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Brain Plasticity and Regeneration

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Brain plasticity includes the enormous changes of normal prenatal and postnatal development, responses to normal experience such as the springtime reemergence of bird song, and responses to injury. This broad view of plasticity brings together the large and growing fields of developmental neuroscience, learning and memory, and responses to injury. Such a synthetic view is essential now that these fields are being elucidated at cellular and molecular levels. The major stages of normal brain development are very similar to those of plasticity induced by experience. Particular cellular or subcellular details are similar, depending on the specific case. Importantly, these common steps are the very ones we most need to understand if the outcome of brain and spinal cord injury is to be improved. Knowledge of brain plasticity will be the basis for innovative treatment of such injuries. Relevant mechanisms reviewed here include chemical stimulation of receptors, regulation of gene expression in surviving cells, gene introduction by viral or cellular vectors, cell-cell interactions such as guidance of axons, and replacing neurons lost by injury. Increasing knowledge of plasticity and its application to therapy offers promising approaches for improving the outcome of cerebral and spinal injury, making optimism unavoidable.

What is Neuroplasticity?

An unknowing and immobile baby develops into an intelligent and independent person. Observations like this are so striking that for centuries people have accepted the idea of plasticity (change) of the mind. Yet until the second half of this century, plasticity of the mind was not thought to involve plasticity of the brain (1). Progress in understanding the mechanisms underlying brain plasticity has come from clinical observations and especially from animal research.

In the spring, a male songbird begins to sing because a remarkable set of structural, chemical, and functional changes occurs in the song centers of its brain. The song center of birds' brains are small in females and in wintertime males (2). Each spring, however, the song centers of *male* birds grow and undergo maturation in a manner similar to the way the normal embryonic brain develops in higher animals, including humans. Many new neurons are formed. These migrate to the appropriate site and then form connections to and from other neurons. Their chemical machinery is soon working, and they begin functioning to produce bird song. The variety of bird songs and the variations in the ways they are acquired among different types of birds emphasize that learning and experience are important in determining the specific bird songs. But first, the appropriate neural components must be formed. The internal trigger for this whole sequence is the male sex hormone testosterone, a small chemical produced entirely outside the brain. Testosterone has this effect at all ages, and, applied experimentally, in both sexes.

The brains of humans and other mammals do not appear to have the capacity for making new neurons or for integrating them into the existing brain, except in the olfactory system. The odor-detecting olfactory nerve cells that extend into the lining of the nose are normally damaged throughout our lives. They are replaced continuously in a fashion similar to the springtime changes in song centers, and similar to the fetal

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development of human brains. As in these two situations, undifferentiated stem cells are found at the base of the olfactory epithelium. The stem cells divide. One of the pair remains at the base of the olfactory epithelium. The other daughter cell migrates as a differentiating neuroblast, and is incorporated into the nasal epithelium. The new neuron elaborates functional processes, one with receptive elements extending into the mucosa and the other extending into the olfactory bulb where it forms functional synapses.

The presence of germative stem cells is necessary and at times sufficient for the capacity to replace nerve cells. The absence of stem cells is probably the reason that we do not replace lost neurons naturally. However, we may have a latent capacity to replace neurons, since all genes remain present, or, alternatively, new cells may be implanted surgically. Within limits, new neurons of host or donor origin can be integrated into mammalian brains by plasticity of axons, dendrites, and synapses and by the metabolic machinery of neurons, all natural processes in all parts of the brain.

In its broad sense, then, neuroplasticity refers to the three processes described: normal development, learning, and recovery from injury. Two major principles pertain. First, it is the combination of time and place that determines every aspect of brain structure and function. The importance of this spatiotemporal dimension applies to every step of brain development, every aspect of normal brain function, and every recovery from injury. One liver cell is like another; if you destroy 30% of the liver cells you are still okay. Each part of the brain, however, has special functions and capacities, which change with age. Second, most details of neuroplasticity apply well to the entire animal kingdom and to all parts of the nervous system (3). For clarity, most of this discussion will be based on the brain of higher animals. Since it is easier to describe changes in the brain's structure than its chemistry and function, this paper will seem to emphasize structure. But structure, chemistry and function are inseparable, so one must remember that changes in one are always accompanied by changes in the other two.

Plasticity in Normal Brain Development

The formation, migration, and aggregation of neurons into brain regions exhibit plasticity, as discussed in preceding papers in this symposium.

TABLE 1: Stages of development

Cell division
Cell migration and aggregation
Elaboration of dendrites
Elaboration of axons
Axonal elongation
Axonal arborization
Synaptogenesis
(Neurochemical and functional aspects)

We begin here by looking at the formation of neuronal connections. Like the earlier steps in forming the brain and in establishing brain function, the formation of axons, dendrites, and synapses starts at specific times in each part of the brain. A few of the molecular events underlying spatiotemporal patterns in the brain are emerging. For example, homeobox genes are a class of genes that initiate the activity of numerous other genes in ways that appear to regulate spatiotemporal aspects of the body plan. They are found in insects, mice, and humans in virtually unchanged form. In mammals, over 20 homeobox genes are expressed in an overlapping spatiotemporal mosaic that includes all parts of the neuraxis (4). The regulation of homeobox gene expression is not yet understood.

Retinoic acid is another important controller of spatiotemporal development. Retinoic acid affects limb structure, the differentiation of some neural precursor cells in vitro, and probably the development of the eye and brain as well (5). It is not known which genes are regulated by retinoic acid acting on its receptor in the cell nucleus.

Primarily by blind production of monoclonal antibodies, a number of other gene products have been identified at particular sites in the developing nervous system. Some of these gene products are made during limited time spans (6). Others, *begin* to be made at specific times in development, but are then expressed persistently thereafter. There is much to learn about these genetic events and their control by other genes and epigenetic events.

Many other genes appear to play regulatory roles in the early nervous system. Many endogenous and exogenous chemicals influence early brain development. Some are harmful, such as ethanol and medications like isotretinoin and sodium valproate. Others are essential regulators of development, such as thyroid hormone, corticosteroids, insulin, sex hormones, and vitamins. Most of the known examples are substances that

had been known to function in later life, before being found to affect development as well (7).

An important group of genes, first discovered as oncogenes, and then proto-oncogenes, has been found to code proteins that regulate other genes. These genes are active and important in normal development as well as oncogenesis, so they have been given a new name: immediate early genes. They are proving important in short-time scale events in neurons. They may form a new bridge between normal development and the plasticity induced by normal experience or injury. Conversely, some genes first discovered as regulators of embryonic development, now turn out to have additional functions in later life. For example, several of the group of compounds called growth factors, found because of their effect on brain development, are proving to have important functions later in life involving brain and other organs. The importance of all of these discoveries is that every gene and every regulatory mechanism provides the possibility for a useful therapeutic intervention.

Elaboration of Dendrites and Axons

The migration of the neuroblasts is directed by chemical cues on the surfaces of the cells over which they crawl (8). Like a caterpillar crawling out on a branch, the neuron migrates along radial glial guides. As a caterpillar changes to a butterfly, the neuroblast evolves into a complex, often beautifully contoured, neuron. During or soon after migration, the neuron cell body sends out two types of extensions, axons (discussed below) and dendrites. Dendrites are relatively short processes that spread out near the cell body to receive information from incoming axons. Each type of nerve cell has a distinctive dendritic pattern. This dendritic pattern is partially determined intrinsically, and partly determined extrinsically, since the pattern is complete only if normal axons contact the dendrite (9). Dendrites require input from axons to survive. If all the axons a dendrite receives are lost, the dendrite itself will be completely lost (10). Dendrites are important throughout life for the formation and function of synapses (11). The general features of nerve cell development, ie, specificity of time and place, and overproduction followed by elimination, apply to the development of dendrite branches, as well as to axons and synapses.

Axons are the long-distance fibers that connect nerve cells. Axons must elongate from the neuronal cell body, find their target and form contacts with it. They then must continue to elongate as the fetus and baby grow. In uncertain circumstances axons must perhaps be eliminated. The initial, pioneer axon, like a migrating nerve cell, follows chemical signals that it detects with an amoeba-like motile growth cone that "sniffs around" for the correct path (12). Later axons of the same type only have to follow the pioneer axons, whose surface they recognize chemically (13). As the brain grows and matures, an axonal path that had been short and straight at the time of initial growth may become very complex in the adult brain. In normal growth and development, the increase in the distances in the brain and the changing shape of the brain pose little problem. Axons have only to elongate to maintain their contact with the dendrite. However, should damage occur to interrupt axonal bundles, then repair of the damage would require renewed "pathfinding" through a now large, complex, and potentially hostile brain. This is a major impediment to recovery after brain and spinal cord injuries. In experimental studies, several possible chemical or physical treatments appear to facilitate axonal outgrowth and synaptogenesis. The most promising involves transplantation of brain parts or peripheral nerve trunks (14).

Synapse Formation and Plasticity

Axons form billions of synapses in the brain. Most of these are contacts with dendrites. These are the "computer chips" with which the brain does its work of solving problems. The brain has more computational power than many of the largest supercomputers combined. In addition, synapses are far more sophisticated than the simple on/off function of computer elements. They have variable capability and they interact with many other synapses to determine the output of a nerve cell, substantially augmenting the power and adaptability of brain function. For some problems, computers perform better when they are operated with software that imitates these features of the brain, the so-called neural networks.

Normal development requires that synapses be formed correctly in development, with matching chemistry between the axon and dendrite. Genetic factors probably determine the major features of the system, such as which axons and dendrites pair to form synapses, the chemistry of the synapses, how many synapses an axon

forms, and how many synapses a dendrite receives. If a neuron does not form enough synapses with the correct target, it will die (15). The price of failure is death. An axon is "rescued" from such death by taking up specific compounds into the axonal ending, and by transporting these compounds back to the cell body. At least some neurons require this source of trophic input throughout life for survival, or at least for normal function.

It is important to overcome the bias, now disproved, that the brain, or any part of the brain, is "hard-wired" during development. The brain is not made by "hard-wired" connections during development the way a telephone switch board is soldered together. The illusion of hard-wiring results from the striking predictability of brain structure and function. Actually, synaptic development is very plastic, involving synapse elimination and modification occurring throughout the time that the net number of synapses is increasing, as well as afterwards. During development, synapses are active; this activity affects which synapses are retained or eliminated. The same is true postnatally, except that synaptic activity is then more directly the result of experience. The process can be seen in the development of visual connection (also see next paragraph). The lateral geniculate nucleus and visual cortex both receive overlapping terminations of input from the two eyes when synapses are first formed (16). Later, the location of these synapses normally changes, resulting in separate, alternating areas for the input from each eye. Experimentally, if you change the activity of these synapses asymmetrically by blurring the vision from one eye (17) or by chemically blocking the nerve impulses from one eye to the brain (18), then you see an increase in the area contacted by the functioning eye. However, if you reduce the activity symmetrically by rearing the experimental animal in complete darkness, you get a fairly normal structure. These three types of experiment show that genetic control alone is insufficient to produce normal synaptic connections, and that structure and function at synapses are inseparable in their effects on brain organization.

Plasticity of Synapses in the Rat Interpeduncular Nucleus

The same general pattern of events has been found in plasticity studies that have used the electron microscope to see the actual synapses. These data are important because plasticity itself necessarily occurs at the individual synapses. Elegant as they are, experiments that look at brain regions rather than the specific synapses require a deductive leap. For example, electron microscope studies of the interpeduncular nucleus (IPN) of the rat midbrain permit display and characterization of the individual synapses rather than of the broad regions that contain many synapses. The principal afferent supply to the IPN comes from the paired medial habenular nuclei (MH) (19). The cholinergic MH axons enter the rostrolateral portions of the IPN on each side, but then form spirals of interdigitating axons that cross the IPN to the opposite side, recurving and recrossing many times. Synapses are distributed along these axons in specific patterns (Fig. 1).

Crest Synapses

This uncommon type of complex synapse consists of two ordinary synaptic contacts on an extraordinarily narrowed dendritic sheet or crest (Fig. 2) (20). Cytoskeletal material present in the crest between the postsynaptic densities probably determines this configuration. There is evidence of local protein synthesis at these sites during development (Lenn NJ, unpublished data, 1985). In the normal adult, 90% of the synapses are left-right paired, ie, in 90% of these complex paired crest synapses, one of the two adjacent synapses is from a left MH neuron, whereas the adjacent synapse of the pair is from the contralateral right MH (21, 22). It is this left-right pairing of afferents onto adjacent synapses of the pair that permits us to ask how this orderly and specific adult organization comes about developmentally *at individual synapses.* It also allows assessment of the response of individual synapses to injury.

Normal Synaptogenesis of Crest Synapses

Crest synapses are present from 8 days of age onward (11), and increase in number and complexity of form for 45–90 days (23). Through 28 days of age, by which time one-fifth of the adult number of synapses have formed, there is preferential formation of same-side (left-left, right-right) pairing at the synapses. That is, both of the synapses of a pair come from the MH of the same side (Fig. 3). By adulthood, 90% of all synapses are left-right paired. The only plausible explanation is that as crest synapses continue to be formed in large numbers, pairing is remodeled

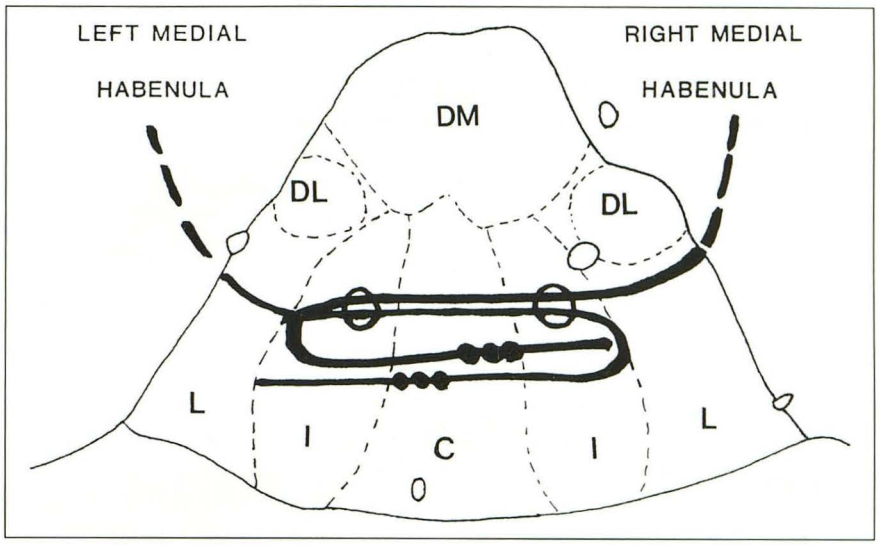

Fig. 1. Cartoon of the interpeduncular nucleus. A cholinergic axon from each medial habenula is shown. Crest synapses, formed by one en passant ending of each axon, are represented by open circles in each intermediate subnucleus (*I*). Closed circles represent other synapses formed by these axons. Modified from Lenn (3).

to eventually produce the adult pattern of 90% left-right paired. In keeping with the findings for large areas of synaptic regions, one may suggest that this remodeling is functionally modulated, perhaps by associative interactions as described above. Before suggesting the likely sequence of steps involved in crest synapse remodeling, review of plasticity after injury will be helpful (anticipating the next section of this review).

Response of Crest Synapses to Deafferenting Lesions

Experimentally, creating a lesion in one MH will cause the death of axons arising from that side. Such axonal death removes the synaptic input from these neurons and axons. This is called deafferentation. Two months after normal *adult* crest synapses are deafferented by a lesion in one MH, 66% or more of remaining synapses are formed by two MH axons that are (necessarily) from the same, unlesioned MH (22). That is, in *adults*, axons from the intact MH appear to grow in to maintain the synapses, but, necessarily the two synapses of the pair are formed with axons from the same—sole remaining—side. This is an impressive degree of reactive reinnervation compared to other brain regions. However, when the MH lesion is made in *newborn* rats, before the initial appearance of crest synapses, the result is even more vigorous. Under these conditions, 96% of crest synapses are formed by two MH axons by 28 days (23), more than in the lesioned adult or the normal animal at this age (24).

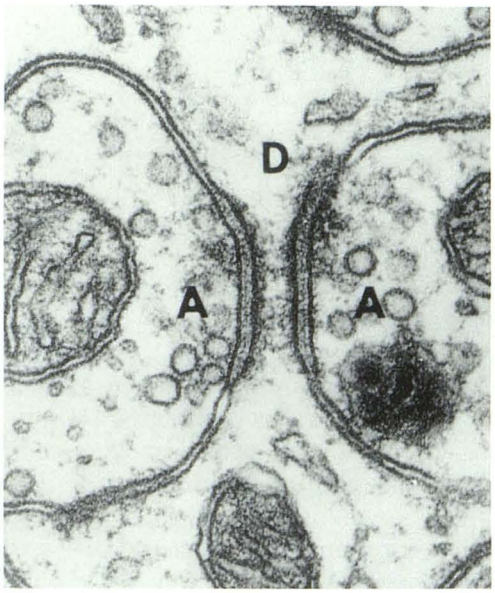

Fig. 2. Electron micrograph of a crest synapse. Two axons (*A*) form parallel, coextensive synaptic contacts on a narrowed dendritic process (*D*). Modified from Lenn (20).

These two sets of data on normal development of crest synapses and their response to injury can be understood by a three-step hypothesis. Step one involves specific recognition between MH axons and the IPN neurons in particular parts of the IPN (Fig. 1). This is required to explain how the localization of these synapses is normally limited to particular parts of the IPN at all ages. It also accounts for the formation of crest synapses seen after neonatal lesions. The second step is the formation of the characteristic structure of crest synapses, two endings on opposite sides of the crest. The feature is best explained

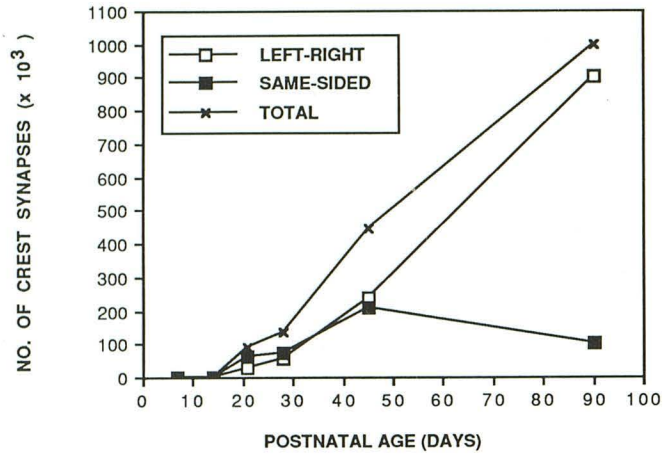

Fig. 3. Development of crest synapses from birth to 90 days of age in rat. The total number of crest synapses at each age studied is plotted, along with the numbers of left-right paired and same-sided crest synapses, respectively. See text for details. Modified from Lenn and Whitmore (24).

by an attribute of the dendrites, not the afferent axons. The strongest evidence for this is the formation of crest synapses by these dendrites after removal of both MH in the neonatal period. Third, functionally modulated synaptic remodeling is the probable basis for the change from same-side paring to crossed left-right pairing at the crest synapses (Fig. 1), as observed in normal development.

Plasticity of connectivity is striking in the case of the spinal projections of cortical neurons. Of course, the motor cortex forms and retains axons that project to various levels of the spinal cord throughout life. However, neurons of the visual cortex also send axons far into the spinal cord during development. These spinal projection axons from the visual cortex are later eliminated without loss of the cells of origin, whose other connections are appropriate to visual function. Importantly, when visual cortex or motor cortex is transplanted to the other's location early in development, the transplanted cortex makes various connections, but retains only those synapses appropriate to its new location, not the synapses appropriate to its site of origin. These data show that genetic and external influences interact, to form diverse patterns at different times and different places, none of which can be described as hard-wiring.

Plasticity Induced by Experience

Brain activity can be considered on two time scales, moment to moment and longer term. We must be able to react to moment-to-moment events if necessary without special attention, and without forming memory of them. Moment-to-moment changes in the brain are mostly electrical, with associated instantaneous changes in the size and shape of existing synapses and with complex chemical events, lasting no longer than the picture on your TV screen. Longer term changes, including normal development, memory, and learning, are different. Progress in understanding how memory and learning occur was stifled until recently by the dogma that the brain's structure was unchanging. It is now evident that the process of synapse formation and elimination continues throughout life and is responsible for longer term functional changes.

In fact, plasticity of the mind is beginning to be understood in terms of structural, functional, and chemical plasticity of synapses. An example shows how an external event induces synaptic plasticity. If a cat pays attention to a pattern of light, synapses that are especially sensitive to that pattern are strengthened and retained (25). If the cat is not attentive, these synapses are not strengthened and may be eliminated. In both cases, the visual information traverses the cat's retina, optic nerves, and thalamic projections to cortical neurons in the same way. The difference lies in whether or not there is simultaneous activity in a second type of synapse coming from diffuse brain-stem projections of catecholamine or cholinergic neurons and contacting the same cortical neurons. This second type of synapse is special in that when active it enhances dendritic responses to visual input by activating voltage-sensitive ion channels (26). When the visual input lowers the membrane voltage, the ionic response is larger than if the voltage-sensitive channel were closed. This process is called *associative*, because activity in two pathways must be associated for the effect to occur. The associative effect is retained, because the enhanced ionic response promotes retention and strengthening of the visual synapses, enhancing future responses to the same input. This retention of enhanced responses is *learning*, called associative learning because of how the effect is produced. It may equally well be considered a form of memory, in the literal sense. While the chemical details differ, the same mechanism has been shown to produce associative learning in other regions of the brain, including the hippocampus, which is so important in memory function and epilepsy (27).

Plasticity due to altered function has been studied experimentally in the visual system. These experimentally induced alterations are different than associative learning, in that their effects are limited to particular times during development in mammals. In Amphibia, where regeneration of visual connections occurs, the same plasticity can be induced at any age. In these experiments, conditions that act to reduce the function of one eye lead to reduced synapses from that poorly functioning eye and increased synapses from the contralateral good eye. Thus blurring of vision from one eye, chemically blocking the nerve impulses from one eye to the brain, complete darkness, creation of strabismus, and rearing in an environment with only vertical lines, all modify the synaptic territory and strength for the abnormally functioning eye and increase the synaptic territory and strength for the normally functioning eye.

In tadpoles, it is possible to induce regeneration of the optic nerve after it is severed. Indeed, at critical periods, one can harvest an excised eye from a donor tadpole of the same age, implant that donated eye near to the normal eye of a host tadpole and then sever the optic nerve of the adjacent host eye. In that circumstance, the two adjacent (host and donor) eyes will each regrow optic nerves that then connect with the optic lobe to create a three-eyed tadpole.

In this special circumstances, the determination of synaptic territory has been shown to involve an associative process mediated by action of voltage-sensitive ion channels, as in the cat visual cortex (28). These experiments show that genetic control alone is insufficient to produce normal development, and that structure, function, and chemistry at synapses are inseparable in their effects on brain organization.

Associative learning may also be involved when infant rhesus monkeys and infant humans can find a toy after it is put under one of two cups while they watch (29). In a Piaget-type, two-trial, A not B experiment, the experimental subject is shown two cups, A and B. In the first trial, the subject watches the experimenter put a toy under cup A. The subject then looks for the toy and easily finds it under cup A, on the *first* try. In the second trial, the subject watches the experimenter put the toy under cup B and then tries to find it again. What happens next depends on age, associative learning, and developmental change. Before specific ages, 2 months for monkeys and 9 months for humans, the subjects again look under cup A, before they turn to cup B. Apparently, the reinforcement received by finding the toy under cup A in trial 1 outweighs the direct visual input of seeing the toy put under cup B in trial 2. After these specific ages, monkeys and humans both find the toy under cup B on the first try in trial 2.

The correct answer on the second trial depends on the dorsomedial frontal cortex. The age at which the babies find the toy on the second trial correlated with a change in the structure and chemistry of the brain area involved. Removing this area in *prenatal* monkeys does not affect later function, because neighboring areas of the brain take over the structure and function. However, damage to this area later, even in infancy, leads to persistent dysfunction (30). Incomplete damage and vigorous long-term therapy and education should both result in a better outcome. Other examples of synapses with experience for which details of the chemistry are known include habituation of snout retraction when snails are touched on the snout repeatedly and the response of fruit flies to light (31).

Plasticity after Injury

We have seen that synapses are made and modified during normal development and learning. This section addresses their response to injury, the third type of neuroplasticity. Our knowledge of synaptic changes after injury comes from animal experiments, but some features of human disease, described in the next section, appear to follow the same principles. Brain damage removes nerve cells and axons, including all of their synapses. Additional changes occur in neurons that had synaptic connections with the damaged nerve cells, even though those neurons are distant from the injury and not directly damaged. The effect on the distant undamaged neurons depends upon whether the distant cells sent axons to the damaged area or received synapses from it. Cells that sent axons to the area of damage will survive if they have other connections to undamaged areas. They can also form new synapses with any surviving nerve cells within the damaged part of the brain. This may restore function, especially if combined with appropriate training. Distant nerve cells that have lost their input from the damaged area, may show decreased function even though the cells are healthy. Later, these cells may attract sprouts from nearby axons and make synapses

with these sprouts, again with the possibility of improved function.

However, such naturally occurring neuroplasticity varies in extent and functional effect, as detailed in many experimental studies of different parts of the brain (32). The changes can be deleterious, for example when spastic rigidity adds to the dysfunction caused by weakness and incoordination in children with cerebral palsy. Also, since life styles and life experiences are often altered after an injury, additional effects will result from such altered experience acting on an altered nervous system. There are limited data about such phenomena, much of it incidental to studies of normal development and plasticity induced by experience. Examples of effects of injury have been mentioned above in the discussion of synapses in the interpeduncular nucleus, lesions in the visual system, and lesions in the frontal cortex in rhesus monkeys. In fact, the experiments that started the modern study of neuroplasticity were of this type. It was known that frog optic nerves regenerate after being cut. Sperry did this, but turned the eyeball upside down (33). He then tested the frog's vision by holding flies in various positions near the frog. Normally, the frog's tongue strikes at a fly accurately. But with the eye upside down, there were three possibilities. If the eye reconnected to the brain in the same pattern as before, eye rotation would make no difference and the frog would get the fly. If reconnection was haphazard, the frog would strike randomly, possibly getting better with practice. But if each nerve cell in the eye reconnected to the same place in the vision center of the brain that it selected before, the frog would strike at a spot diametrically opposite to where the fly was held. In fact, this last is what happened. The frog acted as though the fly were located where it would have been in order to be seen by the particular spot on the retina before rotation of the eye. It acted according to which part of the eyeball saw the fly rather than where the fly was located. Experiments since have revealed effects of such things as age at operation, surgical details, repeated injury, and, most recently, drug treatments that can be advantageous or negative (26, 28).

Evidence of Plasticity in Human Disease

In our concern for patients, we try to apply to human disease the results of experiments on neuroplasticity in other species. We need to know how differences between people and other animals affect the application of experimental data to our patients. At present, we know only three major examples of human brain plasticity in response to injury. In the human *visual system*, strabismus *in infancy* lead to decreased vision. The baby fixes one eye on objects. The brain seems to ignore what is seen by the other eye, as though its function is suppressed to prevent confusion from two mismatched views of the world arising from unaligned eyes. It seemed rather magical that if this went on for several years, the vision in the suppressed eye decreased permanently and often severely. What was not anticipated until experimental work was done, was that the very organization of the synapses in the vision centers of the cerebrum changed in this situation. Many of the synapses from the nonfixated eye were eliminated, leading to the deterioration of vision in that eye. No comparable loss of synapses will occur if the eyes first become crossed later in life, nor can the loss of synapses be overcome after infancy. Such visual loss from uncorrected crossed eyes is a preventable structural and functional developmental disorder in the human. It has a critical period in the same sense that we speak of critical periods in child development as optimal times for learning language or other functions. This is an excellent example of both advantageous neuroplasticity in that double vision is eliminated, which would have been especially important before modern medical care, and deleterious plasticity in that significant recovery does not occur after the critical period, even with surgical correction of eye position.

Plasticity in the *motor system* is evident in several ways. One is the recovery of motor function after injury. Because this recovery occurs over weeks or months after injury, it cannot be ascribed to early, reversible disturbances of metabolism. The extent of recovery depends on the extent of damage, among other factors. Functional motor deficits disappear by 7 years in 50% of children who had them at 1 year of age (34). However, recovery occurs at all ages, and many adults enjoy similar resolution. Asymmetrical synkinesis (involuntary movement of one hand when the other is moved) is common with unilateral motor dysfunction (hemiparesis) in early childhood (35), but is uncommon after adult injury. Similar animal experiments suggest that synaptic plasticity is involved. In humans, synaptic plasticity is also suggested by the absence of facial weakness in hemiparesis of prenatal

onset versus hemiparesis of later onset (36). This age effect is absent when the hemiparesis is bilateral. These data indicate that there is a critical period, that normal synapse elimination is modified after injury, and that intermediate effects occur during the period from birth to 1 year of age.

It is agreed that damage to the *language* areas of an infant produces less loss of function than similar degree later in life (37). Even older children usually recover better than adults. Two types of plasticity may be occurring. The first is the recovery due to neighboring areas of the brain taking over language function, especially those areas with related normal functions. The other is recovery due to language function appearing in the opposite side of the brain. The latter increases the size of the language centers on the right side of the brain in non-right handed patients with brain damage. The age range in which such plasticity appears to occur is long, but poorly delineated.

Potential Therapeutic Interventions

Until now, acute therapy of brain injury has been limited to preventing any increase in the brain damage and allowing nature to take its course. Chronically, we use experience, education, and training to stimulate recovery and to retrain function. Since therapy is a form of experience purposely imposed on an injured brain, consideration of therapeutic options should draw on knowledge of plasticity induced by experience, as well as plasticity induced by injury. In children, normal developmental plasticity comes into play as well. Thus, all aspects of plasticity converge in our area of greatest concern, finding novel treatments for neurologic diseases, especially those that are time-limited and leave stable dysfunction.

Profound alterations in the brain are associated with normal brain development, learning to talk as an infant, improving a tennis serve, studying a new language, learning to walk after a stroke, or singing in spring if you are a songbird. These activities involve normal development, facilitation by functional activity, cognitive learning, recovery of function after damage, and the role of a small molecule like testosterone in triggering the complex structural and functional change that is bird song.

We always knew that the mind could change. We now understand that the brain also changes. Future work will uncover the chemical bases for these changes and develop chemical therapies that will initiate, modulate, or augment change. Every spatial, temporal, functional, and chemical aspect of injury may prove to be a site of possible therapy. Every chemical change that is harmful can potentially be blocked. Every cell surface receptor, second messenger or higher order messenger, and every gene promoter or blocker can be potentially activated or blocked by some exogenous chemical or induced alteration in gene expression. Every gene that is no longer functional can potentially be restarted. Each functioning gene can potentially be reset to a different level of function or turned off. Experiences can be modified.

There is evidence that combining these approaches enhances recovery from injury. The clearest examples of this are the experiments that combined "patient" experience with chemical treatment after surgically induced hemiparesis in cats (38). In brief, recovery was enhanced by combining practice (walking a narrow beam) with amphetamine administration. Conversely, recovery was diminished by haloperidol. Practice alone was better than amphetamine alone, but both together were best. Although not yet understood in detail, this striking observation offers much promise.

In cases of severe damage, good recovery cannot be achieved by therapy directed at the remaining tissue. This may be because too many neurons and glia are lost, because a specific type of important neuron is depleted, or because barriers such as distance inhibit axonal regeneration. In such cases, the greatest promise for future therapies involves the application of molecular biology, tissue culture and tissue transplantation. For example, a cerebellar biopsy that does not cause clinical dysfunction contains millions of granule cells. If modified in tissue culture as suggested above, these "new" neurons could be implanted into a damaged part of the patient's brain. Similar possibilities arise for implantation of olfactory stem cells, and possibly of other neurons or glia. Immature neurons have been successfully transplanted into almost every brain region in experimental animals. In an increasing number of instances, these grafts survive, grow, and form functional interconnections with the host brain. Implantation of artificial materials, glia, and peripheral nerve where they are needed may facilitate axon elongation by providing a proper growth surface (39).

Much attention has been given to treating Parkinson disease with fetal brain tissue. But Parkinson disease is a very special case. A single-cell type is needed for the chemical it produces. For a long time, the patient's needs may be met by simply taking the chemical by mouth. When there are no longer cells to convert the oral medication to its effective form, it may suffice to transplant such cells anywhere in the general region. However, transplants used to treat most brain injuries will need to do much more, including axon pathfinding and synapse formation. It has generally been thought that fetal cells were required for transplant therapy, leading to ethical concerns. It is suggested, however, that cells obtained postnatally from premature babies should be suitable in many cases. This avoids major ethical concerns. Postnatally obtained germinal cells would allow use of more cells, and operation of the normal cycles of control and effect that are already present in these nerve cells. Volunteer donors of biopsy tissue would provide additional options.

Pediatrics is an important area for application because premature infants are the ideal recipients, and children should do better with transplants than adults, according to results in other mammals. Gene regulation has already been achieved in some cases, but primarily in tissue culture. Since all genes are present in all cells, it is possible that mature neurons can be induced to multiply and differentiate to a desired type of neurons, but this is most likely if tissue culture and transplantation allow the genetic engineering to proceed in vitro.

Our goals and expectations for treating brain damage are thus much broader and more specifically formulated than current therapy implies. This is the clear message of the body of knowledge about neuroplasticity. The therapeutic ideas presented here may seem very speculative, but then experiments of the type underway today were equally speculative 3–5 years ago, and inconceivable shortly before that. Above all, this review has tried to present some of the evidence that makes the probability of such therapy virtually inescapable. Identification of damage, functional assessment of host and implanted tissue, and surveillance for long-term tissue changes are among the reasonable roles for neuroradiology in the implementation and evaluation of such therapy.

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