

CRITICAL REVIEW OF RECENT PUBLICATIONS OF BETHE AND NISSL.

By ADOLF MEYER, *Worcester, Mass.*

Since my "Critical Review of the data, etc. of Modern Neurology" was written, April, 1898, several publications apart from the one of Apáthy have appeared which claim a complete change in the current views. Apáthy's work deals so exclusively with invertebrate material that I leave its review to one better prepared. The articles here referred to are those of Bethe and Nissl.

Bethe (1) mentions as the most important findings of Apáthy the discovery of the numerous fine fibrils in the afferent fibers, and the peculiar origin of the one large fibril of the efferent fibers from a net-work around the nucleus of a ganglion cell. This inner net-work anastomoses with a more superficial net-work of finer fibrils which collect there from the splitting up of afferent fibers.

Bethe's fibril-stain shows clearly the existence of individual fibrils in the nerve fibers of vertebrates, embedded in a homogeneous substance. At the bifurcation of posterior root-fibers part of the fibrils go into one branch and part into the other. In such bifurcations Bethe has never observed any fibrils passing from one branch into the other, such as is the case in dendrites. It is, moreover, easy in these specimens to say which is the course of a fiber, because the collaterals always leave with the same distal divergence.

The cell pictures are in many respects the negatives of the Nissl specimens; but the eagerness with which the nucleus attracts the stain makes it difficult to bring out the fibers near the nucleus. In small bipolar cells the fascicles of fibrils pass through from one dendrite to the other, dividing into bundles

at the subsequent subdivision of the dendrites without any splitting up of individual fibrils. From the long description of the conditions in other cell types the following data are important:

1. Fibrils are present not only in the neurite, but in the dendrites, passing through the cell-body from one dendrite to the neurite or from one dendrite to another.

2. Intracellular net-works as described by Apáthy in invertebrates are probably not present in vertebrates. At best there is an occasional bifurcation of a fibril, the two branches going into different dendrites.

The origin or final distribution of the fibrils is not established; the fibrils are claimed as the unique 'conductors,' although no experience with experiments on vertebrate material is brought forth.

Bethe (2) further reports the remarkable results of his studies on the nervous system of arthropods, and especially the interesting fact that in *Carcinus* he was able to cut out the 'cells' of the motor fibers of the second antenna, without destroying the neuropil connecting the receptory and the motor fibers, although the operation severed the neuropil also from the brain and from the abdominal ganglia. After twelve to twenty-four hours, the tonus, reflex-irritability, and even the summation of stimuli, could be demonstrated again; the only obvious abnormality was an exaggeration of reflex-irritability. On the third or fourth day the phenomenon disappeared and the antenna became paralyzed and remained so. On this result Bethe bases his view that the nerve cells have merely trophic functions and are, perhaps, the bearers of reflex-inhibition. He uses the word 'nerve-cell' in the 'preneuronic' sense, meaning by it merely the nucleus with the surrounding protoplasm, but not the processes.

Such a division is easy in the arthropods; but in vertebrates it would meet considerable difficulty. It would certainly be necessary to remember that the 'cell body' in arthropods comprehends a much smaller part of the neurone (using this word for what grows out of a cell-unit of the embryonic tissue) than that of a vertebrate. This point is, of course, duly con-

sidered by Bethe; but many a neurologist who is not acquainted with the nervous system of invertebrates is apt to become a victim to the ignorance of this difference. The very fact that Bethe goes to the text-books of physiology and anatomy for his 'authority' of the use of the word 'nerve-cell'; and that he seems to seriously believe that men familiar with the 'neurone-theory' proper, speak of memory-cells, etc. in the sense of 'cell-bodies' for memories, ignoring the processes, would force us not to take his word 'Nervenzelle' as a serious histological expression. A 'nerve-cell' of an arthropod after Bethe's nomenclature is only a very small part of a 'nerve-cell' in the modern sense of the word *neurone*; the size of the *processes* of those small cell-bodies is such as to warrant the viability of the tissue for a period of two to three days, just as we know that a peripheral nerve in man, when cut through, preserves its electrical excitability for at least two days, during which period the excitability both to the faradic and to the galvanic current may even be slightly increased (similar to what is mentioned in the experiment on the arthropod); then begins a gradual diminution and only at the end of the first week or even as late as the middle of the second, do we find the minimum excitability. With perfect knowledge of this fact, we maintain what we said concerning the 'motor neurone,' and the only consequence of Bethe's experiment on our general view would be this: that, if we could destroy the nucleus of the segmental efferent neurones without injuring the rest of the cell, the function of the cell would probably last at least as long as the excitability of a cut nerve. Between this and the extermination of the 'neurone-theory' there is a long distance.

The rest of the paper is devoted to a noteworthy sketch of a physiological conception of psychic activity, culminating in the idea, that all psychic activity is the play of the outside world on the fibril net-work of the nervous system.

While Bethe keeps in the main carefully to the description of the fibrils and to his experiment, Nissl (3) takes a far broader sweep in his apotheosis of the 'gray matter.' The article is psychologically interesting, but difficult to render in abstract.

The sum total of the results of his studies of the cell-bodies in poisoning and disease has convinced Nissl that the real core of nervous function is only imperfectly touched by the histological findings. Apáthy and Bethe have established the view of M. Schultze, that the fibrillary substance is the highest degree of differentiation of cell-plasm of the animal body. It develops to a great extent beyond the cell and persists outside of it. 'Ich schneide damit die hochwichtige und zur Zeit absolut ungelöste Frage nach dem Wesen der grauen Substanz an.' Nerve cells and their ramifications are not the essential criterion of the gray matter. It is characterized wholly by the presence of 'molecular' substance in which the other elements are embedded. Apáthy claims that in the invertebrates the probably homologous neuropil is a continuous (anastomosing) net-work of elementary fibrils. This condition is not established for the vertebrates, but we have proof for the view that the functionally highest parts of the nervous central organ contain large amounts of this substance which cannot be glia and the existence of which 'cannot possibly be simulated by the sum of nerve-cell processes plus the non-nucleated glia in connection with non-medullated and medullated nerve fibers.' The proof of this consists in the consideration that the dendrites in Bethe's specimens ramify without division of the fibrils and that the number of fibrils in the dendrites is so small after a few bifurcations that the extremely numerous ramifications of the dendrites in many Golgi pictures is sheer impossibility. 'They cannot be the expression of division of dendrites but must have another meaning.' At least a part of the Golgi dendrites are supposed by Nissl to be neurites which originate in the gray matter and go to the nerve cells to form the pericellular net of Held, demonstrable also in Bethe specimens. Nissl goes so far as to say that the cells extend only as far as they are visible in the 'acute alteration' in Nissl specimens.

Nissl finds himself forced to give up the neurone-theory and to assume the following elements in the central nervous system:

"(1) nerve-cells and (2) a specifically nervous substance

which is no real nerve-cell protoplasm, but a modified cell protoplasm which is found partly within the nerve cell in the form of fibrils, partly outside forming the enormous masses of (inter-cellular) gray matter which is, anatomically, to be considered a very delicate continuous net-work ('Gitterwerk') of elementary fibrils, together with the much coarser pericellular net which probably also consists of fibrillary substance and belongs already to the central gray matter, not to the cell-body; secondly, it appears in the form of fibrils as the most essential constituent of the nerve fibers." Nissl gives two remarkably striking pictures of pericellular nets from Bethe specimens, and three illustrations of cortex of the mole, of the dog, and of man, from corresponding regions, showing very clearly the greater amount of 'gray matter' between the cells in man. (The higher the development of an animal, the fewer the nerve-cells in an equally large space of cortex.) The comparison shows that the superficial layer of the cortex varies least; an increase in 'gray matter' is largely visible in the second and third layer. Nissl says (page 1028) correctly that any hypothesis must be dropped (we should say modified) as soon as even one single fact has been demonstrated to disagree with it. With this insight he proceeds to undo the neurone-theory 'once forever,' and even his own hypothesis of specific nerve-cell function, since he has 'discovered' the 'gray substance' and the fact that the cell-changes described by him cannot be an expression of disturbed function but merely that of a chemical or physical alteration. The existence of various cell-types in the nervous system is none the less evident to him. The more elaborate forms of function in the highest species of the animal series undoubtedly depend on an increasing division of labor of the cells in the higher cell-communities. 'From this point of view the idea, somewhat strange to our usual thought, becomes intelligible (?), that the highest functions of the vertebrate body are not directly attached to cells, but to a living substance, the morphological arrangement of which reminds one much rather of anything else than of cells. We need only look into our body carefully

to convince ourselves readily that the most differentiated sense-organs, or the voluntary muscles, offer similar relations.'

Everything seems to indicate that there is a division of labor in the nervous system in this sense, that the nutrition, metabolism and the elimination of effete material in the gray matter and in the tracts of fibrils is attended to by the nerve-cells, and also the task of accumulating the necessary energies for the production of heavy work, so that enough vital power is ready for the real nervous substance even in answer to the slightest stimuli. This view of such a dualism is necessary to explain the apparent contradiction between the intimate spacial relationship between nervous substance and nerve-cells and on the other hand the independence of the two morphological components of the nervous system.

This short sketch merely presents the general trend of argument of Nissl. His long and not lucid paper contains many hints of things which must as yet be withheld from the world; many of the 'facts' are obtainable only with Bethe's method which is also withheld. Many expressions are given meanings which seem to be the fountain-head of confusion; I mention only his use of the term 'cell.' Nissl's cell is a decidedly expurgated affair, a sponge through the holes of which the 'real nervous substance' grows quite irrespective of the fact that the fibrils and the expurgated cell-concept are together that which we are accustomed to call cell for reasons too simple to be offered to Dr. Nissl. The same holds for 'gray matter' of which nobody would ever think that it meant what Nissl wants it to mean. Perhaps this terminology is necessary to produce the degree of obscurity so popular for certain kinds of 'demonstrations.'

The experiment of Bethe establishes physiologically the correctness of the view of Nansen (see page 124 of my review and plate 15, fig. 1) of which both Bethe and Nissl seem ignorant; and Nissl's 'gray matter' is a realization of what Golgi puts forth as the greatest obstacle to the neurone-theory, his *réseau nerveux diffus* (my review, page 126) not mentioned with one word by Nissl who seems in more than one way to make

an easy fight with the uncomfortable results of Golgi's method. Nissl's gray matter is supposed to consist of fibrils yet to be discovered, but it is already made the sanctum of the omnipotent unknown 'nervous function.' And Bethe tries to make us forget the pangs of not knowing any material memory-substrata by drawing before our eyes a very plausible picture of general biological concepts, which has not a word to say concerning the essential problems of functional organization and differentiation. Nissl's dictum of the extermination of the neurone-theory reminds one of boys who make a snow man, decapitate him and declare solemnly that they have killed him. It would be interesting to know what life the snow man had and what Nissl's (and Bethe's) neurone-theory looked like before its light began to fail. The motto which Nissl puts at the head of his article seems to be intended for other people only; or will it be said to apply to Nissl himself as well? 'Wer die Geschichte der Nerven-anatomie und Nervenphysiologie des letzten Jahrzehnts prüft und durchgeht, der muss in der That in den vielen, mit grosser Zuversicht aufgebauten und durch alsbald bekannt gewordene, an die Ironie des Schicksals mahnende neue Thatsachen enttäuschten und widerlegten Theorien eine Warnung erblicken, jetzt schon Ansichten über die Funktion von Theilen aufstellen zu wollen deren Erkenntniss noch weit—weit von einem wünschenswerthen Ziele entfernt ist. (B. Stilling, 1856).'

The status of the neurone-problem developed a year ago is not changed essentially to-day. It will be a difficult task—but one which must be worked over—to bring into harmony the widely differing pictures produced by the methods of Golgi, of Ehrlich, of Bethe, of Nissl, etc., to work through all the important experimental reactions with these methods and to refrain from putting bright guesses down as statements of facts. It is quite evident that we are still very far from a complete picture of the architecture of the nervous system; but not so far that we should allow ourselves to be thrown out of the saddle by every little addition of detail. The neurone-theory deals primarily with genetic and trophic relations, and as such it is a

good working hypothesis, though full of unsolved problems. The question of function of the nervous system is today at best one of activity of aggregates of neurones, and if we want to specialize further, we will do best to start from the known and not from the unknown. Many of us have the feeling that notwithstanding the veto of Golgi and the considerations of Nissl we are perhaps not forced to accept a 'réseau diffus' outside of what we know as processes of cells and certainly few people will follow Nissl in willingly despising what we have and in putting the sole emphasis on the 'non-classified residuum,' the storehouse from which the supplies for all the hopes and the remedies for all the woes are expected to be furnished to those disappointed with what is safely established and with the usual methods of acquiring new knowledge.

LITERATURE.

1. Bethe, Ueber die Primitivfibrillen in den Ganglienzellen von Menschen und anderen Wirbelthieren. *Morph. Arbeiten von Schwalbe.* Vol. VIII, p. 95-116, Tafel IX and X.
2. Bethe, Die anatomischen Elemente des Nervensystems und ihre physiologische Bedeutung. *Biolog. Centralblatt.* Vol. XVIII, p. 843.
3. Nissl, Nervenzellen und graue Substanz. *Münch. Med. Woch.* 1898.