent neural development is concentrated in, although certainly not confined to, early postnatal life.

We begin this chapter by examining the evidence that early experience shapes a range of human mental capacities, from our ability to make sense of what we see to our ability to engage in appropriate social interactions. The neural basis of these experiential effects has been analyzed in numerous parts of the brains of experimental animals, including the auditory, somatosensory, motor, and visual systems. Here, rather than surveying multiple systems, we will focus primarily on the visual system because research on this system has provided a particularly rich understanding of how experience shapes neural circuitry. We will see that experience is needed to refine patterns of synaptic connections and to stabilize these patterns once they have formed. Finally, we will consider recent evidence that critical periods in many systems are less restrictive than once thought and, in some cases, can be extended or even "reopened."

Understanding critical periods in childhood and the extent to which they can be reopened in adulthood has many important practical consequences. First, much educational policy is based on the idea that early experience is crucial, so it is important to know exactly when a particular form of enrichment will be optimally beneficial. Second, medical treatment of many childhood conditions, such as congenital cataracts or deafness, is now predicated on the idea that early intervention is imperative if long-lasting deficits are to be avoided. Third, there is increasing suspicion that some behavioral disorders, such as autism, may be caused by impairment of reorganization of neural circuits during critical periods. Finally, the possibility of reopening critical periods in adulthood is leading to new therapeutic approaches to neural insults, such as stroke, that previously were thought to have irreversible consequences.

Development of Human Mental Function Is Influenced by Early Experience

Early Experience Has Lifelong Effects on Social Behaviors

One of the first indications that early social and perceptual experiences have irreversible consequences for human development came from studies of children who had been deprived of these experiences early in life. In rare cases, children abandoned in the wild and later returned to human society have also been studied. As might be expected, these children were socially maladjusted, but surprisingly, the defects proved to persist throughout life.

In the 1940s, the psychoanalyst René Spitz provided more systematic evidence that early interactions with other humans are essential for normal social development. Spitz compared the development of infants raised in a foundling home with the development

of infants raised in a nursing home attached to a women's prison. Both institutions were clean and both provided adequate food and medical care. The babies in the prison nursing home were all cared for by their mothers, who, although in prison and away from their families, tended to shower affection on their infants in the limited time allotted to them each day. In contrast, infants in the foundling home were cared for by nurses, each of whom was responsible for several babies. As a result, children in the foundling home had far less contact with other humans than did those in the prison's nursing home.

The two institutions also differed in another respect. In the prison nursing home, the cribs were open, so that the infants could readily watch other activities in the ward; they could see other babies play and observe the staff go about their business. In the foundling home, the bars of the cribs were covered by sheets that prevented the infants from seeing outside. In reality, the babies in the foundling home were living under conditions of severe sensory and social deprivation.

Infants at the two institutions were followed through their early years. At the end of the first 4 months, the infants in the foundling home fared better on several developmental tests than those in the prison nursing home, suggesting that intrinsic factors did not favor the infants in the prison nursing home. But by the end of the first year, the motor and intellectual performance of the children in the foundling home had fallen far below that of children in the prison nursing home. Many of the children in the foundling home had developed a syndrome that Spitz called *hospitalism* and is now sometimes called *anaclitic depression*. These children were withdrawn and displayed little curiosity or gaiety. Moreover, their defects extended beyond emotional and cognitive signs. They were especially prone to infection, implying that the brain exerts complex controls over the immune system as well as behavior. By their second and third years, children in the prison nursing home were similar to children raised in normal families at home—they were agile, had a vocabulary of hundreds of words, and spoke in sentences. In contrast, the development of children in the foundling home was still further delayed—many were unable to walk or to speak more than a few words.

More recent studies of other similarly deprived children have confirmed these conclusions and shown that the defects are long-lasting. Longitudinal studies of orphans who were raised for several years in large impersonal institutions with little or no personal care, then adopted by caring families, have been especially revealing. Despite every effort of the adoptive parents, many of the children were never able to develop appropriate, caring relationships with family members or peers (Figure 49–1A). More recent imaging studies have revealed defects in brain structure correlated with, and presumably due to, this deprivation (Figure 49–1B).

As compelling as these observations are, it is difficult to derive definitive conclusions from them. An influential set of studies that extended the analysis of social behavior to monkeys was carried out in the 1960s by two psychologists, Harry and Margaret Harlow. The Harlows reared newborn monkeys in isolation for 6 to 12 months, depriving them of contact with their mothers, other monkeys, or people. At the end of this period, the monkeys were physically healthy but behaviorally devastated. They crouched in a corner of their cage and rocked back and forth like autistic children (Figure 49–1C). They did not interact with other monkeys, nor did they fight, play, or show any sexual interest. Thus, a 6-month period of social isolation during the first 18 months of life produced persistent and serious disturbances in behavior. By comparison, isolation of an older animal for a comparable period was found to be without such drastic consequences. These results confirmed, under controlled conditions, the critical influence of early experience on later behavior. For ethical reasons, these studies would not be possible today.

Development of Visual Perception Requires Visual Experience

The dramatic dependence of the brain on experience and the ability of that experience to shape perception is evident in people born with cataracts. Cataracts are opacities of the lens that interfere with the optics of the eye but not directly with the nervous system; they are easily removed surgically. In the 1930s, it became apparent that patients who had congenital binocular cataracts removed after the age of 10 years experienced permanent deficits in visual acuity and had difficulties perceiving shape and form. In contrast, when cataracts that develop in adults are removed decades after they form, normal vision returns immediately.

Likewise, children with *strabismus* (crossed eyes) do not have normal depth perception (*stereopsis*), an ability that requires the two eyes to focus on the same location at the same time. They can acquire this ability if their eyes are aligned surgically during the first few years of life, but not if surgery occurs later in adolescence. As a result of these observations, congenital cataracts are now usually removed, and strabismus is corrected surgically, in early childhood. Over the