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Support for the chemoaffinity interpretation of synaptic formation has come mainly from repeated demonstrations since 1940 that development and regeneration of fiber systems in CNS yield orderly function under conditions that preclude functionally-acquired adaptation as if the growing fibers somehow sort themselves and selectively establish appropriate synaptic relations guided by differential intercellular affinities. This interpretation has always included an unproven assumption that the orderly functions observed were dependent on orderly synaptic associations in the neural networks involved. Alternative interpretations based on physiological coding, resonance, or on any scheme whereby orderly function might obtain in randomized or disordered nerve networks have never been definitely excluded. More direct demonstration that the growing nerve fibers selectively bypass a majority of neurons to connect only with those that are functionally appropriate has long been needed. Convincing evidence of this kind has now been obtained from histological studies on selective regeneration in the optic system of fishes conducted recently with D. G. Attardi and currently with H. L. Arora. The research findings to be reviewed also include for the first time striking experimental evidence for chemotaxis in the growth patterning of central fiber pathways. We find that different optic axons, even when surgically deflected, will preferentially grow into and follow different central routes to reach their proper synaptic zones in the tectum. (Supported by USPHS Grant No. M3372.)

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Evidence Behind Chemoaffinity Theory of Synaptic Patterning*

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Those who have had occasion to follow developments dealing with selectivity in the growth and termination of nerve fibers may recall that older ideas of selectivity expressed in terms like 'chemotaxis,' 'chemotropism,' 'neurotropism,' and 'galvanotropism'--and accepted early in the century by Cajal and others--were given a very rough time during the 1920's, '30's and '40's, when a large mass of evidence advanced by the embryologists in particular seemed to pretty well rule out any selectivity whatever in nerve growth, favoring instead a purely mechanical interpretation. The numerous examples of apparent selectivity described earlier were all thought to be more correctly reinterpreted on a mechanical basis, particularly in terms of the orienting effects of mechanical stresses on tissue ultrastructures and the resultant formation of mechanical guide lines in the growing medium.

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At the height of this anti-selectivity movement I was led, by reasoning from quite different sorts of data, partly behavioral, to postulate again in 1939 a form of selectivity in nerve growth even more extreme than previously conceived. The hypothesis, in brief, suggested that the patterning of synaptic connections in the nerve centers is governed from the beginning very strictly, in even its most refined functional detail, by highly specific chemical affinities that exist inherently among the different types of neurons involved.

Initially this idea seemed hardly less wild than some of the opposing interpretations like the 'Resonance Theory' that it was proposed to replace. When tested experimentally, however, study after study through the '40's and into the '50's yielded results that fitted nicely the hypothesis: Whenever I disconnected central fiber systems and transplanted or scrambled them by rough surgical section, regrowth led always to orderly functional recovery even where the conditions precluded functional readjustment. It was as if the scrambled fibers somehow always unsorted themselves and managed to "home in" on their original and proper terminals.

I concluded from these results that the individual cells and fibers of the brain and cord carry identification tags, presumably cytochemical in nature,

by which they are distinguished one from another almost to the level of the individual neuron--and further, that the growing neurons are extremely choosy when it comes to establishing their intimate permanent linkages, each cell joining in synapsis, i.e. only with those for which it has a special chemical affinity.

There were other features to this chemoaffinity theory, that there isn't time for here, but taken as a whole, the scheme offered an explanation of the developmental patterning of the central nervous system that seemed to have distinct advantages over other ideas that prevailed at the time including 'neurobiotaxis,' 'disuse atrophy,' bioelectric fields, stimulogenous fibrillation, and mechanical contact guidance. It also fit nicely with related developments in experimental embryology and genetics on the one hand and in ethology or instinctology on the other, tying many loose concepts together in an orderly picture.

Nevertheless there have always remained a number of persisting objections to the hypothesis to prevent an all-out acceptance: (a) In the first place, we have never actually seen growing nerve fibers bypass a series of empty neurons to zero in on their proper terminals; this always had to be inferred

indirectly. Further, it has been pointed out that (b) the same results could conceivably be accounted for without recourse to all these chemical specificities--or without the assumption of selective reconnection--by the application of certain physiological coding and detector principles operating in randomized networks. The "Resonance Principle" of Weiss, on which related findings were explained for nearly 20 years, was just such a scheme in which synaptic connections were conceived to be completely non-selective, diffuse, and universal in their downstream relations. (c) Others have objected that there just aren't enough distinct chemical labels available in the embryo (the number required runs literally into the millions and possibly billions!). A consideration of this plus the further task of interconnecting all the postulated millions of chemically specific units into functionally adaptive brain circuits brings some of our modern information theory buffs to protest that (d) there simply isn't room in the zygote for enough 'bits of information' to handle these details on the astronomical scale required.

It is only recently that we've had success in finding any kind of direct answer to this series of objections. This has come in the past few years from histological studies on the optic system of fishes in which I was joined in

1959-'60 by Dr. Attardi and in the past year and a half by Dr. Arora. In brief, we have finally managed to demonstrate quite directly by histological methods the postulated selectivity in nerve growth and synaptic formation. The new evidence shows that fibers growing from different parts of the retina preferentially select separate central pathways as they enter the brain, and that they eventually find and connect with specific target zones in the midbrain tectum.

As indicated in the first slide, the main optic trunk is severed in these experiments and then the eye is opened and half of the retina is removed in order that the course and termination of the remaining fibers from the intact half-retina may be differentiated histologically. The next two slides (quickly) show other examples of the procedure and the result. Note that the upper half retina projects to the lower half tectum, the front half retina to the posterior tectum and vice versa. In the third following slide is presented a summary of the results. As indicated in the diagrams, removal in separate cases, of the top half, of the retina, the bottom half, the front, the back or the outer peripheral hemi-retina resulted respectively in different and consistently distinctive regeneration patterns. At each of the many successive forks in the

trail back to their diverse tectal destinations the various fiber groups characteristically made different and correct choices. (Slide) Even when the main medial and lateral bundles are cut and crossed on each other where they approach the tectum, the deflected fibers abruptly recross on themselves within the nerve scar to find and to enter again their correct channels.

Much of this evidence has just appeared in the last issue of Experimental Neurology, so I'll not dwell further on details except to point out that the published black and white photomicrographs don't give an adequate impression of the findings as they are seen directly and in color. The next slide shows how the newly regenerated optic fibers that appear in the upper third of this section of the tectum stain red and pink and thus can be picked out, especially at higher powers, from among other unregenerated fiber systems in the background that stain black characteristically with this modified Bodian stain.

The next slide is from a case with the peripheral retina ablated. The peripheral lateral zone of the tectum at the lower edge is clear of optic fibers except again in the parallel layer where they pass straight through enroute to the central zone above where they form a typical rich plexiform layer. For comparison we see in the next slide the opposite tectum where no retinal lesion

was involved. Here the regenerated plexiform layer extends in typical fashion all the way down through the peripheral zone to the lower border.

In trying to account for this orderly selectivity of fiber growth and reconnection, we believe our original explanation is still adequate in terms of two or more gradients of embryonic differentiation that sweep across each other at right angles. This plural cross polarization impressed on retinal and tectal fields would stamp the cells in both retinal and tectal fields and the surroundings each with its latitude and longitude expressed in chemical code and with matching values between the retinal and tectal maps. (Slide) The same cytochemical factors extended into the growing fiber tips of the ganglion cells could be utilized for guiding the respective fiber types into their separate proper channels at each of the numerous forks or decision points which they encounter as they make their way back through what is essentially a multiple Y-maze of possible pathways.

(Last slide) Among those who work primarily with the mammalian visual system, there is an inclination to dispense the foregoing interpretation as something that may apply perhaps to fishes and frogs but not to respectable animals like cats, monkeys and people. As can be seen, the partial crossing

of fibers at the chiasm in mammals gives difficulty, and worse, the fact that the nasal half-retina of one eye terminates in close register with the temporal half-retina of the other eye looks like a direct contradiction.

However, by the incorporation of a couple of simple modifications that we assume must have taken place in the course of evolution, the same interpretation works nicely also for the mammals including man: First, we must assume that fibers from the temporal pole of the retina have evolved a lateral growth affinity or tendency to veer laterally especially in the chiasma region. Secondly, we must postulate that the radial axis has been substituted for the nasotemporal axis in marking the longitude of the retinal ganglion cells. The D-V up-down axis is used for latitude as in the lower forms. This would give the required correspondence for identical points between nasal and temporal half-fields and would leave the old nasal-temporal properties for layering and other purposes as indicated.

A scheme quite similar to this can be drawn up for neurogenesis of the pathways and centers involved in somesthesis, and presumably the interpretation applies generally to the developmental patterning of fiber pathways and synaptic connections throughout the nervous system.