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Diaschisis
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A BETTER UNDERSTANDING of the mechanisms of spontaneous recovery following stroke may provide insight into achieving clinical interventive measures to accelerate and enhance post-stroke recovery. This progress review focuses on one such mechanism, Von Monakow’s controversial and often misunderstood theory of diaschisis.1 Although the extensive literature on recovery of stroke function is not reviewed,2–10 selected studies and theoretical issues potentially related to diaschisis are discussed.

Diaschisis is but one of several general theories of recovery of function which classically include: a) vicariation—the taking over of functions of the damaged area by regions not originally involved in the performance of lost behavior, b) redundancy—recovery based upon uninjured neurons that normally contribute to that behavior, i.e. the distribution of a function throughout the cerebral cortex, c) behavioral substitution—the learning of new behavioral strategies to compensate for the deficit, d) recovery from diaschisis—the temporary functional “shock” or deactivation of intact brain regions remote from but connected to the area of

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primary injury. These older theories of recovery, although quite different from recent objective observations of sprouting or denervation supersensitivity proposed to mediate recovery of function, are not mutually exclusive. The unspecified mechanisms for the alleviation of diaschisis could involve the growth of new axon terminals or the multiplication of postsynaptic receptors.

While changes in neuronal function are common to all of these theories, recovery of function is clearly a multifactorial process including: the resolution of extracellular and/or intracellular edema; reestablishment of cerebral blood flow (CBF) in "penumbral" areas after ischemic stroke or subarachnoid hemorrhage-related vasospasm; and restitution of tissue function after intracerebral hemorrhage (mass effect). Interventions to promote these events may directly improve clinical outcome by reducing the extent of initial damage. Thus, acknowledging the many different approaches to recovery after brain injury, this review will discuss only diaschisis.

Although the term diaschisis has often been used loosely, few publications\(^5, 11, 12\) adhere to Von Monakow's original description written in German,\(^1\) language barriers having contributed to the confusion and debates.\(^13-15\) Diaschisis (from the Greek meaning "shocked throughout") has been simplistically described as the cerebral counterpart of spinal shock. Recent experimental, neurophysiological and metabolic data support the initial interpretation of spinal shock as due to the loss of descending facilitatory activity producing a transient loss of spinal reflexes below the level of cord transection. Because the brain circuitry is relatively more complex than that of the spinal cord, understanding the mechanisms underlying cerebral diaschisis will be more difficult.

In the 1870's, Brown-Sequard, the most notable predecessor to the concept of diaschisis, described remote effects of focal brain damage ("actions at a distance").\(^2\) He proposed that brain lesions produced excitatory and inhibitory effects causing disruption of function in regions distant from the site of damage.\(^3\) Von Monakow, developing these ideas more fully, introduced the term diaschisis to describe "abolition of excitability" and "functional standstill". His theory of diaschisis, which excluded previously held concepts of irritation and active neural inhibition, was necessarily dependent upon the interpretation of functional brain organization. In contrast to the discrete localization of cortical function held by many of his contemporaries, Von Monakow noted: "The generally accepted theory according to which aphasia, agnosia, apraxia, etc., are due to destruction of narrowly circumscribed appropriate praxia, gnosis, and phasia centres, must be finally discarded on the basis of more recent clinical and anatomical studies. It is just in the case of these focal symptoms that the concept of complicated dynamic disorders in the whole cortex becomes indispensable."\(^4\) Von Monakow's perspective of "distribution of nervous function along several sections of the medullary tube" (neuroaxis), was "Jacksonian" in nature.

Von Monakow emphasized 4 important aspects of diaschisis:

1) Damage to one brain area can, by loss of excitation, produce cessation of function in regions adjacent to, or remote from but connected to the primary site of damage. The physiological process upon which the local initial symptoms are based, may be regarded as a shock confined to distinct nervous structures which have to be defined more precisely from the anatomical point of view. The local character (dependent upon the site of the lesion), the closer content, and also the manner of compensation for impairment of innervation, endows this shock with a special position, and makes it seem justified to classify it separately from other forms of shock. For this type of shock I shall use the term diaschisis. Consequently, diaschisis represents an 'interruption of function' appearing in most cases quite suddenly (this applies to all other types of shock as well) and concerning certain widely ramified fields of function, which originate from a local lesion but have their points of impact not in the whole cortex (corona radiata, etc.) like apoplectic shock but only at points where fibers coming from the injured area enter into primarily intact grey matter of the whole central nervous system.\(^11\)

Although, Von Monakow usually reserved the term diaschisis for sudden onset of some symptoms, he also proposed a "slowly creeping diaschisis"\(^12\) for which recent experimental evidence has lent credence.\(^16\)

2) Diaschisis was a clinical diagnosis whose presumptive mechanism was loss of excitation to intact regions rather than neural inhibition:

"In other words, massive lesions of commissural fibres in the left hemisphere will interrupt dynamically the points of entry and exit of fibers in the cortex of the right hemisphere, which will impair a number of more complicated nervous processes (apraxia, aphasia, agnosia)."\(^41\)

3) Diaschisis "undergoes gradual regression in well defined phases" such that resolution will parallel re-sumption of function in areas of diaschisis. With the recent neuroscientific focus on potential repair mechanisms following brain damage, Von Monakow's concept of a Darwinian struggle between diaschisis and an active repair process by unspecified restorative mechanisms, is indeed insightful:

"Any injury suffered by the brain substance will lead (as for lesions in any other organ) to a struggle for the preservation of the disrupted nervous function, and the central nervous system is always (although not always to the same degree) prepared for such a struggle; . . . The final result of this struggle (schism) will vary for each given area of the brain depending on the number and distribution of battling forces . . . and this is why the residual symptoms (pure sequels of the defect) will rarely be the same in different individuals."\(^41\)

An exception to the general rule of the transient state of diaschisis, is "diaschisis protractiva" wherein the cerebral shock cannot be spontaneously compensated for by active repair mechanisms.\(^11, 15\)

4) The "wave of diaschisis" follows neuroanatomical-
cal pathways apreading from the site of injury. Von Monakow refers to three types of diaschisis, illustrating their spread through classical fiber paths:

a) Diaschisis cortico-spinalis — progression of functional depression from a motor cortex injury to the spinal cord along pyramidal tract fibers.

b) Diaschisis commissuralis — functional contralateral cortical depression via axons of the corpus callosum following injury to the cortex of one hemisphere.

c) Diaschisis associativa — intracortical fiber-mediated depression of function in intact cortical areas neighboring the locus of injury.

Von Monakow proposed that three types of diaschisis usually occur simultaneously, but one form may predominate depending upon the "injured connections" and the degree of cortical development in the species under study.

Only during the last three decades have methodological advances been developed for the scientific investigation of diaschisis. Additionally, the concept of chemical neurotransmission has been accepted and the antiquated terms "shock" and "functional standstill" have no direct counterpart in modern neurophysiology. Investigations of the theory of diaschisis have recently used two approaches: 1) the study of remote effects of lesions on such variables as spontaneous or evoked electrophysiological activity, neurotransmitter levels, synaptic receptors and CBF and metabolism; 2) the manipulation of recovery of a particular behavioral symptom after brain injury.

Although alterations of neurotransmitters, sprouting of new neuronal processes, and changes in cerebral metabolism occur simultaneously at sites distant from actual injury, and bearing in mind that various interventions can influence behavioral recovery, causal effects are difficult to substantiate. For example, the concept of pharmacological restoration of behavioral deficits following brain injury\(^1\) assumes that drugs which cannot be acting upon lost neurons exert their effects upon intact systems rendered nonfunctional by the primary lesion.

More convincing would be a demonstration of the correlation of pharmacological manipulation of symptoms with alterations of physiological markers of the remote effects of lesions.\(^1\) Unfortunately, because of the multiple (and many unknown) drug effects in injured brain, and lack of a strict relationship between structure (or neurotransmitter) and a single behavioral function, it is difficult to firmly ascertain the etiologic mechanisms of manipulated recovery.

The separation of causal and beneficial effects from those only correlated with recovery of function (epiphenomena), demands an interdisciplinary study of behavior and neurophysiology. Detrimental changes following CNS lesions may also occur, e.g. neuronal sprouting after spinal damage may produce spasticity.\(^2\) In the injured brain, establishment of aberrant connections may impede rather than facilitate recovery.\(^3,4\) Because of these complexities there are few unequivocal experiments supporting any of the theories of recovery of function.

In the last decade, tomographic and autoradiographic technological advances have accelerated the study of remote functional effects of stroke. There has been repeated confirmation\(^5\) of the original observation that changes in structurally normal brain neuronal function are attended by proportional and parallel changes in the cerebral oxygen metabolic rate (CMRO\(_2\)), glucose utilization (CMRGluc) and — because of the so called coupling phenomena — CBF. This relationship is maintained in the brain as a whole, regionally, and even at the local level. Most early studies of diaschisis were restricted to stroke patients, were limited in their interpretation of the location and extent of the lesion. In contrast recent localization of pathology based upon radiologic technical advances in computerized tomography (CT) and magnetic resonance imaging (MRI), provide more accurate localization of pathology.

**Experimental Studies of Diaschisis**

**Spinal Cord**

As discussed above, the term diaschisis can be considered analogous to spinal shock, and is used by some clinicians in this context only. Supporting the classic interpretation that spinal shock is due to the loss of descending excitatory input is the report of immediate alpha motor neuron hyperpolarization after cooling and rewarming, respectively at higher cord levels.\(^6\)

Post-cord transection measurements of glucose utilization using \(^14\)C-deoxyglucose (2DG) in the monkey have recently indicated more complex and widespread effects appearing in many segments above and below the level of the injury.\(^7\) Increased CMRGluc in some lamina was interpreted as a loss of tonic descending inhibition, and while reminiscent of diaschisis, the loss of active neural inhibition was not included in Von Monakow's theory. The observation of hypermetabolic lamina adjacent to hypometabolic lamina after cord transection suggest caution in the interpretation of data, especially negative results, when measures from large regions of neuropil are combined.

**Brainstem Lesions**

Since a vast number of pathways interconnect brainstem, diencephalic and telencephalic neuronal aggregates, a brainstem vascular lesion might be expected to exert transynaptic effects at many distant loci. In stroke patients, brainstem lesions inducing stupor or coma are associated with diminution of supratentorial perfusion and metabolism roughly correlating with both the state of arousal and altered EEG patterns.\(^8\)

Conversely, patients with severe brainstem stroke resulting in total paralysis but normal arousal ("locked-in syndrome"), have normal CBF.\(^9\)

The classic work demonstrating coma in the cereau isolé preparation was interpreted as a remote effect of the diffusely projecting mesencephalic reticular formation altering forebrain function.\(^10\) Although the critical involvement of the mesencephalic region in the regulation of wakefulness has long been accepted, recent work has focused on the complex interactions of di-
verse nuclei within this region, and has utilized strategically placed lesions.

In the rat, large unilateral lesions interrupting most of the brainstem-forebrain pathways resulted in marked ipsilateral decreases in CMRGlucortical and subcortical gray matter. Destruction of the rostral reticular formation in stages first on one side and then after some time period, the contralateral side, did not produce enduring coma. This attenuated effect was interpreted as lesions performed in sequence producing less diaschisis. Lesions done in stages may be likened to slowly growing tumors which produce less symptomatology than acute lesions of the same magnitude. This effect of the Jacksonian "momentum" of a lesion or "slowly creeping diaschisis" is still poorly understood.

Experimental animal studies have examined changes in forebrain metabolism after stereotaxic lesions of specific brainstem nuclei. Electrolytic lesions of the rat raphe serotonergic somata resulted in moderate depression of CMRGlucortical in other brainstem nuclei and the hippocampal dentate gyrus without altering metabolism in other forebrain regions. Unilateral lesions of the locus coeruleus (LC) reportedly caused either very moderate or no change in cerebral metabolism. Glucose utilization was markedly reduced in the ipsilateral cerebral cortex and latero-ventral thalamus (by 10% and 15% respectively) or unchanged. Cortical resting metabolic rates measured using the histochemical stain alpha-glycerophosphate dehydrogenase (α-GPDH) were unchanged. In contrast, the depression of α-GPDH in the entire ipsilateral cortex following focal cortical injury is exaggerated by lesions of the LC. This data is compatible with the hypothesis that the LC "modulates" activity of other systems.

In the rat, 6-hydroxydopamine-induced substantia nigra lesions have simulated the dopamine (DA) deafferentation of Parkinson's disease. Resulting physiologic changes include mildly deceased CMRGlucortical in the ipsilateral frontal cortex, not reversed by administration of DA agonists, mild ipsilateral striatal metabolic depression and marked hypermetabolism in the ipsilateral habenula and globus pallidus. These latter effects, in contrast to the frontal cortex hypometabolism, are alleviated by apomorphine or L-Dopa. These metabolic changes, which are associated with ipsilateral DA postsynaptic hypersensitivity and behavioral abnormalities, are not found in animals showing spontaneous recovery of function. Although these studies satisfy most of the criteria for diaschisis they are rarely discussed in this framework. That the target structure of the substantia nigra shows only a mild metabolic depression despite the almost total DA deafferentation may result from the sparing of the non-DA afferents constituting the major inputs to the striatum. There may be no presently detectable direct metabolic counterpart to the presumptive primary neural abnormality of Parkinson's Disease i.e. the loss of nigro-striatal input. Transneuronal hyperactivity resulting from loss of tonic inhibition, reflected by increased pallidal glucose utilization following substantia nigra lesions, can occur after brain injury — and incorporating this concept is essential to present-day revision of the theory of diaschisis.

In summary, remote supratentorial functional effects of brainstem reticular and nigro-striatal lesions have been clearly demonstrated using cerebral metabolic measurements. Transient, transsynaptic effects secondary to lesions of either of these anatomically and physiologically unique systems could potentially be considered diaschisis.

**Thalamus**

The thalamus constitutes a major relay and integrative nuclear cluster, including the sensory, motor, limbic systems, as well as the ascending brainstem reticular formation. Thus, interruption of neuronal function such as occurs in thalamic stroke, can give rise to a constellation of different clinical expressions including sensory loss, ataxia, speech alterations (thalamic aphasia), visual-spatial deficits, global or selective amnesia, hemi-inattention (neglect), psychomotor retardation, akinetic mutism, thalamic dementia and possibly coma. Apart from designated functional roles of the ventrobasal complex and geniculate bodies, precise clinico-anatomic correlations of other thalamic nuclei are lacking. However, selected human studies (including stereotaxic thalamotomy) have suggested the dominant ventral-lateral and intralaminar nuclei play a significant role in the mechanisms of attention. Lesions of the left or right medio-dorsal nucleus may produce verbal and visual amnesia respectively, while bilateral lesions may result in global amnesia or dementia. Some of these thalamic injury syndromes have also been reproduced in nonhuman primates.

In view of the dense thalamocortical projections, it has been speculated that these behavioral consequences of thalamic damage result from cortical dysfunction after loss of these important cortical afferents — perhaps a loss of cortical "activation." Some particular patterns of symptoms may only reflect "specialized cortical functions." This could be interpreted as a diaschisis, since such effects would be remote from the lesion and recovery is often remarkable after thalamic stroke even when initial symptoms are severe.

Electrophysiological data from both human and animal experimentation shows that there is marked ipsilateral cortical EEG slowing following unilateral lesions in many of the "non-sensory" thalamic nuclei, particularly the intralaminar, medio-dorsal, ventral-anterior and the reticular nuclei. These effects, which depending on the size of the lesion last for weeks or longer, reportedly affect the entire ipsilateral cortical mantle. Lesions of a "specific" projection nucleus, such as the ventral-posterior-lateral nucleus may not result in EEG slowing or the effects are restricted to the somatosensory cortical projection area. Unilateral lesions of the rostral pole of the thalamus (anterior-ventral and reticular nuclei) in the cat, depressed both seizure activity and sleep spindles over the ipsilater-
eral cortical hemisphere without attenuating cortical evoked responses. This suppression of cortical circuitry involved in the generation of synchronous discharge without reducing cortical excitability can be considered a selective remote cortical effect of injury to the anterior thalamus. But whether the mechanism of this effect is intrathalamic or a disruption of the diffuse cortical projection system is unclear. A similar depression of synchronous discharge, ipsilateral alpha rhythm blockade, has been described following unilateral stroke involving these nuclei.

Positron emission tomography (PET) and single photon emission computerized tomography (SPECT) studies of patients with recent ischemic or hemorrhagic unilateral thalamic stroke, have clearly demonstrated matched reductions in ipsilateral cortical perfusion, CMRO$_2$ and CMRGlut involving the entire ipsilateral cortical mantle. Although correlations between distribution and severity of cortical metabolic depression, the particular thalamic nuclei involved and clinical symptoms are indeterminate, studies suggest an association between the degree of cortical hypometabolism and behavior deficits. Additionally, there is a significant trend between recovery of cortical metabolism and clinical improvement.

Experiments involving thalamic lesions in rats show some correspondence with this human data. After unilateral electrolytic lesions of the ventro-medial nucleus of the thalamus, there is an ipsilateral reduction of cortical metabolic rate directly proportional in severity to the size of the thalamic lesion.

Since cerebral energy metabolism essentially reflects sodium pump activity and hence the density of pre- and postsynaptic events, the cortical metabolic depression after pure thalamic lesions may involve any number of factors including: 1) anterograde Wallerian degeneration of thalamo-cortical terminals; 2) retrograde degeneration of corticothalamic neurons secondary to lesions of their thalamic terminals; 3) transynaptic degeneration of cortical neurons secondary to loss of thalamic afferents; 4) reduced functional activity of cortical neurons (without degeneration) after a loss of thalamic input. Metabolic depression invoked by the first two mechanisms, rather than an index of diaschisis, is a simple manifestation of direct injury to neurons. The latter two mechanisms involving transynaptic processes capable of recovery, could qualify as physiologic measures of diaschisis. The disproportionate magnitude of cortical metabolic depression after thalamic lesions, relative to the density of thalamo-cortical projections, makes the anterograde degeneration a tenuous explanation. Retrograde degeneration of corticothalamic neurons and cortical transsynaptic neuronal death are rare, if not absent, in the adult mammalian brain. A loss of dendritic spines from cortical neurons does occur after deafferentation but has not been reported following thalamo-cortical disconnection. Electron microscopic studies are needed to determine any potential association of metabolic disturbances with morphological changes (such as dendritic spine atrophy) that would reflect postsynaptic membrane adaptation to alterations of thalamic input. The trend for recovery from cortical hypometabolism seen after thalamic stroke would be consistent with this view. Alternatively, the diffuse cortical hypometabolism subsequent to thalamic lesions may result from a non-specific process of “deactivation.” Other postulated mechanisms for the accommodation to loss of thalamic input to the cortex include collateral sprouting or postsynaptic receptor supersensitivity. The observations of cortical hypometabolism after thalamic injury are somewhat similar to those seen in the rat visual cortex following enucleation, or the somatosensory cortex after the removal of whiskers. Recovery of synaptic density in the deafferented dentate gyrus in the rat follows a roughly similar time course to that of metabolic recovery in peripheral deafferentation models.

Thalamic lesions in animals and humans induce mild contralateral cortical metabolic depression. This very transient effect may occur via second-order corpus callosum connections and represent a transcallosal diaschisis. Hypometabolism of the ipsilateral basal ganglia has also been reported following thalamic stroke and experimental lesions, and is likely mediated via the extensive thalamo-striatal projections. Bilateral metabolic depression in other subcortical structures has also been described following experimental unilateral thalamic ventromedial nuclear lesions.

Striatum

Data regarding the remote functional effects of striatal lesions are sparse. The effects of experimentally induced caudate lesions in animals were mild, transient and not reproducible by similar putamenal lesions. Of the few anecdotal reports of patients with stroke involving the striatum, none were “pure,” but also involved adjacent internal capsule and hence possibly thalamo-cortical fibers. In these cases, mild metabolic depression affecting the entire ipsilateral cortical mantle and thalamus, has been described. These cortical effects may be secondary to degeneration of cortico-striate fibers rather than diaschisis.

Unilateral striatal lesions in the rat, using the neurotoxin kainic acid (which presumably spares the tract fibers) has no apparent effect on ipsilateral cortical metabolism. However, the increased CMRGlut in the ipsilateral globus pallidus and substantia nigra (pars reticulata) presumably reflects a GABA-mediated transsynaptic loss of inhibition blocked by pretreatment with systemically administered muscimol.

Cholinergic System Lesions

The cholinergic system has received considerable attention following the demonstration of the role of hippocampal and cortical cholinergic projections in memory and cognition, as well as in the pathogenesis of Alzheimer’s disease. Unilateral lesions of the nucleus basalis of Meynert (NBM) or the septohippocampal pathway in rats suppresses cholinergic function in the
deafferented ipsilaterals structures as well as reducing cortical EEG, while bilateral lesions cause learning and memory deficits. Recovery of function resulting from collateral sprouting of surviving cholinergic neurons, has been observed. Neurotoxin-induced lesions of NBM also depress ipsilateral CMRGlucose as early as 3 days after surgery, maximal in the primary frontal cortex projection area with recovery between 7 and 30 days. Whereas recovery of hippocampal hypometabolism induced by medial septal lesions occurs by 3 months, that produced by complete destruction of the fimbria-fornix and cingulate cortex persists for longer than 6 months postinjury. That these metabolic effects of lesions result from cholinergic deafferentation was clearly demonstrated by 1) high linear correlations between percent reduction in CMRGlucose and measures of acetylcholinesterase (AChE) and 2) the striking and parallel recovery of both AChE and CMRGlucose resulting from cholinergic grafts six months following cholinergic deafferentation. Administration of oxotremorine, a cholinergic agonist, and atropine, a cholinergic antagonist, is associated with respective improvement and deterioration in the behavioral and metabolic responses to injury.

These models of cholinergic deafferentation satisfy criteria for diaschisis by providing evidence for an association between synaptic functional alterations and behavioral deficits, strengthened by the parallel response of these measures to pharmacological manipulations. While there is no spontaneous recovery after severe cholinergic deafferentation, a favorable reaction to pharmacological manipulations or grafting suggests that this model is an example of “diaschisis protactiva.”

The use of CBF, SPECT, and PET techniques in Alzheimer’s disease patients has demonstrated a preferential parieto-temporo-occipital association cortex metabolic depression; this is likely not the result of innominato-cortical cholinergic deafferentation because of the different anatomic, namely prefrontal, cortical innervation by the cholinergic system. Progressive supranuclear palsy, a degenerative disorder affecting the basal ganglia and most brainstem ascending systems, is marked in some patients by an intellectual impairment termed “subcortical dementia,” reminiscent of prefrontal lobe damage. While the prefrontal cortex is pathologically intact, PET studies have revealed a marked metabolic depression corresponding to the behavioral deficits. This prefrontal hypometabolism is thought to result from loss of several afferent systems to this cortical area, including the cholinergic projections. The pattern of symptoms and the PET data can be considered an example of “slowly creeping diaschisis” and suggests that replacement of the failing neurotransmitter(s) may improve the intellectual deficit in this disorder.

White Matter Lesions

Animal white matter lesions made just beneath the cortical surface (undercutting), result in marked EEG slowing. In contrast, electrolytic lesions of the posterior limb of the internal capsule produce inconsistent, transient effects. In humans, “pure” white matter lesions are difficult to confirm, and small infringements on neighboring grey matter (e.g. thalamus, pallidum) contributing to the lesions’ manifestations, may go undetected by present imaging techniques. Physiological observations in deep hemispheric syndromes have included; 1) lack of the normal sensorimotor cortex cerebral blood flow activation during contralateral hand movements in patients with capsulo-thalamic infarcts; 2) reduced CMRGlucose in cortical and thalamic regions ipsilateral to caudate and internal capsule lacunar lesions; 3) reduction in precentral and central cortical blood flow ipsilateral to internal capsule infarcts. Other studies of smaller white matter lesions have shown no cortical metabolic impairments. Taken together, these observations suggest that damage to the thalamus itself or to thalamo-cortical fibers is necessary for development of behavioral symptoms and cortical hypometabolism.

Lesions of the optic radiations reportedly induce ipsilateral metabolic depression in the deafferented visual cortices. Patients studied weeks after the onset of lateral homonomous hemianopia still exhibit this visual cortex depression. The discrepancy between the transient metabolic effects of enucleation and the lasting metabolic depression following optic radiation lesions, although possibly species specific, more likely results from the different points of interruption of this multiple relay circuit.

Transcallosal Diaschisis

Kempinsky’s experimental contributions to the study of diaschisis should not be overlooked. He primarily studied electrophysiological responses contralateral to unilateral cortical lesions produced by diverse methods (ablation, electric cautery, vascular ligation, and freezing). However there are some shortcomings which limit interpretation of his data which include possible variations in the depth of ether-induced anesthesia, lack of quantification of evoke potential and EEG data, and the absence of histological verification of prior corpus callosum section done in some cats. In none of the animals with the callosal section was a depression of evoke potentials observed, however some of the cats with large lesions did show EEG amplitude reduction contralateral to the cortical injuries. Despite these factors, Kempinsky interpreted his data as strong support for Von Monakow’s theory of diaschisis.

Although it is tempting to invoke a mechanism of transcallosal diaschisis for the commonly reported CBF depression contralateral to a stroke, such studies are flawed by confounding variables prior to or following the acute event. Such factors include chronic hypertension, previous cerebral infarction, large vessel occlusion and “steal” phenomenon, increased intracranial pressure, transtentorial herniation, drug effects, and changes in PaCO2, hematocrit, and arterial blood pressure. The effect of these variables on cortical function, contralateral to a stroke, as measured by CBF, CMRO2, or CMRGlucose is unknown.

Animal experiments circumvent some of these confounding variables in the human studies. In models of
focal cerebral ischemia there are reportedly variable decreases in contralateral CBF and CMRGlu post-arterial occlusion106-117 some refuting114 and others supporting116 the concept of transcallosal diaschisis.

Not recognized by Von Monakow was the loss of neuronal function in intact brain depleted of neurotransmitter because of a shift from synthesis of transmitters to proteins for repair by remote injured neurons innervating these areas.118,119 The LC is one candidate for such an effect118 because of its diffuse intracortical projections, as small cortical lesions may cause transient retrograde reactions with resulting widespread alterations of noradrenergic (NE) transmission in several CNS regions.

Experimentally induced right middle cerebral artery territory ischemia has been shown to effect transcallosal physiologic changes remote from the site of injury.120-125 There is widespread reduction of neurotransmitter levels from brainstem neurons, as well as behavioral hyperactivity. The postulated association between post-right hemisphere cortical injury evoked hyperactivity and depressed NE levels in intact regions is supported by the blockade of hyperactivity by daily administration of the NE uptake blocker desmethylimipramine at doses not affecting activity in sham-operated controls.121 It is quite likely that other neurotransmitters including DA,124-128 serotonin128 and GABA,129,130 whose levels also change in intact brain remote from cerebral ischemia, contribute to the clinical profile. As emphasized by Robinson and Bloom21: "...the idea of stroke as a local injury producing its effect by disruption of local mechanisms of function is inadequate conceptually and misleading clinically..." They suggest that the mood depression often occurring following stroke may be a manifestation of such remote pathophysiological events rather than a psychological reaction to disability.

**Functional Effects in the Ipsilateral Cortex**

Initial and delayed neurologic functional improvement following cortical stroke has been viewed in terms of recovery from a state of diaschisis, i.e. a partially reversible functional depression of the cortical area surrounding a site of necrotic damage. However, confirmation of this mechanism is difficult as electrophysiological activity, CBF, and metabolism may be disrupted within an ischemic penumbra beyond the boundaries of the infarct.131 Human PET studies of CBF and CMRO2 have demonstrated the frequent occurrence of the "misery-perfusion" syndrome over morphologically intact cortical regions in the first 2-4 days following stroke, a situation of hemodynamic failure that occasionally persists into a chronic stage.132 Depressed cortical functions ipsilateral to cortical stroke may, in addition to the ischemic process per se, result from a constellation of factors including tissue edema, increased intracranial pressure with or without brainstem compression, diffusion of toxic waste products from the necrotic core, and selective neuronal cell death without necrosis. Furthermore, the extension of ischemic necrosis to subcortical white matter may isolate the overlying cortex from its afferent input and sever efferent axons. This "undercutting" process can produce depressed cortical function based on the previously discussed mechanisms other than a diaschisis. Finally, a spread of necrosis to subcortical nuclei may depress the functional activity of the cortex. As in the case of transcallosal diaschisis, the study of post-infarct intracortical diaschisis is difficult but experimental cortical lesions, albeit not free of all confounding variables, offer a more controllable data base.

Animal studies have correlated behavioral disabilities (e.g. reaching for food with the appropriate limb) and a depression in sensory evoked potentials recorded in tissue adjacent to small electrolytic lesions placed in the motor cortex. Normalization of the evoked potentials in intact cortex adjacent to the lesions paralleled recovery of behavior.133,134 In contrast, enhancement of evoked responses recorded in intact cortex adjacent to small cortical lacerations has been reported,135 possibly heralding post-traumatic epilepsy.136 A diffuse reduction in ipsilateral hemispheric oxidative metabolism measured by enzymatic α-GPDH histochemical staining has been described following focal cortical trauma.134 Reduced monoamine neurotransmitter levels in cortex remote from but ipsilateral to the injury have been reported also.120-126,128 Intracortical diaschisis has been a postulated mechanism for the depressed cortical perfusion surrounding an area of infarction in aphasic stroke patients.137 The advent of the PET scan has made it possible to discriminate between primary metabolic depression and primary hypoperfusion. Matched decreases in CBF and metabolism ipsilateral to cortical infarction have been reported.55,68,69,138,139 Such reduction of CBF and CMRO2 beyond infarct boundaries has been reported in patients,140-142 and animals43 with chronic occlusion of either the internal carotid or middle cerebral artery (MCA). Widespread depression of early 1-Isopropyl-l-tyrosine amphetamine uptake involving almost the entire cortical mantle ipsilateral to chronic MCA territory infarction has also been observed with SPECT, even in the absence of an arteriolar occlusion at angiography.144 Selective cortical cell death without tissue necrosis could cause this metabolic depression; it occurs experimentally in penumbral areas,145,146 but appears rare in humans.146,147 Available metabolic data from experimental cortical ablation or freeze-lesions19,116,117,148-150 suggest that intracortical diaschisis is of minor importance, perhaps because maintenance of a functional cortex depends on many afferents other than those from the cortical lesion site.

**Functional Effects in the Subcortex**

Patients with primarily cortical stroke have shown definitive ipsilateral thalamic and/or basal ganglia metabolic depression occurring within hours, but also found years later, in PET study.55,68-70,139,151-155 Putative clinical correlates of these remote metabolic effects include verbal memory deficits without aphasia associated with left thalamic hypometabolism and motor speech deficits related to reduced left caudate nucleus CMRGlu.51,154 Thalamic medial-dorsal and/or ventral basal nuclear complex glucose hypometabolism ipsilateral to unilateral anterior or posterior corti-
cal lesions, has been reported.148-150, 153, 156 While these thalamic hypometabolic responses to cortical ablation predominantly reflect retrograde degeneration, some may represent a diaschisis mediated by transsynaptic actions either from cortico-thalamic or intrathalamic pathways.

Reduced striatal CMRGlu, although occurring less consistently than in the thalamus, has been reported following unilateral ablations of the ipsilateral frontal cortex.116, 148-150, 155 Additionally, modulations of the striatal neurotransmitters DA, glutamate, and GABA have been reported following such lesions.127, 128, 129 Frontal lobe ablation-induced neglect is associated with the remote metabolic effects in monkeys.139 The analysis of the metabolic changes after frontal ablation following prolongation of the neglect syndrome by diazepam138 could clarify any causal relation between the metabolic and behavioral changes. Interestingly, transneuronal glucose hypermetabolism has been observed in the pallidum ipsilateral to a frontal ablation in rats149 but not monkeys.150, 155 The remote effects of unilateral frontal cortex lesions on cerebral metabolism have been quantitatively examined using cytochrome oxidase histochemistry in the rat.150 The latter investigation has shown that injury produces a bilateral hypometabolism in the pallidum and several other extrapyramidal structures; an effect reversed by amphetamine. These findings are possibly related to this drug’s acceleration of recovery from hemiplegia discussed below.

Electrophysiological data from the hippocampus after cortical lesions has been cited as evidence against diaschisis.156 Dendritic field potentials evoked by stimulation of the monosynaptic hippocampal-commissural pathway were recorded before and after unilateral lesions of the ipsilateral entorhinal cortex. The absence of postlesion evoked response changes was interpreted as an absence of diaschisis. This study has been criticized by others157 and hippocampal CMRGlu measurements have indicated a depression of function following similar entorhinal lesions.161, 162

A number of diencephalic and brainstem nuclei other than thalamus and basal ganglia exhibit metabolic changes following experimental cortical ablation. The time course, neurochemical and behavioral correlations of these remote metabolic effects are not known. The affected nuclei show no clear histologic neuronal degeneration to account for the metabolic changes. The metabolic depression found in the ipsilateral pontine nuclei in monkeys155 may reflect degenerating cortical pontine terminals, transsynaptic depression of activity (degeneration of excitatory corticofugal afferents) or both. Conversely, changes in metabolism and neurotransmitter levels seen in the region of the LC ipsilateral to frontal cortex lesions19, 120-127 have been interpreted as a retrograde reaction of the neuronal soma after damage to one or more of its cortical axonal branches. Finally, the hypometabolism seen in the ipsilateral red nucleus,19, 149, 159 subthalamic nucleus149, 159 and substantia nigra after frontal cortex lesions155 may, in part, represent transneuronal effects secondary to disruption of a motor circuit.

Pharmacological Studies of an Animal Model of Hemiplegia

In an attempt to explain the mechanisms of hemiplegia following motor cortex damage, Von Monakow described “diaschisis cortico-spinalis”, a reversible functional depression of remote intact structures. Experimental pharmacologic manipulations in hemiplegic animals have been shown to accelerate recovery while also affecting cerebral metabolism and neurotransmitter release at a site remote from the primary lesion. Unilateral sensorimotor cortex ablation in the rat produced pronounced but transient contralateral hemiplegia evident on the beam-walking task. Amphetamine, administered in moderate doses was combined with the beam-walking experience. A single administration of the drug one day post-operatively enhanced recovery compared to saline controls and the beneficial effects endured and were maintained long after the drug was metabolized. In animals given amphetamine and kept in a small cage to prevent ballistic movements during intoxication, no promotion of recovery was observed indicating the necessity to combine drug and experience. Haloperidol blocked this treatment effect and when given alone in a single dose, also markedly retarded recovery, implicating the catecholamines (CA) in recovery of function.163 This effect has been replicated in the cat whose more severe hemiplegia responds favorably to delayed (10 days post-surgery) multiple but spaced administrations of amphetamine combined with beam-walking experience.164

The mechanism of these effects is uncertain but diaschisis has been suggested to explain the rapid behavioral improvements produced by this pharmacologic treatment plus behavioral experience.19 Alternative interpretations include: the reversal of lesion-induced input or depleted neurotransmitter, longterm potentiation,63, 165, 166 and behavioral substitution. A CA-related diaschisis is supported by the observations that single infusions of NE,167 or systemic administration of the amphetamines phentermine168 or phenolpropanolamine,169 combined with experience also promote recovery from hemiplegia. The DA agonist apomorphine and the DA uptake-blocker methylphenidate do not promote recovery from hemiplegia in this model.170, 171 Further biochemical support for CA-related diaschisis is the observation in post-operative treated animals of increased NE turnover in the ipsilateral LC (whose neurons project to forebrain and cerebellum172) and the cerebellum contralateral to the cortical lesion compared to saline treated controls. Such changes could indicate a treatment-induced alleviated or compensated “crossed cerebellar diaschisis” which has been associated with supratentorial stroke discussed below. Metabolic studies in this model suggest a diaschisis as there is a widespread depression of 2DG utilization especially prominent in the ipsilateral red nucleus and LC following unilateral sensorimotor cortex lesions.19 Paralleling the pharmacological manipulation of behavioral recovery is the respective improvement or worsening of post-surgical hypometabolism by amphetamine and haloperidol.19 However,
since these CNS metabolic effects are diffuse, delineation of anatomic selectivity is necessary before a specific structural correlate of treatment-accelerated functional recovery can be established.

Crossed Cerebellar Diaschisis

Cerebellar hemisphere hypometabolism contralateral to supratentorial infarction was first described by Baron et al using PET and the steady-state oxygen-15 method.173-175 This phenomenon has since been reported in about 50% of patients with stroke and those with supratentorial neoplasms, studied by tomographic mapping of perfusion CMRO2, CMRglu, or I-iodoamphetamine uptake.183, 186, 187, 188, 189

Significant contralateral cerebellar hypometabolism (CCH) has been observed in patients with isolated lesions of the frontal cortex,55, 176, 179 parietal cortex,107, 179, 183 thalamic and basal ganglia areas,107, 174, 177, 179, 183 and internal capsule.9 The CCH is most prominent with large lesions involving two or three cerebral lobes, or after smaller lesions destroying most of the internal capsule at the level of the basal ganglia. The size and location of the lesion rather than severity of hemiparesis appear to be the best predictors of CCH in stroke patients. Additionally, CCH has been seen in patients with pure motor hemiparesis related to the internal capsule lacune,88, 89 as well as in patients with large infarcts and no hemiparesis,176, 178, 179, but not in hemiparetic patients with a presumed pontine lacune.9

 Interruption of the cerebro-cerebellar loop is thought to be the most likely mechanism of this remote transneuronal metabolic depression.174, 175 Its frequent association with frontal and parietal cortical lesions — the origin of the cortico-pontine fiber tract180-183 fits this hypothesis. Since cortico-pontine projections provide predominantly excitatory input to the contralateral cerebellar granule cells,189, 190 damage to this system could “deactivate” the contralateral cerebellum, hence the term “crossed cerebellar diaschisis.”112, 113 Although CCH was not specifically studied, experiments in monkeys149, 150 have shown ipsilateral pontine nuclei hypometabolism after cortical ablation. CCH has been difficult to observe in patients with pure motor hemiparesis related to the internal capsule lacune,88, 89 as well as in patients with large infarcts and no hemiparesis,176, 178, 179, but not in hemiparetic patients with a presumed pontine lacune.9

In conflict with the theoretical interpretation of CCH as a diaschisis is examples where CCH persists or even worsens post-infarction.55, 107, 176, 177, 179, 181 Furthermore, CCH may develop in association with slowly growing supratentorial tumors,178, 179 indicating that acute brain injury is not essential for its development. Thus, two essential criteria for a diaschisis, namely sudden onset and a transient response are lacking in CCH. While other examples of slowly developing diaschisis have been discussed, the lack of CCH reversibility is a major theoretical problem. Other possible explanations include anterograde transneuronal degeneration, known to occasionally develop years after adult-onset supratentorial stroke.193, 194 Since dendritic alterations as early as 2–3 days after deafferentation have been described,195, 196 the acutely detectable CCH might represent early metabolic responses expected to precede irreversible morphological alterations.195 The lack of recovery of CCH and its apparent progression to degeneration sharply contrast with the other examples of transynaptic depression discussed above. Nevertheless, recovery of CCH has actually been reported in a few stroke patients, suggesting that this process is not necessarily inescapable. While the mechanisms for recovery are unclear, they may represent a link between reversible diaschisis and irreversible degeneration.197

As yet, there is no well established clinical expression of CCH. In a recent study of seven patients with pure internal capsular infarcts, no obvious association between CCH and ipsilateral limb ataxia was found.198 Thus, until large scale prospective studies are undertaken, the phenomenon of CCH, although the most consistent evidence of transneuronal functional depression in humans, will remain poorly understood in terms of pathophysiology, clinical correlations and therapeutic implications.

In addition to effects on the contralateral cerebellum, supratentorial lesions may result in a mild, less profound metabolic depression in the ipsilateral cerebellum.55, 107, 176, 178 This observation has been challenged199 because of the lack of an adequately matched control group with respect to age and vascular risk factors, as well as a nonhomogeneous study group. Furthermore, its reported association with impaired consciousness,107 suggests a role for supratentorial edema and herniation.

Concussion

Experimental data suggest that the sequelae of cerebral concussion may reflect midbrain muscarinic cholinergic hyperactivity.197 Supporting this theory is the reproduction in cats of transient behavioral and EEG changes mimicking concussion following acetylcholine agonist (carbachol) infusion. An increased 2DG utilization in cholinergic neurons remote from the site of trauma was observed in a concussion model. Such a cholinergic pathological hyperactivity may act upon other intact systems to produce symptoms of concussion. These findings are compatible with the theory of diaschisis if it is modified to incorporate disruptive hyperactivity as well as loss of facilitatory input from damaged areas.

Permanent Diaschisis

Schneider15 first conceptualized a permanent diaschisis, “diaschisis protractiva,” to explain the surgical alleviation of the hemianopsia contralateral to posterior cortical ablation in cats.198 Animals with longstanding loss of orienting responses to stimuli in the visual field contralateral to a large unilateral posterior cortex ablation recovered after a lesion of the contralateral superior colliculus or intercollicular commissure. The subcortical lesions were thought to abolish a pathological intercollicular tonic inhibition resulting from the unilateral cortical ablation.198, 199 Another possible example of permanent diaschisis is the amphetamine plus visual experience restoration of depth perception after bilateral visual cortex ablation in cats.200
This effect is blocked by haloperidol adding further support for a role of CA in a diaschisis. Preliminary cytochrome oxidase histochemistry indicates that this treatment also reverses the hypometabolism in the superior colliculi which follows visual cortex lesions.201

Therapeutic Implications

A recent double-blind pilot investigation suggests that the animal data on the treatment of hemiplegia may be applicable to human stroke.202 Eight patients with stable motor deficits studied within ten days of their first stroke, were randomly assigned to treatment or control groups. Motor performance was objectively scored prior to, and 24 hours following a single oral administration of either 10 mg of d-amphetamine sulfate or a vitamin placebo. Intensive physical therapy of the affected limbs was provided for all patients following drug or placebo, to induce the necessary relevant experience as determined from the animal studies. A statistically significant improvement in motor scores over pretreatment values was seen in all patients receiving amphetamine plus physical therapy, compared with lack of improvement in the control group. Other drugs with non-specific, potential therapeutic effects on diaschisis include naloxone, piracetam, and GM1 ganglioside.

Haloperidol and alpha-noradrenergic antagonists have been reported to retard recovery in aphasic stroke patients.203 Recovery can be accurately predicted using a mathematical model based on the test results of the Porch Index of Communicative Ability.204 Patients on alpha-blockers, in contrast to those on beta-blockers or no medication, showed a significant retardation of recovery as compared with the predicted recovery. The transient reinstatement or enhancement of post-stroke neurological deficits by CNS depressants such as benzodiazepines,198 phenytoin,200, or anesthetic agents suggests that recovered neuronal function, in contrast to normal function, is much more vulnerable to disruption by pharmacological agents.

Concluding Comments

Kempinsky proposed79 “essential criteria” for diaschisis including 1) a circumscribed injury, 2) a neuronal basis for the depressive effects, 3) its occurrence at a distance from the injury, 4) identification of the fiber tract involved, and 5) a reversible process.

The above criteria still appear valid. Regarding distance from injury, at least one synapse must exist between the lesion and the target structure that is in the proposed state of diaschisis. A synapse lying within the target structure could potentially reflect only presynaptic events or direct reactions to axonal injury, thereby confounding interpretation of the data. Reversibility is a necessary requirement in order to exclude the direct effects of the primary injury; however, in the case of permenant diaschisis, its demonstration would require surgical or pharmacological interventions.

Ideally, in a modern conception of diaschisis the physiological indices of this phenomenon should correlate with a behavioral symptom, and both should parallel improvement with time and response to manipulations. With prolonged lack of normal afferent input or function, diaschisis may result in morphologic alterations. The disruption of function in the target structure may result from a loss of either excitation or inhibition. In cases of low afferent input activity or in the presence of numerous other inputs to the target structure, diaschisis may not occur. Conversely, if the lesioned area constitutes the sole or major input to the target structure, a readily detectable diaschisis must occur. Diverse mechanisms, possibly including repair processes such as sprouting and/or denervation supersensitivity, could allow the target structure to accommodate for the loss of input from the lesioned area.

While none of the experiments discussed in this review completely satisfy all the criteria for diaschisis, they do provide persuasive evidence for certain aspects of the theory. Only if this concept stimulates future work which provides some understanding of recovery of function will such a general theory of reaction to brain injury prove worthwhile.

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