

1950 ✓ 39

## NEURONAL SPECIFICITY

R. W. SPERRY

Reprinted for private circulation from  
WEISS, ed.: *Genetic Neurology*  
(The University of Chicago Press, 1950)  
PRINTED IN U.S.A.

## NEURONAL SPECIFICITY

R. W. SPERRY

*Department of Anatomy, University of Chicago, Chicago, Illinois*

IN HIS Leipzig lectures of 1898, on the specific energies of the nervous system, Hering (1913) proposed that different classes of sensory and central neurons and the excitations which they transmit must differ from one another in quality. His proposal was based on the apparent impossibility of accounting for qualitative differences in sensation with only homogeneous impulses routed over different pathways. The central course taken by afferent impulses he conceived to depend upon the quality of the impulses as well as upon the anatomical pathways available. Much the same idea was expressed by Head (1920) and by other early neurologists on essentially similar grounds.

Qualitative specification of neurons has been inferred on an entirely different basis in early investigations of growing nerve fibers. The selective manner in which various fiber types manage to acquire their proper terminals in normal development and under certain conditions of regeneration led Langley (1898), Cajal (1928), Tello (1915), Harrison (1935), and others to assume that the different classes of neurons differ in their chemical makeup.

The subsequent failure, however, of electronic methods to reveal any important qualitative differences in the impulses conducted over different sensory pathways resulted in a general decline of interest in the concept of neuronal specificity and specific nerve energies. This trend was furthered by the demonstration that in many cases the apparent selectivity of nerve-fiber growth and termination could be explained in terms of stereotropic and other mechanical factors (Weiss and Taylor, 1944), without postulating chemotropic specificity.

Important new evidence of neuronal specificity was discovered by Weiss (1922-41), in a series of experiments dealing with the homologous function of supernumerary limbs in amphibians. These results greatly extended the earlier information and demanded reconsideration of the entire question. Motor fibers of the limb musculature were

demonstrated to differ qualitatively among themselves according to the particular limb muscle innervated. Similar specificity was found to be present also in the proprioceptive innervation of the limb muscles. Not only was the existence of neuronal specificity proved in these experiments, but it was shown, furthermore, to be much more extensive and refined than had previously been thought. What is more, Weiss was able to show that this myotypic specification of the limb nerves is brought about as a result of the peripheral contacts which the outgrowing fibers form with the limb musculature. Each muscle, it was concluded, possesses a chemical specificity of its own and imposes a corresponding specificity upon both its sensory and its motor nerve fibers. A similar capacity on the part of the cornea to specify its exteroceptive innervation was also demonstrated (Weiss, 1942; Kollros, 1943).

In addition, these experiments disclosed that the functional selectivity between central nervous system and peripheral end-organs is determined by the qualitative specification of the peripheral neurons. After various developmental alterations, the timing of the central discharge of the motoneurons regularly became adjusted to suit the particular muscles with which the fibers connected. When the peripheral connections were changed, the central firing shifted accordingly. With regard to the sensory nerves, likewise, the responses evoked by their stimulation were shown to be correlated consistently with the peripheral terminations.

These new concepts regarding peripheral nerve specificity pertaining to (a) its extreme refinement, (b) its induction by end-organ contacts, and (c) its influence in determining the functional relations between center and periphery have all been upheld and repeatedly confirmed in later investigations. In the visual system, evidence has been obtained (Sperry, 1943-45a), that the optic fibers differ from one another in quality according to the particular locus of the retina in which the ganglion cells are located. The retina apparently undergoes a polarized, fieldlike differentiation during development, which brings about local specification of the ganglion cells and their optic axons. The functional relations established by the optic fibers in the brain centers are patterned in a systematic manner on the basis of this retinal specificity. Analogous specificity has been found to exist among the central association neurons of the visual pathways which link the primary visual centers with the motor systems of bulb and cord (Sperry, 1948a). In this tectobulbar and tectospinal system the functional relations formed between optic tectum and the lower-

level motor systems are likewise governed by the constitutional specificity of the intra-central neurons.

The fibers of nerve VIII supplying the various vestibular endings of the inner ear (i.e., the cristae of the three semicircular canals; the maculae of utricle, saccule, etc.) are also specific in character according to the particular end-organs with which the fibers connect in the labyrinth (Sperry, 1945b). The central reflex relations formed by these fibers in the vestibular nuclei has been found to be regulated by this specificity in such a way that the central associations always match the peripheral terminals. Specificity is also indicated among the neurons of the vestibular nuclei on which the fibers terminate.

In the genesis of cutaneous local sign it is necessary for the cutaneous fibers to form functional relations in the centers that are precisely adjusted to the particular areas in which the fibers terminate in the skin. It has been shown that the cutaneous fibers are subject to a refined local specificity (Sperry and Miner, 1949). Experiments in progress (Miner and Sperry, 1950; Miner, 1950) indicate that the entire integumentum undergoes a refined fieldlike differentiation in development and that the local specificity of the cutaneous fibers is induced by the particular kind of skin in which the sensory fibers happen to terminate. When thoracic nerves are forced to terminate in the digital skin of a transplanted limb, they form reflex connections appropriate for limb digits rather than for thorax.

Additional experiments on the motor innervation of the extrinsic eye muscles have revealed a myotypic specificity similar to that reported by Weiss for the limb nerves (Sperry, 1947). The motor ocular neurons of IV and VI, however, become specified by self-differentiation, apparently, before the fibers reach their respective premuscle masses. The oculomotor neurons of III, on the other hand, seem to depend for their final specification upon contact with their respective muscles. Unlike the limb nerves, though, they lose the capacity to be respecified by foreign muscles at a very early stage of development. This difference between limb and ocular nerves suggests the possibility that neural specificity in the course of vertebrate evolution may have undergone an increasing degree of central self-differentiation and early determination.

Studies on neuronal specificity have been carried out thus far almost exclusively on the amphibians because of their recognized advantages for embryological experimentation plus the regenerative capacity of their central nervous system. However, results of the same kind have recently been obtained in the visual system of teleost

fishes (Sperry, 1948b, 1949); and study of the function of supernumerary fingers in a human patient (Weiss and Ruch, 1936) has indicated the existence of similar relationships in man. Although it is to be expected that many of the details of neuronal specification and its role in neurogenesis as worked out on the amphibians will be found to vary in the higher vertebrates, the basic principles probably will not be subject to any radical modification.

Further evidence of neuronal differentiation can be found in the selective action on the nervous system of various viruses, bacteria, and other parasites; degenerative diseases; histological stains; hormones, drugs, toxins, and other chemicals. Variations in numerous other physiological and morphological properties are also indicative of qualitative specificity. In general, the type of nerve specificity demonstrated by phenomena of this kind is of a less refined order than that demonstrated by the methods involving phenomena of development and regeneration.

The evidence, on the whole, is now sufficiently extensive to indicate the presence of refined qualitative specificity throughout the entire nervous system. The sensory fibers have been found to be approximately as heterogeneous in character as are the elementary qualities of sensation which they mediate. Where local sign properties are involved, as in vision, pain, and touch, further qualitative differentiation is correlated with the topographic arrangement of the sensory endings. As mentioned before, the motor fibers differ according to the particular muscles which they supply (or major fractions thereof in the case of muscles with more than a single origin). In the autonomic system, also, there is good reason to believe (see Langley, 1898) that the pre- and postganglionic fibers are as diverse in their constitution as in their function. Within the centers likewise, chemical specification has been found to parallel closely the functional differentiation.

Cell differentiation in the nervous system alone is as multifarious as that of all the other tissues of the body taken together. In addition to the diversity of the primary motor and sensory neurons, which approaches that of the tissues they innervate, there exist multiple orders of extra specificity in the complex of association neurons within the centers.

It follows that the end-organ tissues must also possess a refined chemical differentiation far beyond what is visibly manifest. Not only is each muscle constitutionally distinct, but, in addition, the tendons, fasciae, ligaments, joint surfaces, periosteum, and entire in-

tegumentum must now be considered subject to local chemical specification in so far as their sensory innervation is subject to local sign properties. Formerly it was thought that the learning and conditioning process was responsible for all such refined functional differentiation of the nervous system, but it has now become evident that it is built into the system by inherent developmental processes which depend on local differentiation of the tissues involved.

Neuron specificity is presumed to arise by processes of cell differentiation similar to those that cause developmental differentiation in other tissues. In the nervous system, however, the result frequently is more subtle and involves no visible distinctions. The over-all process of differentiation is presumed to follow a treelike pattern, as a rule, with the gross subdivisions being set off first and these, in turn, successively subdivided to produce increasing refinement. As a result, the chemical properties of the individual neuron elements, as finally determined, are not haphazardly arranged but exhibit systematic familial relationships reflecting rather closely the functional relations.

Many neurons form a wide variety of functional associations. For example, some of the second-order vestibular cells send an ascending axon branch into the motor ocular nuclei and also a descending branch that fires other cell types at various lower levels of the bulb and cord. Similarly, many sensory fibers form a variety of functional associations in different segments of the cord and medulla. Thus, although the specificity of a neuron determines what other particular cells it is able to excite, this selectivity is not restricted to a single cell type. It may encompass a variety of neurons, but always according to a precise plan. Along with its excitatory associations, a neuron may possibly also maintain an array of inhibitory relations with antagonistic cells. In any case, the developed pattern of biochemical associations within the centers is of an extremely complex and delicate design. It is in neurogenesis that the developmental processes attain their peak of refinement and complexity.

The induction of specificity throughout a neuron merely by the end-organ connection of its axon tip (Weiss, 1941, 1942; Miner, 1950) points to some type of chain reaction which starts at the fiber tip and passes over the whole extent of the nerve cell. That induction can be accomplished under such conditions may be significant with reference to the problem of embryonic induction in general. This specification of nerve cells through their terminal contacts is to be contrasted with specification achieved through direct self-differentiation of the cell bodies themselves within the ganglia and central

gray. The final specificity of a given neuron in many instances probably represents a complex product of the two processes.

The attainment of differentiation through terminal contacts with tissues far distant from the cell bodies releases the nervous system in some instances from certain of the limitations of differentiation to which other tissues are subject. In the ventral columns of the cord, for example, where there emerge in the limb segments as many different types of neurons as there are muscles in the limbs, it becomes possible for motor cells of quite diverse specificity to lie adjacent to and erratically intermingled with one another because their specification is acquired via axonal contacts with the musculature.

Thus far the evidence indicates that the pattern of specificity on either side of the sagittal mid-plane is a mirror image of that on the other. The neurons of the biceps brachialis, of the dorsal quadrant of the retina, or of the V sensory nucleus, for example, are apparently alike on right and left sides. If this holds throughout, it means that any given nerve cell could maintain only symmetrical relations on each side of the mid-line. Wherever asymmetrical excitation is initiated from unilateral stimulation, separate sets of neurons must be present to carry the impulses across the mid-line. Otherwise, it would have to be assumed that a neuron on the left side and the corresponding cell on the right side, as, for example, Mauthner's neuron, must each possess its own right-left specificity. Although this is entirely possible, supporting evidence for it is lacking. Asymmetrical associations might also be formed by a single neuron, provided that there was a temporal delay involving a shift of differentiation between the formation of synapses on one side and on the other.

To date, little more than a beginning has been made in attacking the many problems relating to the establishment of neuronal specificity. It is only in a few instances that we have begun to obtain some idea of how it arises and how it determines the properties of the developed system. With regard to the underlying chemistry of the phenomena, no direct evidence whatever is available, although some tentative suggestions have been proposed (Weiss, 1947) regarding its possible nature and operation. The tremendous range and multiple dimensions of the qualitative differences required in the nervous system favor some kind of protein specification. The studies most relevant at present are probably those dealing with the chemical basis of antigen-antibody relationships, which likewise involve multiple specificities. Thus the methods of immunochemistry would seem to hold promise for future analysis.

Other problems remain concerning the manner in which neuronal

specificity influences function. Although it is clear that basic functional selectivity is directly determined by the specification of the neurons, the exact way in which this is brought about is still in question. Possibly the primary influence of neuronal specification is upon the physiological processes of excitation and conduction (Weiss, 1936). It is also conceivable that the primary effect may be upon the growth processes to cause formation of specific structural associations (Sperry, 1950). It is equally plausible that both the foregoing types of influence may be operative either separately or in some combination yet unsuspected.

Specific nerve energies of the sort conceived by Hering (1913) are not ruled out merely because their presence is not revealed by electronic methods. The foregoing evidence that neurons mediating different sensations actually differ in their chemical constitution invites renewed consideration of the possibility that their impulses also differ in quality and that this partly conditions the pattern of spread through the centers. Since the days of Hering little advance has been made in the understanding of the neural basis of sensory qualities, and it remains as difficult as ever to account for different qualities of sensation with only homogeneous impulses routed over different pathways.

#### REFERENCES

- CAJAL, S. RAMÓN Y. 1928. Degeneration and regeneration of the nervous system. Translated and edited by R. M. MAY. 2 vols. London: Oxford University Press.
- HARRISON, R. G. 1935. *Proc. Roy. Soc., London, s.B.* 118:155-96.
- HEAD, H. 1920. *Studies in neurology*. Vol. 2. London: Henry Frowde and Hodder & Stoughton, Ltd.
- HERING, E. 1913. *Memory: lectures on the specific energies of the nervous system*. Chicago: Open Court Pub. Co.
- KOLLROS, J. J. 1943. *J. Exper. Zool.*, 92:121-42.
- LANGLEY, J. N. 1898. *J. Physiol.*, 22:215-30.
- MINER, N. M. 1950. Ph.D. thesis (in preparation).
- MINER, N. M., and SPERRY, R. W. 1950. *Anat. Rec.* 106:151.
- SPERRY, R. W. 1943. *J. Comp. Neurol.*, 79:33-55.
- . 1944. *J. Neurophysiol.*, 7:57-69.
- . 1945a. *J. Neurophysiol.*, 8:15-28.
- . 1945b. *Am. J. Physiol.*, 144:735-41.
- . 1947. *Anat. Rec.*, 97:293-316.
- . 1948a. *Anat. Rec.*, 102:63-75.
- . 1948b. *Physiol. Zool.*, 21:351-61.
- . 1949. *Proc. Soc. Exper. Biol. & Med.*, 71:80-81.
- . 1950. Mechanisms of neural maturation. In: *Handbook of experimental psychology*. Edited by S. S. STEVENS. New York: John Wiley & Sons.
- SPERRY, R. W., and MINER, N. M. 1949. *J. Comp. Neurol.*, 90:403-24.

- TELLO, J. F. 1915. Probl. Lab. Invest. Biol. Univ. Madrid, **15**:101-99.
- WEISS, P. A. 1922. Akad. Anz., Akad. d. Wissensch. Wien, **59**:22.
- . 1936. Biol. Rev., **11**:494-531.
- . 1939. Principles of development, Part IV: The development of the nervous system (neurogenesis). New York: Henry Holt & Co.
- . 1941. Comp. Psychol. Monog., **17**:1-96.
- . 1942. J. Comp. Neurol., **77**:131-69.
- . 1947. Yale J. Biol. & Med., **19**:235-78.
- WEISS, P., and RUCH, T. C. 1936. Proc. Soc. Exper. Biol. & Med., **34**:569-70.
- WEISS, P., and TAYLOR, A. C. 1944. J. Exper. Zool., **95**:233-57.