is accompanied by the liberation of heat, the presence of which Schiff has demonstrated even up to the nerve-centers, under the influence of fear, of excitation of the senses, of any cause —in a word—which produces cerebral activity."

Lecithin—"a conspicuous component of the brain, nerves, yelk of egg, semen, pus, white blood-corpuscles, and the electrical organs of the ray"—suggests its identity as at least one of the sources of energy we are seeking by the fact that if merely allowed to stand at the ordinary temperature its solutions acquire an acid reaction and are decomposed. In the intestines it sometimes breaks up into its constituents: fatty acids, glycerin, phosphoric acid, and *cholin* (Howell). Neurin is, in reality, cholin, and therefore a decomposition product of lecithin. As previously stated, Tappeiner[31] obtained fatty acids as a result of cholic-acid oxidation. These facts, of course, are only cited as mere landmarks to indicate that we are dealing with oxidizable bodies. As far as the nerves themselves are concerned, therefore, it seems probable that we have in lecithin an agency capable, by the character of its molecule,—*i.e.*, carbohydrates, phosphorus, etc.,—of acting as a potent source of working energy when brought into contact with the oxidizing substance; and in cholesterin the main waste-product of nerve-catabolism.

Admitting, then, that we have in the lecithin of myelin a body capable of acting as a source of energy in a way similar to myosinogen in muscle, how does the oxidizing substance of the blood-plasma reach it? The nodes of Ranvier and the neurilemma that covers them allow silver stains to reach the axis-cylinder, but the myelin itself does not permit of this. This suggests that the nodes themselves—*i.e.*, the rings forming them—may allow the blood-plasma to filter through them, thus bringing the oxidizing substance in immediate contact with the axis-cylinder. The finer anatomy of nerves indicates that such may be the case. Indeed, the nodes referred to occur at regular intervals, and separate the nerve, as is well known, into as many segments, which recall, in a measure, the muscle-fiber and the liver-cell or, at least, features characteristic of both these structures. If the blood-plasma can penetrate the

[31] Tappeiner: Zeitschrift für Biologie, Bd. xii, S. 60, 1876.

nodes of Ranvier as do stains, there only lies between it and the axis-cylinder an extremely delicate layer of protoplasm,—Mauthner's sheath,—which in no way would impede the entrance of the fluid into the axis-cylinder itself.

The term "cylinder" suggests the tubular shape of the latter: in accordance with Remak's view that it consists of a delicate, longitudinally striated tube, filled with an albuminous liquid. The prevailing view, however, is that of M. Schultz, who considers the axis-cylinder as made up of fibrils united by an intervening unknown substance. This seems to me to vividly recall the arrangement of muscular fibers as regards their relation with the blood-plasma: *i.e.*, minute fibers into which the plasma may freely enter. Again, we must not lose sight of the fact, in this connection, that the axis-cylinder is nothing but the elongated axon of a neuron, and that the fibrillæ now referred to, therefore, represent the intimate structure of a neuron's axon. Now, as Schäfer holds that these fibrillæ are extremely fine tubes filled with fluid, and as the character of this fluid is not known, I have good reason to believe that *they are channels for the blood-plasma:* i.e., *for the oxidizing substance.*

But there is another feature which points to the axis-cylinder as a channel for the oxidizing substance: *i.e.*, the fact that the so-called "medullary sheath"—*i.e.*, the myelin itself—contains a supposed "supporting frame-work." The striæ representing them were at first termed "clefts" or "incisures" by Schmidt, Lautermann, and others, but Ranvier considered them as protoplasmic septa which subdivide each internodular segment of the nerve into several conico-cylindrical chambers. W. H. Wynn,[32] who gives an excellent review of this subject and the results of personal researches, refers to those of Rezzonico[33] and Golgi,[34] who "from the examination of fibers treated by a mixture of bichromate of potash and osmic acid, and afterward by nitrate of silver, find that each cleft is occupied by what appears to be a thread of darkly-stained substance passing *spirally around the fiber.* They consider," he

[32] W. H. Wynn: Journal of Anat. and Physiol., April, 1900.
[33] Rezzonico: Archivio per le Sci. med., Torino, vol. iv, 1880; and Gazzetta med. ital. lomb., Milano, vol. i, 1879.
[34] Golgi: Arch. per le Sci. med., Torino, vol. iv, 1880.

adds, "that the supporting frame-work of the sheath consists of *a chain of funnels* surrounding the axis-cylinder, each funnel being formed by a spiral thread." Tizzoni[35] "believes that there is but one net-work closely investing the axis-cylinder, and that it is *in connection with* the slits of Lautermann." McCarthy is stated to have shown that, "after a nerve has been hardened with picric acid and ammonium chromate, the medullary sheath contains minute, rod-like structures, which pass rapidly between the axis-cylinder and the primitive sheath so as to give the cross-section of a fiber the appearance of a wheel. The rods stain with carmine and hæmatoxylin, which do not stain the myelin. It is not possible to isolate the rods as separate elements, for they are not distinct from one another, but united." Finally he refers to the fact that Lautermann, von Stilling, Roudanowski, and McCarthy all believe that there is "a system of *hollow canals* in the sheath of the axis-cylinder," and himself reaches the conclusion that the cones they form are protoplasmic, and not composed of neuro-keratin, as is usually held. He divides "each cone into six segments placed at regular distances apart and converging from the primitive sheath to the axis-cylinder." This is well shown in the annexed illustration, reproduced from his paper. If we now consider the segments as canaliculi leading from the axis-cylinder, we can readily see how the blood-plasma can penetrate the myelin and its oxidizing substance, and these bodies carry on, when brought into contact, a reaction similar to that which occurs in muscle-fiber. Indeed, if the various features enumerated are collectively considered, it will become apparent that *the myelin, or white substance of Schwann, when in contact with the oxidizing substance of the blood-plasma undergoes a reaction in which chemical energy is liberated.*

When we consider that the axis-cylinder is, as stated, the continuation of a neuron's axon, it is not difficult to account for the various phenomena, known under the general term of "nerve-degeneration,"—*i.e.,* the disorganization of myelin, the dissolution of the myelin, etc.,—at the distal end of a nerve,

[35] Tizzoni: Archivio per le Sci. med., vol. iii, fasc. 1, 1878.

when the latter has been cut. Very suggestive, in this connection, are the following lines by Professor Barker[36]: "Waller proved that if a motor nerve was severed there resulted complete degeneration of the fibers in the peripheral end, even

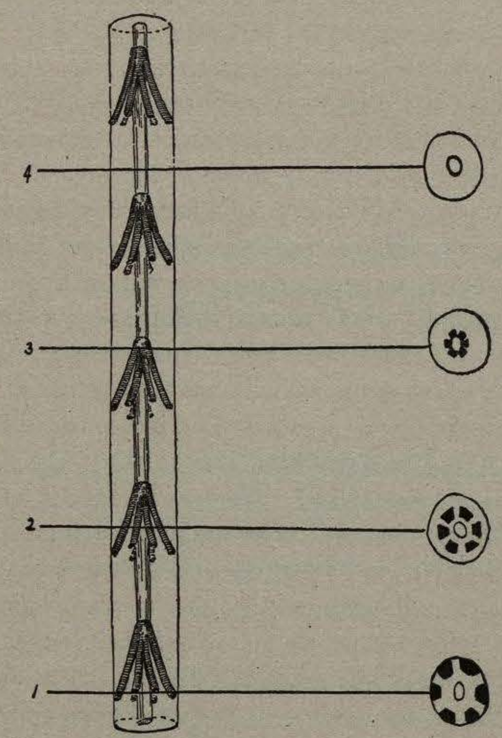

DIAGRAM OF RELATION BETWEEN LONGITUDINAL AND TRANSVERSE SECTIONS, SHOWING CONES CUT ACROSS AT DIFFERENT LEVELS.

1, at base of cone; 2, through middle of cone; 3, through apex of cone; 4, through interval between two cones. In 1, 2, and 3 the cone segments and protoplasmic sheaths are seen. In 4 only the thin protoplasmic sheaths beneath primitive sheath and around axis-cylinder are visible. (*W. H. Wynn.*)

to the muscles which they govern, the central end remaining apparently intact. As a matter of fact, the changes characteristic of the Wallerian degeneration could not, as a rule, be traced farther in the central end than to the first node of Ranvier." Stewart[37] states that "in the degenerated nerve

[36] Barker: *Loc. cit.*, p. 740.
[37] Stewart: "Manual of Physiology," p. 607.

the substances soluble in ether are relatively increased owing, in part, to fatty degeneration of the axis-cylinder," and that "the percentage of phosphorus is markedly diminished (Mott and Barratt)."

Another process which seems to acquire a certain degree of light is nerve-regeneration. It is obvious that if we grant the axis-cylinder, as the extension of the axon, all functional and nutritive attributes, we may easily explain peripheral nerve-degeneration, but not regeneration, the peripheral segment being unprovided for by reason of the section. We know, on the contrary, that a piece of the nerve must be removed in order to prevent reunion, and that otherwise in two or three weeks, and often earlier, its functions will be restored. New cylinders and fibrils grow, acquire myelin, and, perhaps, guided and assisted by (nucleated) neurilemma, soon meet those of the peripheral segment and become connected with them. Physiological functions of a normal kind must underlie this process even in the peripheral end of the nerve; otherwise union would not take place. Finally (we can only refer to a few of the more prominent processes involved in the vast subject now claiming our attention) the functional phenomena that follow after division of the cord distinctly indicate the continuation of nutrition and the functional activity—though impaired—in the distal fragment. Foster, for instance, says: "In the mammal (dog) after division of the spinal cord in the dorsal region regular and apparently spontaneous movements may be observed in the parts governed by the lumbar cord. When the animal has thoroughly recovered from the operation the hind-limbs rarely remain quiet for a long period of time; they move restlessly in various ways; and, when the animal is suspended by the upper part of the body, the pendent hind-limbs are continually being drawn up and let down again with a monotonous rhythmic regularity suggestive of automatic rhythmic discharges from the central mechanisms of the cord. In the newly-born mammal, too, after removal of the brain movements apparently spontaneous in nature are frequently observed. But all these movements, even when most highly developed, are very different from the movements, irregular and variable in their occurrence, though orderly and purposeful

in their character, which we recognize as distinctly voluntary." Indeed, the nervous energy that myelin and the oxidizing substance procure is that which allows a frog deprived of its hemispheres and its middle brain "to sink in water as though the animal were of lead."

The axis-cylinder composed of fibrils into which blood-plasma penetrates being continuous with the axon of a neuron, we are brought to realize the nature of the parallelism between the functional phenomena of the latter and those of the suprarenal glands to which I have already referred. But we must not lose sight of the fact that each "medullated" nerve-fiber is divided by the nodes of Ranvier into as many subdivisions, and that each internodal segment receives its own supply of plasma. Does the neuron receive its supply through this chain of segments, or, rather, through the axis-cylinder that passes through them? That the former mechanism alone prevails is improbable, since so prominent a part of the entire structure as its cell-body, the seat of its nucleus, would hardly be supplied in so indirect a manner. The very importance of its functions betokens the existence of direct supply. Does such a vascular system exist? Fortunately, we have not far to seek.

The Circulation of the Neuron.—Barker, in a review of the facts that have been adduced for or against the neuron doctrine,[38] concludes that "it may be said, with fairness, that the control instituted by hundreds of histologists in various parts of the world has practically in every instance in which the method of Golgi or the method of Ehrlich has been employed gone to confirm the conception that the neuron is a unit in the sense of Waldeyer." The latter investigator's words, giving the gist of his doctrine, are also quoted: "If we review the main advance, made certain by the anatomical investigations discussed, it lies, in my opinion, in the sharper limitation, now possible, of the anatomical as well as the functional elements of the nervous system (for such we have to consider the nerve-units-neurons), and also the discovery of collaterals, with their end-arborizations, by Golgi and S. Ramón y Cajal." The following lines of Waldeyer's are also

[38] Barker: American Journal of Insanity, July, 1898.

quoted: "If we assume, with Golgi and B. Haller, the existence of *nerve net-works,* the conception is somewhat modified, but we can still retain the nerve-units . . ."—all of which tends to show that, while the neuron doctrine stands on a solid foundation, there is a stumbling-block in its way which has not as yet been removed. Especially is this true since the investigations of Apáthy, of Naples, who, after several years' study, has unquestionably demonstrated the existence of a net-work of what he terms "neuro-fibrils."

That Apáthy's "neuro-fibrils" as well as Golgi and Haller's nerve net-works are *not* nerve-elements, but fine capillaries which serve for the circulation of blood-plasma, seems to me probable. In the following extracts the italicized words will serve to call attention to the various links between these structures and others that we have analyzed. Professor Barker summarizes Apáthy's views as follows: "Apáthy has been convinced for some twelve years that the nervous system is composed of two varieties of cellular elements entirely different from each other: nerve-cells and ganglion-cells. The *nerve-cells,* the architecture of which is quite in accord with that of *muscle-cells,* give rise, he thinks, to neuro-fibrils. A neuro-fibril, in turn, passes out *of a process of a nerve-cell* and then goes *through a number of ganglion-cells,* and ultimately, after leaving the last ganglion-cell with which it is connected, passes more or less directly to a muscular fiber or to a sensory cell. The neuro-fibrils are, as *conducting substance* for the nerve-cells, what the *muscle-fibrillæ are as contractile substance for the muscle.* The pathways to be followed by the neuro-fibrils are predestined from the earliest embryonic stages, for they correspond, according to Apáthy, to the *intercellular protoplasmic bridges.*" That we have all required elements in support of my belief is evident; we have seen that muscle-fibers are, in reality, delicate tubes; that vascular channels for the transmission of blood-plasma should be protoplasmic is as obvious as is the need of their penetrating into and out of the cells.

What appears to me as conclusive evidence is indirectly afforded by the deductions of Ehrlich, suggested by his study of the methods of staining living nerve-cells and their processes with methylene-blue. "Ehrlich found," says Barker, "that by

injection of a solution of methylene-blue dissolved in salt solution *intra vitam* into the *blood-vessels* of an animal, the *axis-cylinders* of many of the nerve-fibers (see Fig. 1), as well as numerous (particularly sensory) nerve-endings (see Fig. 2),

FIG. 1.—NERVE-FIBERS FROM A FROG INJECTED WITH METHYLENE-BLUE (METHOD OF EHRLICH). (*After Kölliker.*)

The axis-cylinders are stained dark blue. In places the myelin sheath is somewhat stained. The nodes of Ranvier and the divisions of the fibers at some of the nodes are well shown.

were stained after a time, when exposed to the air, an intense-blue color, the other tissue-elements remaining little or not at all affected." It seems clear that, if a solution introduced through blood-vessels can stain the axis-cylinders, the liquid within the latter must be more or less a continuation of that in the blood-vessels. Again, I have suggested that the blood-plasma, including its oxidizing substance, was the liquid in the axis-cylinders; that this is true is shown by Ehrlich's observation that "the conditions in the nerve-structures essential to the methylene-blue reaction" were, he thought (1886): "(1) oxygen saturation; (2) alkalinity." I have shown that these are the essential attributes of blood-plasma.

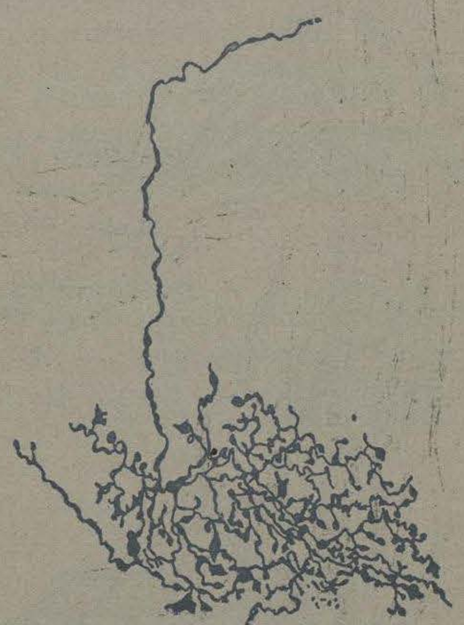

FIG. 2.—SENSORY NERVE-ENDING STAINED WITH METHYLENE-BLUE (METHOD OF EHRLICH) IN THE EXOCARDIUM OF THE LEFT AURICLE OF A GRAY RAT. (*After Smirnow.*)

This seems to me to afford an insight into the physiological chemistry of the axis-cylinder of the neuraxon when a short distance below the latter it has become a medullated nerve. Indeed, the prevailing view that the myelin represents a protective and insulating coat may at least be said to be open to doubt, especially when coupled with the facts that its chemical composition is unknown, and that there is another external coat: the neuro-keratin neurilemma, which suggests, by its composition, that it is an isolating covering and that it also fulfills this

rôle in non-medullated nerves. That the myelin is the seat of a combustion process during which heat is liberated and a decomposition product, cholin, is formed, we have seen. If we now consider the composition of the active component of myelin, lecithin, *i.e.,* carbohydrates and phosphorus, and its analogy, as regards carbohydrates, to myosinogen, the probability that it serves as a source of energy, as does the latter when in contact with oxygen, suggests itself. That such is the case, however, is shown by the fact that the contents of the neuraxon or axis-cylinder fulfills the conditions necessary for methylene-blue staining, as laid down by Ehrlich, *i.e.,* oxygen saturation and alkalinity, the characteristics of blood-plasma. Indeed, it seems to me permissible to conclude that:—

1. Myelin, or the white substance of Schwann, is to nerve-structure what myosinogen is to muscle-fiber: i.e., *its immanent source of energy.*

2. The axis-cylinder and the canaliculi derived therefrom are made up of fibrils that serve as channels for blood-plasma.

3. A part of this blood-plasma penetrates into the axis-cylinder through Ranvier's nodes.

4. Lecithin, a body composed mainly of hydrocarbons and phosphorus, the active constituent of myelin and a prominent component of the electric organ of the ray, when exposed to the action of the oxidizing substance liberates energy: i.e., *nervous energy.*

Continuing our quotations from Professor Barker's article, I will introduce the various points of comparison which appear to me to sustain my interpretation of Apáthy's neuro-fibrils. "Inside the ganglion-cells a reticulum of fine fibrils derived from the neuro-fibrils in transit can be stained a beautiful deep-violet color by Apáthy's chloride-of-gold method." That the latter method can be considered as similar in action to the methylene-blue method and that the stain follows the same channels and affects the same chemical constituents of the plasma is shown by the following remark of Professor Barker's: "With a little care and a good sample of methylene-blue the *nerve-endings* and the *axis-cylinders* of medullated fibers, with which they are continuous, can be stained in a way far surpassing in constancy and completeness the best results of the uncertain gold-chloride procedure." As the methylene-blue and a modified chloride-of-gold stains were those mainly used by Apáthy, no confusion can occur on this score.

Indeed, if we convert all of Apáthy's neuro-fibrils into minute capillaries, their identity as inherent parts of the general circulation is placed on a solid foundation by the following remark of Professor Barker's: "The doctrine of the fibrillary nature of the axon and unstainable portion of the protoplasm of the nerve-cell has recently received support from the studies of Lugaro[39] and Levi.[40] The former, too, in his studies of the nerve-cell under pathological conditions—for example, after poisoning with *lead* and *arsenic*—finds that the fibrils may become very distinct in the nerve-cells." That this directly points to the one system through which the morbid changes can occur, *i.e.,* the adrenal system, and that it precisely coincides with the foregoing remarks bearing upon this system, is evident.

The similarity of the neuro-fibril, on the one hand, to the axis-cylinder and its cell-body extensions, on the other, now becomes a normal consequence. "Each neuro-fibril is," Apáthy states, "made up of a large number—near its origin, at any rate —of 'elementary fibrils,' and in the course which it follows elementary fibrillæ are being given off at short intervals until finally the neuro-fibril itself may be reduced to a single elementary fibril." The fibrillary structure of an axis-cylinder is as clearly reproduced here as it can well be; the giving off of fibrils but typifies the irregular distribution of "non-medullated" nerve-fibers, and particularly those of the "sympathetic" system.

All this recalls a structure which appears to me to be intimately connected with the general circulation, the neuraxon and its cellular extensions, and Apáthy's neuro-fibrils—all being considered as component parts of the general vascular system: *i.e.,* Virchow's neuroglia.

The prevailing view concerning the rôle of this structure is that it affords a supporting frame-work for the nervous elements. Both in the white matter and gray matter the medullated nerve-fibers are separated one from the other by a

[39] Lugaro: Rivista di patol. nerv. e mentale, vol. i, 1896.
[40] Levi: Rivista di patol. nerv. e ment., vol. i, 1896.

net-work of glia-fibers. In the gray substance, however, the neuroglia, though present in greater abundance, as a rule, than in the white substance, varies considerably, the net-work of fibers being especially thick in certain parts. "The neuroglia is present in greatest abundance in the gray matter immediately surrounding the central canal of the cord and the ventricles of the brain (the ependyma, as it is called)," says Stewart[41]: a suggestive feature in connection with the views submitted in the present chapter. The neuroglia-cells, as is well known, are of two kinds: those provided with mossy processes and those that have smooth extensions. A large number of investigators still consider that the latter represent true processes, and that, by freely anastomosing, they make up the mesh-work which surrounds the nerve-cells and their prolongations. Ranvier, however, after a searching study of the subject, was led to conclude that the smooth processes of these (stellate) glia-cells, were in reality neuroglia-fibers which merely passed through the latter in all directions, without forming part of the cellular structure *per se.* We have seen that Apáthy's neuro-fibrils, when they left the "nerve-cell," also passed *through* the cells after forming a reticulum in the latter: a feature which suggests that Apáthy's neuro-fibril and the neuroglia-fiber may be structurally similar.

It was formerly thought that neuroglia was a variety of connective tissue, but this view no longer prevails. Indeed, so distinct is the latter from neuroglia that the two structures can be differentiated from each other by the simplest tests; thus, Ranvier and Malassez found that connective tissue placed in cold water was not modified after several days' maceration, whereas neuroglia-fibers were completely destroyed after two or three days. On the other hand, connective tissue was completely destroyed by prolonged boiling in water, while neuroglia was hardly altered under similar conditions. The suggestive relationship between Apáthy's neuro-fibrils and glia-fibers offers some ground for the belief that glia-fibers are also nervous elements. This appears to be sustained by the fact that identical results ensue when nerve-fibers and connective tissue are submitted to the last of the two tests mentioned, the

[41] Stewart: Physiology, p. 671, 1900.