Although many survivors of acute stroke have significant cognitive, language, sensory, or motor disabilities, most stroke patients recover some degree of function. For example, about 30% of patients diagnosed as having "transient ischemia" have actually had cerebral infarction with complete symptomatic recovery. In patients with residual neurologic deficits, dramatic functional improvement can occur over the first 3-6 months. In some individuals recovery can continue over a period of years.

The neurobiologic basis of spontaneous recovery after brain injury is not completely understood. However, fundamental laboratory investigations are beginning to provide insights into the recovery process, and these studies indicate that the rate and degree of spontaneous recovery may be influenced by a variety of factors (Figure 1). In particular, they have also led to an appreciation of the potentially beneficial or detrimental impact of certain drugs on recovery. This paper considers the neurobiology of functional recovery after stroke, emphasizing the impact of drugs on the brain's responses to injury, and explores some of the factors which may underlie differing rates and degrees of recovery among stroke patients.

The strongest predictor of the extent of eventual recovery from stroke is the severity of the initial neurologic deficit. The rate of development of the lesion, its size and location in the brain, and the presence of prior lesions are also important. Nutritional status, age, prelesion experience, and post-lesion training can influence the recovery process in laboratory animals and may be relevant to recovery in stroke patients. For example, Knopman and coworkers found that lesion volume was correlated with recovery from aphasia after stroke. Patients with small lesions recovered fluency whereas those with large lesions had poor outcomes. However, language recovery in patients with intermediate sized lesions depended on lesion location. The importance of lesion location was also demonstrated in a study in which infarct size and location were determined by brain computerized tomography or cerebral angiography and correlated with the motor deficit after stroke. The site (subcortical versus cortical) but not the size of the lesion correlated with ultimate recovery. Grafman and coworkers investigated the relation of preinjury intelligence/education, brain tissue volume loss, and lesion location to the persistence of cognitive deficits after penetrating brain wounds. Preinjury intelligence/education was a more important predictor of postinjury performance than the other variables.

Responses to Injury

The brain's acute responses to injury are likely to contribute to the initial functional deficit and may actually increase the eventual size of the lesion. Cerebral edema is perhaps the most common and most important of these responses to injury. The best evidence suggests that both cytotoxic (cell swelling) and vasogenic (breakdown of blood–brain barrier) edema occur in and around ischemic areas. Edema may influence neuronal function in the area immediately surrounding the lesion (a local functional depression) or by compression in areas distant from the lesion. The presence of edema may render viable brain sensitive to further ischemic damage. Functional worsening or spontaneous improvement in patients after an acute brain injury may be due in part to the development and subsequent resolution of edema. Although the cellular mechanisms responsible for edema are not completely understood, there have been attempts to limit edema with various pharmacologic interventions.

The use of glucocorticoids following cerebral infarction in laboratory animals has had conflicting results. Clinical studies indicate that glucocorticoid treatment is ineffective after ischemic stroke. New treatment strategies being tested in animal models are aimed at interrupting the processes responsible for the swelling following cerebral ischemia and infarction. Gangliosides may reduce edema by "protecting" membrane function. Free radical scavengers may decrease ischemic and postischemic brain swelling by blocking peroxidation and lipoxygenase activity. The 21-aminosteroids, a new class of steroid drugs with little mineralocorticoid or glucocorticoid activity, may also decrease cerebral edema by acting as inhibitors of lipid peroxidation. These new
thorpestic approaches may become more important in the future. In the meantime the usual approach to the treatment of clinically significant cerebral edema includes the use of osmotic and loop diuretics, sometimes in association with forced hyperventilation. These treatments have not been subjected to an adequate clinical trial.

Diaschisis\textsuperscript{15} is another brain response to infarction which may influence recovery and offers the potential for pharmacologic intervention. Diaschisis is a term originated by Von Monakow to indicate remote, functional depression of brain distant from the site of the primary injury. These areas of remote functional depression may contribute to the immediate neurologic deficit and yet may be reversible. Reductions in blood flow and metabolism demonstrated by positron emission tomography in the noninfarcted contralateral cerebral hemisphere\textsuperscript{16} and the contralateral cerebellum\textsuperscript{16} could be manifestations of diaschisis because functional depression is associated with diminished cerebral blood flow.\textsuperscript{17}

Drugs which prolong or increase diaschisis by inhibiting neuronal firing might prolong the functional deficit after brain injury. In fact, local administration of \(\gamma\)-aminobutyric acid (GABA), a central inhibitory neurotransmitter, increases the hemiplegia produced by a small motor cortex lesion in rats.\textsuperscript{18} In contrast, central nervous system stimulants such as amphetamine may reduce diaschisis by allowing functionally depressed brain regions to respond to peripheral stimulation.\textsuperscript{19} Treatment with amphetamine facilitates functional recovery in a variety of laboratory animal models.\textsuperscript{20} A small study has been carried out in a group of highly selected stroke patients which suggests that amphetamine coupled with physical therapy can also promote motor recovery in humans.\textsuperscript{21}

### Adaptive Responses

Adaptive responses are the mechanisms that uninjured brain uses to "take over" functions that were performed by the damaged brain. The basic cellular mechanisms that underlie these processes may be the same as those which underlie normal learning and memory.\textsuperscript{22} Of these processes, which are exquisitely sensitive to drugs, perhaps the best characterized is long-term potentiation (LTP).\textsuperscript{23}

In LTP a brief tetanic stimulation to specific neural pathways produces an increase in synaptic responses that can last for days to weeks. Neurotransmitters such as norepinephrine, GABA, and acetylcholine influence the development of LTP in a fashion which is parallel to their influence on learning and memory. It is not surprising that drugs affecting these same neurotransmitters have an impact on the adaptive responses that occur in functional recovery after brain injury. For example, amphetamine enhances memory retrieval\textsuperscript{24} and the induction of LTP.\textsuperscript{25} Amphetamine is also the best studied drug with the capacity to enhance motor recovery after experimental brain injury.\textsuperscript{20}

Although amphetamine has effects on several neurotransmitters, there is good evidence in laboratory animals that its effect on functional recovery is mediated by norepinephrine. An intraventricular infusion of norepinephrine but not dopamine mimics the amphetamine effect.\textsuperscript{26} Treatment with alpha-adenrenergic receptor antagonists enhances motor recovery\textsuperscript{27-30} while alpha-adenrenergic receptor antagonists\textsuperscript{29-30} and the alpha \(\gamma\)-adenrenergic receptor agonist, clonidine, reinstates beam-walking deficits in recovered rats.\textsuperscript{29-31} Even a single dose of clonidine given 24 hours after cortex injury impairs recovery of beam-walking performance.\textsuperscript{32} The alpha-adenrenergic agents may work by increasing (agonists) or decreasing (agonists) the firing of locus coeruleus neurons, thereby influencing release of norepinephrine at nerve terminals. The alpha-adenrenergic antagonists may block the postsynaptic effects of norepinephrine.

GABA is another neurotransmitter which influences LTP, learning and memory, and functional recovery after brain injury. Stimulation of inhibitory GABAergic hippocampal inputs and the administration of indirect GABA agonists (e.g., benzodiazepines) suppress LTP.\textsuperscript{33} Benzodiazepines impair learning and memory.\textsuperscript{34,35} Thus, GABA or benzodiazepines might interfere with the recovery process, and, as mentioned, intracortical infusion of GABA potentiates the hemiplegia resulting from small cortical lesions in rats.\textsuperscript{18} The deleterious effect of GABA is increased by the systemic administration of phenytoin,\textsuperscript{36} which which may act through a GABAergic mechanism.\textsuperscript{37} The administration of diazepam impedes recovery from the sensory asymmetry caused by anterior medial neocortex damage in the rat,\textsuperscript{38} and yet, both phenytoin and benzodiazepines are prescribed for stroke patients.\textsuperscript{39}
Acetylcholine is another central neurotransmitter with putative effects on LTP and memory processes which may also influence functional recovery. The beneficial effects of cytidine 5'-diphosphate (CDP)-choline on recovery in both animals and man could be due, in part, to an enhancement of cholinergic function associated with the administration of the drug. Most of the data concerning the impact of cholinergic agents on recovery of function is old and inadequate by current standards. Feeney and Sutton hypothesize that the putative effect of cholinergic agents on recovery may be mediated by the influence of these drugs on noradrenergic neurons.

Although the theoretic impact of drugs on LTP and learning and memory provides a way of predicting their observed effects on recovery after brain injury, the physiologic basis of the effects of these drugs on recovery remains speculative. However, many of the drugs with detrimental effects on recovery in laboratory animal models (i.e., clonidine, prazosin, haloperidol and other neuroleptics, benzodiazepines, phenytoin) are used in the treatment of patients after stroke. Preliminary evidence suggests that these drugs may be deleterious in humans. Thus, the drugs given to patients after stroke may be responsible for some of the variability in recovery among patients with similar brain lesions. These potential effects should be considered when specific classes of drugs are prescribed after stroke.

Other rapid, adaptive responses which may contribute to recovery after brain injury are less well characterized. Examples include receptor regulation and rapid morphologic changes in dendritic spines. This morphologic synaptic plasticity has been observed in different species under a variety of conditions and may play a role in learning and memory.

Neuronal Rearrangements

A variety of morphologic and neuronal rearrangements have been demonstrated in adult animals after brain injury. The neuronal rearrangements can be grouped into four classes: regeneration, pruning, collateral sprouting, and ingrowth (Figure 2). Not all of these rearrangements lead to spontaneous recovery. Some neuronal rearrangements are maladaptive and probably contribute to the final functional deficit. It is also clear that these rearrangements do not happen at the same time. Some begin as early as 8 hours after the injury while others take months to develop. Neurons undergo certain cellular processes in each of these types of rearrangement. In all cases the neuronal plasma membrane must bud, a growth cone must form, and the neurite must extend and be guided. Appropriate targets must be recognized, and a permanent neuronal-target relation must be established. It is not known what guides these cellular processes or what leads to the differences in neuronal rearrangements.

Regeneration

Regeneration refers to the response of an injured neuron. The axon proximal to the level of injury extends to reinnervate eventually the appropriate target. The synaptic connection lost during the injury is precisely replaced. Regeneration does not seem to occur in the central nervous system although there are abundant examples in the periphery. It is the ideal rearrangement to restore function. Regeneration would probably take weeks to months depending on the distance between the injury and the appropriate target.

Pruning

Pruning is also a response of an injured neuron and only occurs in highly collateralized nerve cells. When an axon is injured, nearby uninjured collateral axons from the same neuron expand to reinnervate the vacant target. Pruning does occur in the central nervous system and is probably responsible for at least some of the neurite outgrowth described after brain injury. Pruning should lead to restoration of function. To date, animal studies of pruning show that it occurs very slowly, taking months to reach completion.

Collateral Sprouting

In contrast to regeneration and pruning, collateral sprouting is a response of uninjured neurons. The uninjured neuron extends neurites to replace nearby degenerating axons. Collateral sprouting occurs widely in the brain and has been studied extensively in the septal nucleus, hippocampus, and peripheral nervous system. It has been identified in as little as 8 hours after injury and in laboratory animals becomes complete within a month. Collateral sprouting usually results in an increase in the density of sprouting neuronal terminals at the target. The net result is the loss of one connection and an increase in another. This type of rearrangement could lead to malfunction of the target and contribute to the functional deficit after injury.

Ingrowth

Ingrowth is the least well known of the rearrangements. It is also the response of an uninjured nerve to a remote injury. However, in distinction to collateral

FIGURE 2. Theoretic classification of neuronal rearrangements after injury.
sprouting, the growing neuron innervates a foreign target (the ingrowing neuron forms new connections in response to the lost neuronal input at a target). The best-studied example of this rearrangement is sympathetic ingrowth. Intracranial sympathetic fibers arise in the superior cervical ganglion and innervate blood vessels on the surface of the brain. These fibers grow into the brain after injury to certain forebrain cholinergic neurons. Sympathetic ingrowth is regulated, at least in part, by the production of nerve growth factor in the target region. Nerve growth factor is normally transported away from the target by cholinergic neurons. After injury, nerve growth factor accumulates in the target, attracting sympathetic neurons. Ingrowth appears to be maladaptive and worsens the functional deficit after brain injury. It takes months to reach completion but is faster than pruning.

At least three of these rearrangements have been observed in adult animal brains after injury. Pruning is the most likely rearrangement to be functionally restorative but takes the longest to occur. In contrast, collateral sprouting and ingrowth are likely to worsen function or slow recovery by interfering with processes that require learning. These rearrangements occur relatively rapidly. If these theoretic classifications are accurate, the ability of the brain to recover over long periods of time may be the result of whichever type of neuronal rearrangement predominates after injury.

While little is known of the pharmacology of neuronal rearrangements, greater understanding could ultimately lead to powerful agents for facilitating recovery. To be most efficacious, such drugs would need to enhance selectively only the “beneficial” neuronal rearrangements. It is easy to understand how agents that facilitate ingrowth or collateral sprouting might actually impair recovery. Clinical trials with a putative neurotrophic drug, GM1-ganglioside, are currently being carried out in the United States and Europe.

**Clinical Implications and Future Directions**

Over 150 drugs have been reported to be of benefit to stroke patients, but none has been proven to be effective by a careful clinical study. It is intriguing to speculate that many of these discarded agents could actually be of benefit to subpopulations of patients with appropriate brain lesions. The evolving understanding of the neurobiologic processes which underlie functional recovery provides a basis for developing new strategies for the treatment of the brain-injured patient.

It may not be surprising that recovery of function varies from patient to patient even when lesion location and type are similar. The initial deficit and recovery are influenced by a variety of biologic and environmental factors. In addition, drugs prescribed for coincident medical problems may have dramatic effects on recovery. It seems prudent to recommend that most drugs be discontinued whenever medically possible during the recovery period. With more experience it may be possible to predict rational combinations of therapy for patients after brain injury.

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