Central Nervous System Lesions: Sprouting and Unmasking in Rehabilitation

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• Recovery of function following a central nervous system lesion can continue for months or years following the injury. Considerable experimental evidence supports the conclusion that the plasticity of the brain is of importance to the functional recovery. A number of neural mechanisms may be involved in the functional recovery. Two of the mechanisms of neuroplasticity considered particularly likely to play a role, are the following: 1) Collateral sprouting from intact cells to a denervated region after some or all of its normal input has been destroyed, and 2) The unmasking of neural pathways and synapses which are not normally used for the particular function under study but which can be called upon when the ordinarily dominant system fails. The process of unmasking is extensively discussed in the context of the role of rehabilitation in obtaining maximum recovery of function.

Many patients with central nervous system (CNS) lesions recover at least partial function. In fact, the worst signs and symptoms that the patient will exhibit usually appear immediately following the occurrence of the lesion. Part of the early recovery may be related to the resolution of local vascular and metabolic factors such as the reduction of edema and absorption of damaged tissue and to improved local circulation. However, there is no evidence that these factors play a role in long-term recovery of function: Brodal[7] considered that they may be important during, at most, the first 2 months, and Wall[24] concluded that, although they may play a crucial role immediately following the event, it is highly unlikely that they are crucial in the days and weeks following the lesion.

Recovery of function can continue for months or years. But how is brain damage repaired and function reestablished? In essence, the damage is not repaired. Not only is the brain incapable of regeneration by mitotic duplication, a principal repair mechanism of other body tissues such as the liver, but it also appears to be incapable of promoting significant growth of cut axons, such as occurs in peripheral nerves. Therefore, other neural mechanisms must be responsible for the capacity of the brain to recover function.

In recent years, interest has grown in the role of neuroplasticity in recovery of function following CNS lesions. Among the mechanisms invoked have been the following:

1. Diaschisis: the depressed function or loss of functional continuity between various centers or neuron tracts.
2. Regenerative and collateral sprouting.
3. Changes in sensitivity of synaptic transmission.

These changes have been identified by various terms, such as supersensitivity, alterations of the balance of excitation and inhibition, relatively inefficient synapses, substitution, vicarious function and unmasking of preexisting but functionally depressed pathways. This class of changes will be referred to as unmasking in this review.

A review of the entire field of neuroplasticity is beyond the scope of this paper. Such reviews have appeared elsewhere.[10,19] The present discussion will be limited to mechanisms which I consider particularly relevant to CNS lesion rehabilitation, It must be kept in mind, however, that many of the research results reported here were obtained in animal studies, and are not necessarily applicable to man.

In an excellent recent analysis, Wall[24] has argued persuasively for the dismissal of diaschisis and regeneration as possible long-term neuronal mechanisms of recovery of function, and Laurence and Stein[19] have concluded that the relevance of regenerative sprouting (proximal regeneration of an axon after it has been transected and the distal portion has regenerated) to recovery from CNS damage is "probably minimal." Therefore, although it is possible that other mechanisms, including some mentioned above, may also play a role in the recovery, this review will be limited to a of 2 mechanisms, collateral sprouting and unmasking; the first may be of importance, and the second is highly likely to be important in the reha bilitation of patients with CNS lesions.

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Collateral Sprouting

Collateral sprouting refers to "sprouting from intact cells to a denervated region after some or all of its normal input has been destroyed. "19 Collateral sprout- ing has been demonstrated in the septal nucleus and anterolateral thalamic nucleus after damage to the hippocampus afferents, in the dorsal lateral geniculate nucleus after visual cortex lesions, in the olfactory tubercule after olfactory bulb destruction, and in the cerebellar cortex after superior cerebellar peduncle lesion.[19] Laurence and Stein [19] have pointed out that an interpretation of the meaning of sprouting, especially insofar as recovery of function is concerned, depends on an understanding of what triggers this type of reaction and whether it is a specialized response to injury or merely representative of other, essentially normal, synaptogenic functions.

Cotman and Nadler[ll] consider that the term sprouting may have mechanistic implications. They suggest that the term "reactive synaptogenesis" is more appropriate, since it refers to the formation of synapses in response to a stimulus. Furthermore, it distinguishes the process from developmental synaptogenesis.

Although sprouting (or reactive synaptogenesis) may be a mechanism of recovery of function, it also may, in some cases, be maladaptive; equivalence of task of neighboring axons is rare. Different types of axons converge on cells bringing in different types of information and control. If 1 type is lost by a destructive lesion and the survivors expanded to occupy empty sites, the cell may now regain a highly abnormal function. Further studies will be necessary to clarify its importance in the recovery from CNS lesions.

Unmasking

Unmasking designates axons and synapses which are present but not used for the particular function under study, and which can be called upon where the ordinarily dominant system fails.[24] Comparable concepts have been considered for many years. For example, in 1902, Lazarus[20] discussed the formation of alternate pathways in the CNS. He considered that the facilitation therapy of cerebral hemiplegia and aphasia consists in the compensatory use of stillfunctioning nerve tracts and the use of new nerve tracts.

In a discussion of the possible means by which unmasking is accomplished, Wa11[24] noted that a homeo static mechanism might exist where a decrease of input activity would be followed by an increase in excitability. The effect of this adjustment would be that a partial loss of input would produce a compensation so that the remaining input would have a larger effect. For example, a stroke patient who initially reports enormous difficulty in producing a movement experiences an easing of effort required as recovery progresses. This phenomenon has been interpreted in terms of the unmasking of preexisting pathways. [3]

A simple analogy to unmasking of neural pathways may be drawn by considering the development of information transmission methods following the loss of a hypothetical telephone cable system. Let us suppose that the main cables between New York and San Francisco were destroyed in an earthquake. Initially, it might be impossible to call from one city to the other. After a time, however, if the demand for this service were sufficient, someone would discover that it was possible to call the telephone operator in Denver, ask that operator to place a call to the operator in Washington, and ask that operator to call New York. This would be a slow, tedious procedure. However, if demand continued high, the operators at each intermediate city would become more efficient at facilitating the transmission of the telephone information. With sufficient repetition, a very high degree of efficiency might eventually be reached that, though less efficient than the original direct line, would very adequately compensate for the loss. Thus, the preexisting connections (via Denver and Washington) that had not previously been used in the function under study (calling from San Francisco to New York) would be effectively unmasked following a "lesion" (loss of the direct cables), if the functional demand were suf ficiently high.

In the case of recovery following a CNS lesion, the unmasked pathways may be those that had a comparable role (eg, a multisynaptic parallel role, as in the telephone cable model), or those that subserved the same function before the lesion. In the latter case the unmasking may allow a few remaining fibers to perform the function previously performed by the intact pathway. Initially, following the lesion, the function may be blocked (due, for example, to the inability of the few remaining fibers to overcome the normal level of inhibition). The unmasking process may involve the strengthening of the synaptic access of the remaining fibers to the cells that have lost their major synaptic input for that particular function.

A case of recovery from hemiplegia in a patient with a 97% destruction of the pyramidal tract was discussed within the framework of this concept of unmasking[3]; it is possible that the intact 3% of the tract remaining after the lesion was able to receive a greater synaptic input (by unmasking of pathways to the dendritic tree of the remaining cells), and to have a greatly increased influence on the partially denervated interneurons (and, through them, the motoneurons).

Of course, this interpretation is merely a hypothesis. It is also possible that part of the recovery was due to unmasking uncrossed pyramidal tract pathways, as well as being probable that part of this recovery occurred by means of the unmasking of extrapyramidal pathways.

A 3rd class of unmasked pathways would be those that initially were not involved with a particular func-

tion, but that, through a training program, acquired a new functional role. This is a probable mechanism of sensory substitution. [24]

Unmasking in Laboratory Research

A number of research results can be interpreted in the context of unmasking. For example, in a large series of experiments by Wall and his colleagues[21] the effects of partial destruction of the afferent input to a region were observed. This was done in adult rat thalamus by removal of 1 nucleus of the dorsal column nuclei. The destruction was followed by an expansion over days and weeks of the innervated zone into the denervated zone. Similar types of experiments were carried out in adult cats by sectioning of dorsal roots followed by examination of the denervated zones of dorsal column nuclei and of the spinal cord. In each situation, cells which had lost their input began to respond to intact afferents.

Wall and his collaborators have shown that sensory fibers entering the dorsal root terminate in the cord not only in the immediate vicinity of the entry segment but also send long-ranging axons which extend over many segments rostral and caudal to the entry root.[25] Physiologic studies using natural peripheral stimuli show no cells responding to these distant afferents in the intact animal. If electric stimuli are used which have a particularly efficient central excitatory effect because of the synchronization of the arriving volley, small numbers of distant cells are discovered responding to the long-range afferents. [12] If, however, roots close to the recorded cells are destroyed, very large numbers of cells respond to the long-range afferents when either electric or natural stimuli are used.[5] Therefore, there are afferents present which provide a potential source of new input in the presence of degeneration.

When peripheral nerves are cut, the spinal cord cells no longer receive their normal afferent barrage and substances transported from the periphery do not arrive. However, there is no gross anatomic degeneration and therefore synaptic sites are not vacated. The dorsal horn of lumbar segments 6 and 7 in adult cat cord contain somatotopically organized cells with the foot and toes represented medially and the upper and lower leg laterally.

If the sciatic and saphenous nerves are cut in midthigh, the foot and toes become completely anesthetic. These nerves were cut in I leg of adult cats, which were allowed to recover for various periods of time. On the observation day, marked changes were ob-served, allowing Devor and Wa11 [13] to conclude that large numbers of cells in a region of cord normally dominated by afferents from foot and toes begin to respond to other areas of the leg some days or weeks after section of the peripheral axons which previously supplied their excitatory drive. The new receptor fields found in the former toe/foot region are all in skin supplied by remaining intact cutaneous nerves.

No signs of degeneration were detected among the central terminals of the afferents whose periphery had been cut. There was no gross atrophy of the dorsal horn. Therefore it appears that, unlike the situation after dorsal root section, there could be no marked morphologic changes in the cord. Thus, unmasking does not appear to require sprouting.

In a study of the primary visual cortical neurons of cats, we noted the existence of weak, nonvisual inputs to these visual cortex cells; the responses to these inputs were of approximately double the latency of the visual responses, and were synaptically insecure.[22] These weak pathways may be comparable to the spinal cord pathways unmasked in Wall's studies.[24] Our sensory substitution studies, in which, for example, a blind person learns to "see" with the information from a TV camera, delivered through an array of skin stimulators and reaching the brain via cutaneous neural pathways,[2B] may also be interpreted in terms of unmasking pathways.

A number of drug studies provide evidence of unmasking: Studies on cats revealed that chloralose anesthesia increases the size of cortical evoked potentials in areas of convergence, and after administration of thiopental anesthesia, cells in the cat visual cortex increase their receptive fields and the types of stimuli to which cells respond. It is likely that in these studies, the drugs are, temporarily, unmasking pathways. This has been further discussed elsewhere.[3]

Synaptic plasticity can be considered as a mechanism of unmasking. This subject has recently been reviewed by Eccles,[14] who considers synaptic plasticity to be manifested by long-lasting changes in synaptic potency, with concomitant morphologic changes of both the pre- and postsynaptic structures. In a study of synaptic plasticity of hippocampal neurons, he noted up to 40% increase of the synaptic spines on the dendrites of granule cells.

Another morphologic substrate for unmasking may be the variable nervous system described by Hirsch and Jacobson[16] : They have provided evidence for the existence of 2 basic neuronal systems: an invariant system, mostly laid down before birth, and a variable system, which develops largely after birth and is dependent on the individual organism's environment and personal experience. They pointed out that such concepts are not entirely new: Cajal in 1909 suggested that small variable cells may be responsive to environmental influences, and thus responsible for the plastic or modifiable aspects of behavior. The variable system discussed by Hirsch and Jacobson [16] may be involved in the unmasking of pathways following a brain lesion, but it is too soon to exclude their invariant category from consideration; while they discussed normal development, they did not address the responses of the 2 systems to injury.

Relevance of Concepts

Two important questions for rehabilitation are: To what extent does recovery of function occur "spontaneously"? What is the effect of rehabilitation programs? Although these questions are discussed extensively elsewhere? [3] we will review laboratory and clinical studies that demonstrate the importance of rehabilitation in obtaining maximum recovery of function.

In cat studies, Chow and Stewart [9] demonstrated that forced usage, gentle, affectionate handling and positive rewards (equivalent to a rehabilitation program) produced visual recovery in cats which had been made amblyopic by eyelid suture. In human studies, Zihl and Von Cramon[26] obtained considerable visual recovery in hemianopic patients. Visual acuity, critical flicker fusion, color perception, and contrast sensitivity improved with their training program. Primate rehabilitation studies and human cerebral palsy motor control programs, discussed below, also strongly support the conclusion that appropriate scientifically based rehabilitation programs lead to functional improvement.

Although most of the factors in the following discussion have not been studied in relation to sprouting and unmasking, I consider their evaluation particularly important in relation to mechanisms of neuroplasticity.

1. **Time Course of Recovery**

The neural mechanisms discussed above require time, as well as effort, to produce functional results. Numerous studies show that functional recovery can continue for months and years, and can follow irregular patterns. Motor learning can occur in alternating sequences of acquisition—consolidation, with each consolidation phase being a plateau during which no objective improvement takes place. This can have implications for rehabilitation.

2. **Effects of Delaying Therapy**

Although this factor has not been extensively studied, there is evidence that delaying therapy leads to suboptimal functional outcome. For example, Black's group,[6] in a study of recovery after cortical lesions in monkeys, found that where rehabilitation was delayed for 4 months, recovery after 6 months of therapy reached 67% of peroperative function, vs 82% of recovery in the group in which therapy was initiated immediately.

3. **Age Factor**

Age is a factor in recovery of function, recovery being more rapid and complete in young persons. Jennett and associates" concluded that age determines the possibility of good recovery after coma, young persons withstanding longer coma and still retaining the capacity to recover. The subject is not so simple, however. In some cases an early lesion may have more devastating effects than the same lesion in a fully mature brain,[18] and it is now well demonstrated that brain plasticity is a characteristic at all stages, even in old age. Buell and Coleman[8] demonstrated that, in aged persons (average age 80) the dendritic trees of layer Il pyramidal neurons are more extensive (possibly to compensate for the loss of other cells) than in adults with an average age of 51 years. This
morphologic plasticity in aged brains suggests a neural substrate for recovery of function, although the exact relationships of neural structure to recovery of function remain to be clarified. In any case, advanced age is not a sufficient reason to withhold rehabilitation.

4. **Environmental Effect**

Extensive studies in animals have demonstrated the great importance of environment,[23] revealing that optimal recovery is not obtained simply by restoration of general health or by socialization; an enriched environment, with a great deal of interactive stimulation, is necessary for maximum recovery. Our recent studies (submitted for publication) have shown that a restricted environment greatly increases motor deficit and mortality in hemiplegic rats.

The implications for the clinical management of patients with CNS lesions are undoubtedly great. The study of environmental factors, including inter. active rehabilitation programs, is a particularly important area of rehabilitation research.

5. **Mind-Body Interactions**

The importance of motivation in rehabilitation is well appreciated. The physiologic mechanisms by which this factor and the placebo effect are translated into motor control is a fascinating area of research (discussed further in the author's other publications).

6. **Neuropharmacology**

There is evidence that specific drugs are capable of modifying CNS function that may influence recovery. Alpha-chloralose has been shown, in cats, to increase cortical somatosensory evoked potentials [1] and thus may be able to modify the facility of access of somatosensory information to damaged brain regions. Furthermore, excitatory and inhibitory neurotransmitters may be able to influence the local excitatory-inhibitory balance that appears to be disturbed following a CNS lesion. A drug with temporary effects might allow rehabilitation sessions to be more effective. However, effective use of neuropharmacology in rehabilitation is, at present, merely an exciting research concept.

7. **Functional Rehabilitation Programs**

Functional programs that vary with the patients' interests and prior experience may offer specific ad-

vantages, such as the active participation in repetitive movements. Gauthier's group [15] noted that although specific training with light spots and with a pendulum produced marked improvement in the eye movements of children with cerebral palsy, it was difficult to get the children to cooperate. They then developed a rehabilitation program in which the training was accomplished by means of the projection of children's movies (eg, King Kong) on a small part of a projection screen. With the child's head held immobile, the image was moved on the screen. The child had to use eye movements to follow the image. In 'this way, 2hour rehabilitation sessions could be completed without fatigue to the child. Marked improvement in eye movement control and reading was reported with this approach.

A similar approach was used in the successful rehabilitation of a hemiplegic patient. [3] Recovery was far greater than would have been predicted from the extent of the lesion, which was confirmed on autopsy. Functional rehabilitation (or "meaningful therapy") must be individually designed and thus poses practical difficulties. However, it may be a major reason why home programs developed by a concerned and resourceful family member can be particularly successful.

The foregoing factors can influence recovery of function only through physiologic and morphologic mechanisms. Future research must follow dual lines: l , to demonstrate the effectiveness of particular rehabilitation programs and the importance of particular factors; 2, to study the neural mechanisms by which the rehabilitation programs influence the recovery of function.

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