Most patients treated by physical therapists have suffered some neurological trauma resulting from disease or injury. The traditional teaching used to be that damage of central neurons is irreversible. Within the last decade, however, it has been necessary to cast aside this traditional view because of accumulating evidence that the brain is endowed with remarkable plasticity. This paper reviews experimental evidence revealing morphological and functional changes occurring in the CNS in response to neural lesions. Morphological responses to injury include collateral and terminal sprouting, retrieval of vacated synapses, alterations in the ultrastructure of surviving synapses, and denervation supersensitivity. Functional and adaptive changes induced by injury include the unmasking of ineffective synapses, shifts in receptive fields, and reorganization or altered effectiveness of surviving neural networks. These recovery phenomena attest to the brain’s dynamic properties. These new insights contradict our conventional view of the absence of growth and reorganizational capabilities in CNS neurons. These newly identified “recovery phenomena” are destined to have a significant impact on physical therapy in the future.

Key Words: Nerve regeneration, Nervous system, Neuronal plasticity.
possess similar capabilities but fail to express such capabilities because some critical factor is missing or the cell is in some way prevented from expressing the capabilities?

In addition, the detailed analyses of the phenomena of peripheral degeneration and regeneration revealed that a peripheral nerve lesion induces transsynaptic responses in central neurons not directly involved in the injury. Analogous transsynaptic responses to axonal injury are prevalent throughout the neural axis, including the brain.

These lesion-induced phenomena have been investigated in every region of the mammalian CNS. In succeeding sections of this paper, the CNS responses to rhizotomy, spinal transection, hemisection, double hemisection, a combination of rhizotomy and spinal transection, and specific brain lesions will be reviewed.

**RESPONSES TO DORSAL ROOT LESIONS**

**Behavioral effects of unilateral rhizotomy.** Cutting the dorsal roots on one side and leaving the contralateral dorsal roots intact is an experimental technique used to deafferentate a limb. In this case, the ascending and descending inputs to the lower motor system are intact with only the segmental feedback circuits interrupted. Postoperatively, the animal does not use the deafferentated limb or uses it poorly. Some reflexes return in time, and descending reflexes become exaggerated within a week or two. Goldberger has effectively demonstrated that if the dorsal roots are cut unilaterally from T5 through T13 in cats, the initial effects of the lesion are grave. An animal is unable to walk for the first two postoperative days. The trunk and tail are curved sharply away from the side of the lesion. The ipsilateral hind leg is hyperextended, and the contralateral leg is flexed. If the animal is propped up, it can stand for a second or two before a tremor becomes so severe that the animal falls to the side opposite the lesion. If the animal is supported by its tail, it can take a few steps, but the hind legs are greatly abducted, the lower trunk sways from side to side, the ipsilateral leg does not flex, and the contralateral leg does not extend. All of these disastrous motor signs are the result of interrupting sensory inputs!

After two to seven days, there is some recovery of the uncontrolled locomotion. The body still sways, and the gait is extremely abnormal because the stepping sequence is out of order, but the animal can walk along a runway 30 cm (12 in) wide. By the eighth day, locomotion can be accomplished with more precision, and the animal can walk along a runway 5 cm (2 in) wide. Locomotion continues to improve over the next three weeks. After that, no further signs of locomotor recovery are seen. In the chronic animal, the back remains permanently curved, and the pelvis continues to rock, causing swaying. The questions arise: What mechanisms have become active in the CNS during these two phases of recovery? What has taken place in the nervous system to achieve this improvement?

**Morphological and functional effects of unilateral rhizotomy.** The nature and the time of onset of the early motor recovery following rhizotomy are consistent with the morphological and transneuronal changes that occur in response to dorsal root lesions. These changes include collateral sprouting of viable neurons (as discussed in Part 3), dendritic atrophy of denervated neurons, and activation of ineffective synapses.

Collateral sprouting within the spinal cord was first demonstrated by Liu and Chambers in 1958. Their results have since been confirmed by electron microscopy. Axonal sprouting of dorsal root fibers occurs in response to the unilateral section of all but one dorsal root or to the section of descending pathways.
Descendant fibers also send out collateral sprouts on the deafferentated side, and this sprouting correlates with the behavioral signs of exaggerated descending pathway reflexes. In fact, if the sprouting is severed, the behavioral signs cease.

Dendritic atrophy is one orthograde transneuronal change. Many dorsal horn cells receive direct afferent connections from dorsal root fibers. Hence, rhizotomy constitutes a partial denervation of these cells, and like most cells deprived of their innervation, they undergo atrophic changes. Among the earliest of these changes is dendritic shrinkage. This dendritic atrophy was most rapid and severe in the L7 segment and decreased as a function of distance from L7. These results suggest that the rapidity and degree of dendritic atrophy are functions of the proportion of the cell's dendritic surface that has been denervated. The dendritic atrophy reported in this study was largely irreversible, probably because the cut dorsal root did not regenerate. Even following crush lesions, regeneration of dorsal roots is limited because axons fail to make successful central synaptic connections and the metabolic response of dorsal root ganglion cells to sectioning of their central processes is poor.

Ineffective synapses is another phenomenon revealed by a dorsal root lesion. This is a phenomenon in which previously nonfunctional synapses become functional, as if there were a redundancy of synapses. Some authors have called these synapses "ghosts of the cell's childhood." An anatomical explanation is offered for this phenomenon. After entering the spinal cord, the cutaneous afferent fibers divide into a T-shaped junction, and the two main branches traverse several segments above and below their sites of entry. Within the dorsal horn, these long-ranging afferent fibers undergo an explosive branching, sending out collaterals to make synapses with cell layers beneath. This radiation or divergence continues over many spinal segments. Yet, functionally, in the intact nervous system, any particular area of skin (ie, a dermatome), is represented in one or, at most, two segments of the spinal cord. In fact, the receptive field of a second-order neuron is defined as that very limited region of the skin whose stimulation influences the neuron's firing. Stimuli applied to a cutaneous area outside the receptive field fail to excite the second-order neuron, despite the wide anatomical distribution of primary afferent terminals within the cord. It is as if synapses formed by the distant branches of afferent fibers were dormant or ineffective.

After one dorsal root is cut, a second-order neuron within that spinal segment becomes unresponsive to adequate stimulation within its respective dermatome, as would be expected. But within a few hours after the dorsal root is sectioned, the deafferentated second-order cells begin to respond to electrical stimulation delivered to a neighboring intact dorsal root. At this time, cutaneous stimulation with a more physiological stimulus does not excite the second-order neuron. One week after the deafferentation, however, the second-order neuron will discharge in response to cutaneous stimulation of neighboring dermatomes. In other words, the second-order neuron now has an altered receptive field.

At the present time, the mechanisms whereby sectioning of one dorsal root causes an expansion of a second-order neuron's receptive field are not known. Why do distant, ineffective terminals become effective? Several mechanisms have been proposed by which the excess synapses could be rendered functionally ineffective. Nerve impulses may fail to invade the distal terminals of the afferent fibers. Alternatively, the long-ranging afferent terminals may terminate on their target cells at sites too distant from the site of impulse generation to exert effective depolarization. Or perhaps the distant terminals terminate on interneurons rather than directly on target cells. Another hypothesis proposes that by unknown mechanisms the normally effective synapses somehow repress the synaptic function of these long-ranging afferents. By eliminating effective terminals, rhizotomy may release the distant terminals from this functional repression. In any case, it is as if the CNS establishes many more synaptic connections than are needed in normal circumstances, and these redundant synapses become functional only after a dorsal root lesion.

Current findings suggest that activation of ineffective synapses following deafferentation is not limited to the spinal cord but may be a mechanism at work in other regions of the CNS following brain lesions.

Future studies that investigate expansion or shifts in receptive fields may provide the therapist with a new approach for evaluating a patient's sensory capabilities. In fact, much more clinical documentation of this interesting and unexpected phenomenon is needed.

Perhaps the most interesting lesson to be learned from the unilateral rhizotomy experiments is how function is restored to the apparently paralyzed deafferentated limb. In monkeys, unless the normal (unoperated) limb is restrained, the deafferentated limb is never used in voluntary movements. However, if the unoperated limb is restrained, the monkey learns to use the deafferentated limb. Although the movements of this limb are clumsy and ataxic because of defective postural control, the limb becomes useful within a month.
In summary, dorsal rhizotomy results in profound disturbances in motor behavior, induces collateral sprouting of neighboring dorsal roots, causes dendritic shrinkage of second-order neurons, and permits activation of previously ineffective synapses resulting in expansion of the receptive fields of second-order neurons.

RESPONSES TO SPINAL CORD LESIONS

Immediate effects of spinal transection. When the spinal cord is transected, the dorsal roots of spinal segments above and below the level of spinal injury are spared, but the ascending and descending fibers are disrupted. Hence, cells below the lesion are deprived of descending projections from higher centers, and cells above the transection are deprived of their inputs from ascending fibers. Therefore, spinal transection spares spinal motoneurons their segmental reflexes but deprives them of their descending reflexes. In addition, neurons at the level of the lesion probably suffer as a result of the disruption of the blood supply.

Spinal shock is the immediate effect of spinal transection. Spinal shock is a transient suppression of all reflex activity below the level of the transection. During the initial stage of spinal shock, all body segments below the transection are paralyzed and anesthetized so that voluntary movements and sensation are permanently abolished. The autonomic reflexes below the lesion are also suppressed, accounting for the loss of circulatory tone, anhidrosis, and urinary retention. If a patient receives proper medical and nursing care and survives the diachisis (temporary depression of function), some reflex activity returns in both autonomic and somatic structures, as if spinal neurons were regaining excitability. The duration of spinal shock is species-dependent; it lasts for days or weeks in humans and primates, for hours in cats, and for minutes in frogs. Subsequently, reflex activity returns and becomes exaggerated. In humans, the flexor reflexes of the hips and knees become hyperactive, and the patient assumes the characteristic flexion posture of the spastic paraplegic. McCouch and colleagues were among the first to propose that collateral sprouting within the spinal cord might be an important mechanism underlying the appearance of spasticity in patients with spinal cord injury.

Enhancement of synaptic transmission following spinal transection. In cats, within six to eight hours after spinal transection at T13 or L5, excitatory post-synaptic potentials of a motoneuron in response to IA input have increased amplitudes compared with those in cats with intact cords. Furthermore, after spinal transection, 100 percent of the motoneurons receive IA afferent contacts, compared with only 80 percent before the transection. This synaptic enhancement is probably not caused by growth of new connections because it occurs too quickly; more likely, previously "silent" or ineffective synapses have become operative. Perhaps the spinal transection releases the IA terminals from synaptic inhibition. At any rate, enhanced synaptic transmission of the monosynaptic reflex has been suggested as one important factor contributing to spasticity in the patient with spinal cord injury.

Synaptic reorganization following spinal transection. In the first two days after spinal transection, there is a general disorganization of the boutons belonging to the transected afferents (recent reviews by Cotman and associates and Tsukahara). Once these boutons disintegrate, their vacated synapses are contacted by newly formed boutons from collateral sprouts of surviving afferents. Although evidence exists, particularly from animal experiments, that some fiber tracts undergo abortive terminal sprouting, collateral sprouting of viable neurons has been considered the major adaptive response to spinal transection. As is discussed in subsequent sections, other mechanisms may well be contributing to the return of muscle tone, the appearance of mass reflex responses, and spasticity in the patient with spinal cord injury.

RESPONSES TO HEMISECTION OF THE SPINAL CORD

When only half of the spinal cord is transected, dorsal roots on both sides are spared, but the ipsilateral ascending and descending fibers are disrupted, causing a partial deafferentation of neurons above and below the lesion. Thus, hemisection selectively affects ipsilateral segmental reflexes and contralateral descending reflexes.

Behavioral effects of hemisection. In cats, all reflex activity is depressed in the immediate postoperative period. Within three days, however, reflex activity reappears, and two weeks postoperatively, ipsilateral segmental reflexes are hyperactive. The dorsal roots on the side of hemisection show an enlargement of their receptive fields. Many functional and structural mechanisms have been proposed to account for these behavioral changes induced by hemisection.

The morphological correlates of the posthemisection expansion of receptive fields are collateral sprouting of dorsal roots and activation of ineffective synapses as discussed previously.

Another factor that may contribute to the increase in spontaneous and evoked activity following hemisection is a "release" phenomenon. Several descending pathways that exert inhibitory control over dorsal horn interneurons are disrupted by spinal hemisection. The existence of such pathways came to light only after Melzack and Wall proposed their provoc-
Fig. 2. Double hemisection of the spinal cord at the T5 and T10 levels. These two spinal lesions interrupt ipsilateral ascending and descending fibers without disrupting dorsal root afferents.

The C-type synapses are also functionally distinct. They do not undergo degeneration following dorsal root section or spinal hemisection. Therefore, it appears they must belong to neurons whose cell bodies lie within the intact T5 and T10 levels of the central gray. These findings and other evidence show that the C-type synapses originate from short proprio spinal pathways, such as interneurons that receive impulses from Ia fibers.

Experimental results showing the time course of the changes in the number of synapses following double spinal hemisection are shown in Table 2. Note from data in the table the marked loss of synapses from motoneurons at the T8 and T9 levels of the cat’s spinal cord during the first 72 days after spinal hemisection. This loss represents the degeneration of the presynaptic endings of cut descending fibers. By the 135th day after the hemisection, however, synapses are being restored, and by the 199th postoperative day there is a 78 percent restoration of synapses. The restored synapses have C-type terminals, suggesting that the proprioceptive interneurons are responsible for the synaptic reclamation.

The C-type terminals not only increase in number following hemisection of the cord, but they undergo changes in shape, size, and location. The terminals undergo an elongation, thereby expanding their territorial extension. Furthermore, they may come to occupy dendritic sites that normally do not exhibit this type of synapse (Tab. 1).

The consequence of all these morphological changes in C-type synapses is an increased functional activation of the neural pathways these synapses serve.

This study on changes in C-type synapses following spinal hemisection is important because it identifies specific morphological changes in the size, number, and type of terminals that form synapses with spinal motoneurons following spinal cord hemisection. This synaptic reinnervation following central deafferentation gives rise to segmented neural circuitry with functional properties different from those of the intact spinal cord. This phenomenon quite likely is another important mechanism contributing to the appearance of spasticity in the patient with a spinal injury.

This particular type of synaptic reorganization fol-
lowing a CNS lesion is the first of its kind to be reported. It remains to be determined if analogous synaptic changes are induced by lesions in other regions of the nervous system.

RESPONSES TO COMBINED DORSAL RHIZOTOMY AND SPINAL CORD TRANSECTION

Unilateral dorsal rhizotomy causes a depression of the crossed extensor reflex, but if the spinal cord is transected as well, a strong crossed extensor reflex appears and becomes hyperactive. At the same time, the peripheral field of the contralateral dorsal root ganglion undergoes a dramatic expansion. Collateral sprouting of viable dorsal root neurons is thought to be a major mechanism contributing to the reappearance of the lost reflex and the expansion of the receptive field.

RESPONSES TO LESIONS IN THE BRAIN

Collateral sprouting and synaptic reclamation. These recovery phenomena are not limited to the spinal cord. They have been identified in particular brain regions following specific experimentally produced lesions. Yet, other brain regions have been identified as lacking the sprouting capability in response to deafferentation.

These phenomena have been investigated in the septal nuclear complex in the forebrain of adult rats. This region of the brain receives afferent synaptic terminals from two sources. In the intact or normal structures, fimbrial afferent fibers terminate only on dendrites of the forebrain neuron. Terminals of the medial forebrain bundle (MFB) terminate on both soma and dendrites of the same neurons. Either of these two inputs can be selectively destroyed. Figure 3B shows the results several weeks after a lesion of the fimbria. Note that terminals of the MFB now extend across from their own synaptic sites to occupy a synaptic site vacated by the degenerated fimbrial terminals. The reverse experiment is shown in Figure 3C. Several weeks after the MFB is cut, its terminals degenerate. Now the intact fimbrial terminals produce collateral sprouts. These new axon collaterals grow to occupy the synaptic sites on the soma vacated by the degenerating MFB. Prior to sprouting, the fimbria neuron made no axo-somatic synapses. This experiment provides only one example of synaptic reclamation by collateral sprouts from viable neurons innervating the same target cells in the brain.

Examples of synaptic reclamation or reactive synaptogenesis in other brain regions have been reported. A general example is shown in Figure 4, where one of two boutons contacting a dendritic spine undergoes degeneration following damage to its axon, and the remaining bouton then sends a collateral sprout to reclaim the vacated synapse.

More and more information is being accumulated about collateral sprouting and synaptic reclamation in the brain. It has been determined that only axons sharing a common target send collateral sprouts to the vacated synapses, but these afferent inputs with a common target may arise from very different brain regions, as suggested by the example shown in Figure 3. Furthermore, it has been pointed out that this retrieval of vacated synapses may inhibit restitution of the original innervation pattern.

Collateral sprouting has been identified in the septal nucleus (as described in the preceding example), in the entorhinal cortex, in the red nucleus, and in other brain regions, suggesting that it is a widespread phenomenon. Yet, the trigeminal system has been reported as displaying no collateral sprouting in response to a bilateral section of C1 to C3 dorsal roots. Hence, it would be incorrect to generalize about collateral sprouting; each system must be specifically tested.
The "take-home message" is that lesions, wherever they occur, induce reorganization of the CNS or, in other words, the "hard wiring" of the brain is altered following brain lesions. Patients with brain lesions have different neural connections than individuals without brain lesions.

**Denervation supersensitivity.** This phenomenon was described in detail in Part 2 of this review as a predictable phenomenon occurring at the motor end-plate in response to motor nerve lesions. Denervation supersensitivity is not limited to denervated skeletal muscle but has been demonstrated in at least one brain region (Fig. 5). A normal dopaminergic synapse in the caudate nucleus of the basal ganglia is shown. With death of dopaminergic cells in the substantia nigra, as occurs in Parkinson's disease, the denervated synapses containing dopaminergic receptors develop a supersensitivity to dopamine. The functional consequences of this enhanced dopaminergic sensitivity are several. First, less transmitter substance will produce the same synaptic action as at a normal synapse. Secondly, an exogenously administered agonist of the transmitter has expanded sites at which to act. Denervation supersensitivity is therefore a beautiful compensatory response to neuronal cell death.

It has long been recognized that partial denervation leads to hyper-responsiveness of the postsynaptic element (Cannon's Law). But the mechanisms underlying this hyper-responsiveness are only now beginning to be identified and assessed. It seems likely that both denervation supersensitivity and collateral sprouting contribute to the enhanced motor activity of spasticity, but far more work is required to determine the relative contributions of each of these mechanisms.

**Terminal regeneration in the CNS.** Following a CNS lesion, probably every patient has a secret hope for the regeneration of damaged nerve fibers. Evidence of attempts of central neurons to regenerate injured axons surfaces occasionally, but these regenerative attempts are almost always abortive. Recently, however, a new methodology has been used to investigate this problem. Instead of producing experimental lesions by surgical intervention, lesions are created with neurotoxins.

Surgically produced lesions damage all types of neurons and induce formation of scar tissue. In contrast, neurotoxin-induced lesions damage only a single class of chemically identifiable axons and do not produce any scar tissue. Destruction of serotoninergic fibers descending from serotoninergic (5-HT) neurons in the brain stem is an example of this experimental approach. In the normal CNS these 5-HT neurons project diffusely to all levels of the spinal cord (Fig. 6). After an animal is treated with 5,6 dihydroxytryptamine (5,6 DHT), a specific poison for serotoninergic neurons.
axons, this spinal projection degenerates. Following the 5,6 DHT axotomy, considerable regenerative terminal sprouting occurs. In one month to a year, many of the 5-HT neurons reinnervate the proper target cells. Although the terminals of these new fibers have abnormal density and morphology, their existence is evidence that terminal regeneration can occur in the CNS. This capability is not limited to serotonergic neurons. Following axotomy with 6-hydroxydopamine, noradrenergic neurons of the locus ceruleus have been seen to regenerate into the cerebellum and into the cerebral cortex. In fact, additional examples of axonal regeneration in the CNS are appearing almost weekly in the scientific literature. Hence, CNS neurons are not as totally devoid of regenerative capabilities as traditional dogma led us to believe. This new knowledge justifies a sustained optimism for patients with CNS damage.

CONCLUSIONS

In addition to inducing the structural changes described in the preceding sections, injury of the CNS induces adaptive changes that may be less beneficial for functional recovery. Much of the rationale underlying current physical therapy strategies for the patient with brain injury is to prevent, reduce, or reverse the strength of these undesirable changes.

New examples of lesion-induced phenomena of synaptic remodeling are being discovered each year. None should be viewed as unique or unusual but instead should be studied and incorporated into our thinking when dealing with patients who have suffered neurological lesions. The nervous systems of patients with neurological lesions undergo synaptic reorganization and "rewiring." This reorganization may explain some of the "recovery phenomena," which were previously unaccounted for, including spasticity, abnormal reflexes, and other motor dysfunctions.

Physical therapists must remember when treating a patient with neurological lesions that they are dealing with an abnormal CNS—not only abnormal in the sense of lost function, but abnormal in the sense of altered synaptic functions and altered neural circuitry. They should not forget that the CNS is a dynamic system with tremendous recuperative potential. Central neurons possess remarkable compensatory responses and plasticity. The therapists' challenge for the future is to learn how to cultivate and use this neural plasticity in the rehabilitation of patients with CNS lesions.

Fig. 6. Regeneration of serotonergic (5-HT) axons following drug-induced axotomy. The left diagram shows the spinal projections of 5-HT brain stem neurons. The middle diagram shows almost total degeneration of the 5-HT projection resulting from an injection of the 5,6 dihydroxytryptamine, a poison for 5-HT axons. The right diagram shows the same spinal cord one year later with extensive regeneration of the descending 5-HT axons. (Adapted from Wiklund and Bjorklund.)
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MECHANISMS OF LESION-INDUCED RESPONSES


RESPONSES TO DORSAL ROOT LESIONS


Collateral Sprouting


Dendritic Atrophy


Ineffective Synapses


RESPONSES TO SPINAL CORD LESIONS

Immediate Effects


Spinal Shock


Enhancement of Synaptic Transmission


Synaptic Reorganization


RESPONSES TO HEMISECTION OF SPINAL CORD

Behavioral Effects


RESPONSES TO DOUBLE SPINAL HEMISECTION

Sympathetic Reorganization


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RESPONSES TO LESIONS IN THE BRAIN


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