Historical Observations on Functional Reorganization

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Since the beginning of Neurology, plans for therapy have been recognized to rest on efforts at establishing a diagnosis and on estimating prognosis. Absent modern *in vivo* imaging, for almost 150 years efforts at diagnosis were based on the tacit assumption that the lesion, whatever its cause and in either of the two cerebral hemispheres, creates more or less the same syndrome. The notion of syndromes rested on the second assumption of a fairly reliable correlation between the clinical syndrome and the locus and size of the brain lesion.

This structure-function correlation arose from examination of post-mortem material, the autopsy specimen often available not hours but years after the initial lesion. It was soon appreciated exceptions existed. Either the lesion size exceeded or was smaller than what was assumed to be the basis of the original syndrome. Attempts to explain the discrepancies led to assumptions that the lesion causing the initial syndrome had enlarged in the time from diagnosis to autopsy, or that the acute effects of the lesion affected a region larger than that found at autopsy, or something happened to improve outcome, perhaps subsidence of edema.

The initial arguments for Broca aphasia were based on the first of these notions. The large lesion in Broca's index case was assumed to have grown in the 10 years from onset, so clinicians were justified in focusing their attention on a smaller component of the lesion, located in the area therapy had predicted. Diaschisis was invented as the basis for the second effect, the initially functional disorganization caused by the acute lesion creating some sort of shock wave requiring time to subside, braining func-

tion back in its wake. Subsidence in edema was among the third, the subsidence occurring in a time frame explaining the improvement. Few suggested that the brain itself was capable of some sort of software reprogramming in the hyperacute phase, computer then unknown and remodeling thought unlikely.

Objections to the expanding lesion were not long in coming. Byron Bramwell's case was talking within hours, the infarction found at autopsy being rather small but situated where the Broca area infarction was presumed to create a persisting and major speech and language disorder [1] a finding echoed almost a century later by a series of focal infarcts in Broca area [2]. Interest in this insight increased when more cases in retrospect were seen to have undergone considerable improvement and in too short to be explained as a growing lesion [3]. When viewed in the perspective of a century and with fresh cases to revive long-ignored examples, it appeared that the Broca area infarction was not the cause of Broca aphasia; a far larger lesion, one encompassing the insula and operculum, was required [4]. That initial mutism occurred and rapidly faded forced consideration of some sort of shared function or zone of compensatory tissue ipsilateral or contralateral to the focus of infarction [5]. The persisting syndromes appeared to reflect an originally larger lesion, a principle that applies to other regions as well [6].

Likewise, diaschisis, the term applied to remote effects on blood flow and metabolism [7, 8] has lost some of its initial luster [9]. Imaging has shown remote deactivation from fiber systems projecting from the acute lesion zone. However, the clinical improvements in many cases are at

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1015-9770/04/0183-0258\$21.00/0

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odds with, ahead of, the timetable of fading hypometabolism and have not always affected areas inferred to mediate the improvement in function. Some evidence of remote effects from neurotransmitter pathway disruption point less to diaschisis than to dependency of one system on links to another [10] a point suggested almost a century ago by K. Goldstein.

The criticisms of the stable structure-function relationship dating back into the 19th century contain the inferences of regional or transcallosal mediation of improvement, but few of the authors went beyond the criticism to suggest the mechanisms involved. Faced with evidence of dramatic and rapid improvement in syndromes well ahead of a timetable suggested by subsidence in edema, the standard teachings of a reliably hard-wired brain [11] gradually eroded, the erosion accelerated from the earliest studies of exposed brains at surgery mapped by electrical stimulation [12–15]. Using more modern imaging of CT, now MR, the sanctity of the homunculus reflected in the syndromes of focal rolandic or capsular infarction was also violated by data from war wounds [16] and focal infarcts [17], more recently from transcranial magnetic stimulation over brain regions serving limb function

before and after limb removal [18, 19] and infarction [20]. Recent work at our institution, indicating migration in function may occur [21], has shown the sensitivity of these compensatory mechanisms to relapse with pharmacologic challenge [22].

Happily, much of this is now history, consigned to library shelves, a sign of the dissatisfied gropings for insight on mechanisms of post-lesion improvement achieved prior to modern imaging. Long-dead investigators must be smiling from their graves at the progress currently underway, reviewed in some detail in this, the first such conference on the subject. After decades of struggling to gain attention to this crucial issue of brain function, it is a relief to see the field growing so rapidly. The insights from these investigations have the possibility of understanding the prognosis for a fresh brain lesion to a degree as to understand the underlying signaling systems that mediate the improvement and develop strategies to improve those destined for poor outcomes. If the current author, labeled recently as an aging enthusiast, can offer any suggestions, it is to decouple the dogma of the past from the designs of the current studies and let the data lead the work.

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