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WARREN AND THE BRAIN STEM RETICULAR CORE

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I do not personally believe that the reticular formation of the brain stem figured prominently in Warren McCulloch's overview of the brain, certainly not until the latest years of his life. But if this represents any significant kind of omission (and I doubt that it does), it takes its origin in twin root stocks, the very nature of which specify the man. In the first case, the reticular formation as it was conceived of through the early fifties, with its apparently amorphous structure and lack of precise functional topology, could provide little appeal for the poet-philosopher seeking a neural calculus. Here there was no aesthetic principle, no operational scheme to be deduced, codified, and generalized for descriptive and predictive purposes. In the second, despite the initial characterizations by Horace Magoun and his collaborators during the forties, indicating both upstream and downstream functions for the core of the brain stem (13, 14, 15), the monolithic "nonspecific" nature of the structure (a name that somehow carries over to this day) was not as conducive to theoretical exploration as more fertile fields which lay just above and below. Cortical and spinal systems clearly appealed more to Warren who knew the richness of the former through his work with Dusser de Barenne (4), and the appeal of the latter from later studies performed with Patrick Wall, Paul Dell and J.Y. Lettvin (9).

There can be little doubt that he was aware of the ferment of ideas already working in the literature. For in our early discussions, after he returned from a summer at Old Lyme tanned and enthusiastic, amplifier in hand, he asked me if I had considered the core as a focus of my work. I recall being curious about his suggestion because, with recent attention focussed on "activation" of the electroencephalogram, I had already begun to read Bremer (2), Hess (8), Forbes (5), Jasper (10), and Magoun (15). Having come to McCulloch because of an interest in consciousness-

distorting processes, the reticular formation had begun to seem an increasingly likely place for me to start. His legitimization of this idea was gratifying. So also was his question about whether I had thought of looking at its fine structure. My reintroduction to Cajal's Histologie du Systeme Nerveux (3), had indeed stimulated me, but McCulloch was not thinking of Golgi techniques. He sought order, and the wildly interpenetrating dendrite systems which Cajal had pictured seemed to rule out any immediately definable patterns. Rather, he suggested that I speak to Heinrich Kluver who, rumor had it, could stain cells and axons simultaneously. The early versions of the now classic Kluver-Barerra stains which Dr. Kluver showed me were handsome, yet hardly useful for the kind of circuit analysis I was beginning to envisage. After listening to my description of the new method, McCulloch agreed that Golgi impregnations might be more revealing, proffered emotional support and a place to work, first in Ben Lichtenstein's laboratory, then later in the basement lab itself.

Over the next few years, the picture that slowly emerged was one of increasing order rather than of disorder. Circuit analysis showed unsuspected cohorts of long axons ascending, often monosynaptically, upon basal forebrain and cortex, and descending upon spinal cord. Radiating from these longitudinal conductors, innumerable collaterals probed adjacent and distant fields carrying samples of information to every neural system and every portion of the core. The sonneteer in McCulloch, accustomed to condensation and elision, immediately responded to my summarized description of the core's apparent mission as being "all things to all men". He was also fascinated by the inpouring of collaterals and terminals from virtually all other systems of the brain, making of it a veritable *centrum receptorium* as Kohnstamm and Quensel had predicted more than half a century earlier (12). This deluge of heterogeneous afferent impulses and the intensive intercommunication amongst reticular neurons themselves led him to the concept of circulating and redundant command. Here, every locus possessed potential command function and it was that site, the earliest receptive of information urgent to the organism's heed or well being, that gained temporary functional ascendancy. This fluid, highly dynamic concept of core activity reflected not only McCulloch's elegant interpretation of the unique intercon-

nectivity characteristic of reticular formation, but also his old love of the sea, and harkens back to the interactive relationships among a naval crew in action.

However, the structural characteristic which he apparently found of greatest potential interest was the rigorous rostrocaudal compression of dendritic domains demonstrated by most large cells in the medial two thirds of the medullo-pontine reticular core (18). The curious, almost two-dimensional packing of these cell-dendrite systems along the length of the core had been likened to a stack of poker chips (18). This analogy became the first model for the neural module concept, an idea which was to be utilized with considerable success later at spinal cord (19), cerebellar (24), and cerebral cortical levels (7, 25). For McCulloch, the poker chip analogy provided a putative model for reticular core function and the concept was elaborated in several communications with William Kilmer and others (11).

Several quotations from one of their papers will epitomize their position. Of these, portions of the abstract to their chapter in Systems Theory and Biology (11) are especially revealing:

> ...(the) basic structure is that of a string of similar modules, wide but shallow in computation everywhere, and connected not merely from module to adjacent module, but by long jumpers between distant modules... We propose a radical set of nonlinear, probabilistic hybrid computer concepts as guidelines for specifying the operational schemata of the above modules. Using the smallest numbers and greatest simplifications possible, we arrive at a reticular formation concept consisting of 12 anastamotically coupled modules stacked in columnar array... Our concept employs the following design strategies; modular focussing of input information; modular decoupling under input changes; modular redundancy of potential command (modules having the most information have the most authority); and recruitment and inhibition around reverberatory loops.

Somewhat later in this article, after indicating how telencephalization has usurped some core functions and greatly enriched others, Warren restates his position regarding the centrality of core function. "But for all the RF's reliance on the discriminatory, associational, memory, abstractional, computing and programming powers of the cortex, it apparently has never

relinquished its central command function to the cortex. The evidence for this is both anatomical and physiological. Only the RF has a wealth of direct or monosynaptic connections to and from all other central nervous structures. Only the RF is able to arouse, put to sleep, and turn off (override in a crisis) the rest of the entire forebrain. And only the RF has the position and connectivity to possibly make computations wide enough (of sufficient scope) and shallow enough (in logical depth) to always arrive at good gross modal (integrative) decisions within a fraction of a second, given the requisite information".

In the 15-30 years which separate the core concept elaborated by McCulloch from today, some rather dramatic changes have occurred. The trend has been steadily toward individuation of cell groups on the basis of axon trajectory, functional specificity, and chemical characterization. This thrust has proven so intense that some investigators have suggested a progressive culling out of cell groups from the core matrix as their specific affinities are identified, leaving the old reticular formation terminology only for those whose precise characteristics are still in doubt.

First and most impressive has been the chemical characterization of significant portions of the core. Massive cholinergic systems playing upon neocortex and archicortex (22) interact with more limited but equally potent monoaminergic cell ensembles (6). The functional roles of dopamine, norepinephrine, and serotonin-rich systems are only beginning to become apparent, not only in terms of their interactive association in the development of reticulocortical and reticulospinal activity, but also in their putative relations to the affects, dystonias, and even the psychoses. Now, more than ever, the term "nonspecific" appears inappropriate as the elegant receptive and projective specificities of the local reticular cell ensembles become apparent (1, 16) and the possibility of intimate neurovascular, perhaps neurosecretory relations becomes recognized (21). Even the classic structural picture of core neuropil with its apparently characteristic spine-covered, radiating isodendritic structure has become suspect as we begin to appreciate the restructuring of dendrites and the progressive loss of spines which occur with maturation (17).

Finally, and in a more speculative mode, much of the deep tectal and tegmental cell matrix of the mesencephalic reticular formation now appears to map the three dimensional spatial envelope surrounding the organism. Specificity of the polysensory representation appears quite as exquisite (1, 23) as the precision of projection from these multiple reticular core sites onto the nucleus reticularis thalami. Here under the conjoint control of thalamus, prefrontal cortex and tegmentum, a miniaturized console of gates monitor all thalamocortical interactions (20, 26), quite possibly selecting on a moment-to-moment basis that item and mode with which we are to concern ourselves during the next frame of time. Here perhaps lies the substrate for selective consciousness - the portal to discriminative perception and cognition, and to relevant, consequential response - all hallmarks of the appropriately behaving brain.

Today, the texture of core detail is vastly richer. Intimate knowledge of relevant substructures has improved by several orders of magnitude. An enormously complex biochemical milieu is being sketched in; one that promises opportunity for therapeutic (or destructive) intervention totally unsuspected in the early sixties. To this degree, the reticular formation differs from the entity which McCulloch conceived and tried to interpret. However, in the final analysis, the changes can be epitomized as those rather of mechanism than of concept. We know more about the connections, how they are triggered and how they trigger others. And yet the reticular core of today, and its connections with the rest of the brain, still fit comfortably into the frame that McCulloch forged when, over twenty five years ago, he addressed that central issue in human existence...why the mind is in the head.

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