tests "characteristic of the group of nucleo-albumins." We are not, therefore, dealing with the group of nitrogenous fats to which lecithin, the main constituent of myelin, belongs, but with what probably represents, not a mere artifact, but an individual constituent which is precipitated by the fixing mixtures. It is important to determine, therefore, the exact nature of the Nissl "bodies," and perhaps by a process of exclusion ascertain that of the unstainable substance.

"Held," says Professor Barker, "undertook a most careful and exact chemical study of the granules in alcohol tissues. Thus, he found that the Nissl bodies are insoluble in dilute and concentrated mineral acids, in acetic acid, boiling alcohol, cold or boiling ether, and in chloroform. On the other hand, they are easily soluble in dilute and concentrated alkalies. With pepsin and hydrochloric-acid digestion he found that the ground-mass of the protoplasm vanished and that the Nissl bodies alone remained undigested: the reverse of what occurred on treatment with an alkali. The Nissl bodies yielded no reaction with Millon's or Adamkiewicz's reagent. Held obtained, however, slightly positive results with Lilienfeld and Monti's microchemical test for phosphorus, and a considerable quantity of the gray matter of the spinal marrow after digestion with pepsin and hydrochloric acid examined by Siegfried, of the physiological laboratory of Leipzig, showed the presence of phosphorus. Held concludes, however, from these various reactions, that the Nissl bodies belong to the group of the nucleo-albumins: a view which agrees with the investigations of Halliburton, who found in the gray matter a nucleo-albumin which coagulated at from 55° to 60° C. and which contained *as much as 0.5 per cent. of phosphorus.*"

The large proportion of phosphorus further sustains the preponderating rôle that the oxygen of the plasma must play in the neuron, owing to the activity of the reaction between these two elements. It also indicates a close relationship between the neuron and all other cellular structures of the organism. Thus, referring to Held, Barker says: "He asserts that in numerous experiments with his method (formol freezing) he has found in the *most different organs* constituents of the cell-body which behave not only tinctorially, but also morphologically, *exactly* as the *stainable substance* in nerve-cells. He described them in *gland*-cells, *liver*-cells, in cells of the *pancreas,* in the cells of some sarcomatous tumors, in certain *connective-tissue cells,* but especially in normal and pathological *lymph-glands.* Cajal[44] also asserts that the stainable substance of Nissl is not specific for the nerve-cells, as he has demonstrated its presence in certain of the *leucocytes* and of the *connective-tissue elements.*" Nissl's bodies appear to me, therefore, as constituting an organized component of the ground-substance of the neuron, a nucleo-albumin rich in phosphorus, which, judging from its similarity to a large number of cellular structures elsewhere in the organism, *represents the cell-structure itself,* precisely as is the hepatic cell when free from glycogen, bile, or the agencies from which these are derived. It is to the neuron what the neurilemma, Mauthner's sheath, etc., are to the internodal segment of a nerve, and includes—as does the protoplasmic membrane of Schwann—the nucleolated nucleus.

The unstainable portion must be the equivalent of myelin: the white substance of Schwann. We have seen that this is also unstainable. Even picrocarmine does not stain it, and Ranvier states that the axis-cylinder becomes stained at the nodes because there is no myelin in this region of the nerve. The similarity between myelin of the nerves and that of the cerebro-spinal system is emphasized by Foster when he says: "Obviously the fat of the white matter of the *central* nervous system and of spinal *nerves* (of which fat by far the greater part must exist in the medulla, and for nearly the whole of the medulla) is a very complex body indeed, especially so if the cholesterin exists in combination with the lecithin, or cerebrin (or protagon). Being so complex, it is naturally very unstable, and, indeed, in its stability resembles proteid matter." This also suggests, however, that protagon, a nitrogenous body containing phosphorus isolated by Liebreich from brain-substance, may be the unstainable substance we are seeking. Hoppe-Seyler and Diakonoff, having found it to be composed of lecithin and cerebrin, the direct connection with the former is not re-

[44] Cajal: Revista trimest. micrografica, vol. i, No. 1, March, 1896.

moved. Protagon readily breaks up into its constituents. Howell states that, "while protagon seems to be regarded as the principal form in which lecithin occurs in the brain, simple lecithin is believed to be present in the nerves and other organs," and he refers to Noll,[45] who found "the quantity of protagon in the spinal cord may amount to 25 per cent. of the dry solids; in the brain, to 22 per cent.; and in the sciatic nerve, to 7.5 per cent." That it is difficult to analyze this question is suggested by his closing remark: "Regarding the synthesis of lecithin in the body, or the physiological importance of the substance, nothing is known." We have seen the important rôle that it probably plays as myelin; its presence in such large quantities, as a constituent of protagon, in the cerebro-spinal system plainly points to it as of the unstainable ground-substance of the neuron.

What is the rôle of cerebrin, which, with lecithin, forms protagon, and from which it is readily separated? In a study of the chemistry of nerve-degeneration Halliburton and Mott[46] refer to the fact that they had previously shown that in general paralysis of the insane "the marked degeneration that occurs in the brain is accompanied by the passing of products of degeneration into the spinal fluid. Of these," says the authors, "nucleo-proteid and cholin are those which can be most readily detected. Cholin can also be found in the blood." Having continued this work, they now find "that this is not peculiar to the disease just mentioned, but that in various other degenerative nervous diseases (combined sclerosis, disseminated sclerosis, alcoholic neuritis, beriberi) cholin can be also detected in the blood." The tests that they employed were mainly two: (1) "the obtaining of the characteristic octahedral crystals of the platinum double salt from the alcoholic extract of the blood"; (2) a physiological test—and a very interesting one, I may add, if the functions of the adrenal system are included in the process, namely: "the lowering of blood-pressure," which the authors consider as "partly cardiac in origin and partly due to dilation of peripheral vessels," and

[45] Noll: Zeitschrift für physiol. Chemie, Bd. xxvii, S. 370, 1899.
[46] Halliburton and Mott: Journal of Physiology, Feb. 28, 1901.

"which a saline solution of the residue of the alcoholic extract produces." This fall "is abolished," they further state, "if the animal has been atropinized." I may incidentally remark that these few lines embody the pathogenesis of most neuroses attended with degeneration, viewed from my standpoint, since we have here the phenomena incident upon arrest of function, auto-intoxication, and toxic suprarenal insufficiency. But directly bearing upon the subject in point is the evident identity of cholin as a product of degeneration. It "has its source in lecithin decomposition and putrefaction," says Howell. But it is likewise, as we have seen, a waste-product of normal nervous-tissue metabolism, being eliminated with the bile in a modified form. That *cerebrin is also a product of putrefaction and of physiological metabolism* is suggested by two facts: it is found in pus-corpuscles and its formula and that of cholin present considerable analogy. Even taking as standard that furnished by H. Müller, which has given rise to considerable controversy, cerebrin is $C_{17}H_{33}NO_3$, while cholin is $C_5H_{15}NO_2$. *Lecithin, therefore, becomes the functional ground-substance of the cell-body of the neuron, just as it is in the nerve. Both in the neuron and its continuation, the nerve, therefore, the vascular fibrils carry blood-plasma, which, by passing through their walls, maintains a continuous reaction, of which the phosphorus of the lecithin and the oxygen of the blood-plasma are main reagents and chemical energy the end-result.* The relationship between the vascular fibrils and the ground-substance, nucleus, etc., is well shown in the engraving on page 558.

But lecithin, though a useful product of metabolism, requires in its formation the aid of protoplasmic function, as does, in the muscle, the elaboration of myosinogen. In the cell-body this is probably performed, we have seen, by structures which the Nissl bodies, as nucleo-albumins, represent. Indeed, in a study of the action of fixatives upon *protoplasm* Hardy found[47] that, "when a soluble colloid is fixed by the action of a fixing reagent, it acquires a comparatively coarse structure in the process, which differs wholly or in part from the structure of the soluble colloid." Again, that these protoplasmic

[47] Hardy: Journal of Physiology, May 11, 1899.

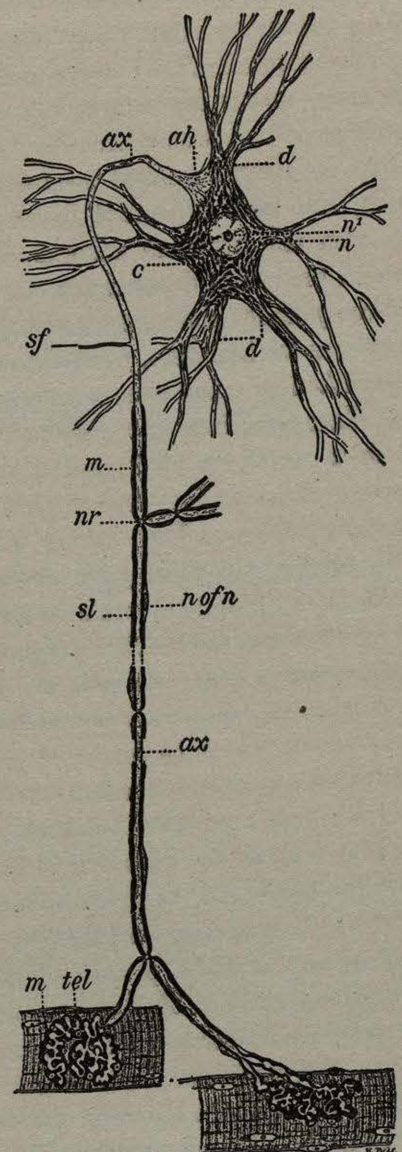

FIG. 3.—SCHEMATIC REPRESENTATION OF THE LOWER MOTOR NEURON.

The motor cell from the ventral horn of the spinal cord, together with all its protoplasmic processes and their divisions, its axis-cylinder process with its divisions, side-fibrils or collaterals, and end-ramifications (telodendrions, or motor end-plates) in the muscle represent parts of a single cell or *neuron*. *n'*, Nucleolus. *c*, Cytoplasm showing the dark colored Nissl bodies and lighter ground-substance. *d*, Protoplasmic processes (dendrites) containing Nissl bodies. (*Barker.*)

structures are supplied by a vascular net-work similar to that of other cellular structures is shown by the observations of Apáthy, who took them for nerve-fibrils. Barker, referring to this feature of his investigations, says: "As to the relations of the neuro-fibrils to sensory surfaces, on the one hand, and muscular tissue, on the other, Apáthy makes very definite statements, especially in the last chapter of his article. A neuro-fibril entering the cytoplasm of an epithelial cell of a sensory surface in the leech breaks up (very much as in a ganglion-cell) into a *finer reticulum* composed of the *elementary fibrils*. A large number of the constituent fibrils, however, perhaps the majority, leave the cell in order to take part in the formation of a complicated *interepithelial fibril-plexus*." Neuron and nerve, therefore, appear to be similar to other organs as functional entities and to be subject to the same laws, including the circulation through them of adrenoxidase.

This explains for the first time why tetanotoxin was found in the nerves by Bruschettini, Marie and others and why, in fact, as shown by Marie and Morax (see p. 1441), tetanotoxin, injected into the tissues, enters and ascends the axis-cylinders of nerves—an observation confirmed by Meyer and Ransom.

The rôle of the blood-plasma seems so clearly defined in the foregoing analysis that I deem it permissible to conclude that *all parts of a neuron—cell-body, dendrites, neuraxon or axis-cylinder—are channels for adrenoxidase-laden blood-plasma.*

Since I thus pointed out in 1903, that the adrenal secretion, converted into adrenoxidase, circulated in the nerves and nerve-cells, Lichwitz[47a] found that in the frog "adrenalin traveled from the lower extremities to the upper, when these were only connected by nerves," thus confirming my observation.

Are dendrites provided, as are the cell-body and the axis-cylinder, with myelin? We have seen that, as stated by Barker, "the stainable substance of Nissl in healthy animals of the same age and species, with the same method of fixing and staining, is tolerably constant in appearance and arrangement in the *cell-bodies and dendrites* of the same group of nerve-cells." He also states that "the axons appear to be entirely devoid of the stainable substance of Nissl"; but Berkley,[48] referring to

[47a] Lichwitz: Arch. f. exper. Path. u. Pharm., March 9, 1908.
[48] Berkley: Johns Hopkins Hospital Reports, vol. vi, p. 89, 1897.

the nerve-fiber terminals which are extensions of the axon, writes: "The researches of Flechsig, as well as my own, have shown that these fine branches are furnished with a thin *layer of myelin* nearly to their termination." As this refers to intra-cerebral nerve-fibers, I am brought to conclude that *the entire nervous system is built upon the same plan:* i.e., *of fibrils containing blood-plasma, surrounded by a layer of myelin. The main constituents of these bodies, the oxygen of the plasma and the phosphorus of the myelin, are thus brought into contact, and nervous energy is liberated.*

All this seems to me confirmed by the manner in which many, now paradoxical, phenomena are accounted for:—

The production of nervous energy, not only by the neuron, but also by the neural myelin, confirms the "avalanche" theory of Pflüger, which, though at first combated by Marey, was sustained by the latter after a series of experiments. Pflüger held that nervous excitation increased along the length of motor nerves: a view which strongly sustains my conclusion. Richet found also that excitation of a sensory nerve was more intense when transmitted from the periphery than when excitation was applied to a part of the nerve nearer to its center (Duval). It is evident, therefore, that an accumulation of energy takes place in sensory as well as in motor nerves.

My views are also sustained by the evidence afforded by nerve-degeneration. Quoting Turck's conception, Professor Barker refers to the Wallerian doctrine as follows: "Converting the Wallerian doctrine into terms of the neuron concept, the following law may be laid down: When it has suffered a solution of continuity, severing its connection with the cell-body and dendrites of the neuron to which it belongs, the axon, together with the myelin sheath covering it, undergoes in the part distal to the lesion acute and complete degeneration. This degeneration includes, not only the main axon, but also its terminals, together with the collaterals and their terminals connected with it."

If the gradual increase of energy along the nerve, or "avalanche" just referred to, is considered as a factor of the function and the sum-total of the energy utilized and is interpreted as made up of *neuron energy plus gradually increased nerve-energy,*

the following main facts connected with nerve-degeneration seem to me to find their explanation:—

Section of a motor nerve will cause degeneration of the peripheral fragment, and atrophy of the muscles supplied by it. I have emphasized the functional importance of a continuous supply of nervous energy, both upon the vascular and cellular elements of any organ.

There is no degeneration of the upper, or proximal, fragment, however, except as far as the first Ranvier node. This has been ascribed to traumatism, but we can readily understand now that section through an internodal segment destroys the mechanism of that segment, the supply of oxidizing substance failing to reach the myelin through the fibrils and their canaliculi. Its nutritional or "passive" function is thus arrested.

That the nerve and even its neuron require some of their own energy to permanently sustain their own life, as emphasized by Marinesco,[49] especially when long stretches of nerve are involved, is shown by the fact that if the seat of its ultimate distribution is destroyed,—a muscle, for instance,—or if it is disconnected from the latter, the nerve may, as sometimes occurs after amputations and peripheral neuritis, degenerate, and the process extend up to and include the cornual cell. That this does not always occur is doubtless due to the fact that the subdivisions of a nerve all contribute to the maintenance of its life, and that the chances that degeneration of a long nerve will occur are proportionate to the number of branches it supplies in its course.

The sensory nerves show the same attributes, but, of course, in a reversed direction. Section of the posterior root above a ganglion is followed by degeneration of the dorsal stump, which may include the extension into the cord. Amputation sometimes causes not only atrophy of the peripheral fibers, but also of the ganglion-cells and their prolongations in the columns. "The living muscle seems so organized that without nervous stimulation it can no more live than can the tropical animal without warmth or the rose without water,"

[49] Marinesco: Neurol. Centralbl., Bd. xi, 1892.

says Morel. How true this is is emphasized by the precaution Nature takes to nourish the nerve throughout its entire length and thus to insure the conversion of the chemical energy contained in its myelin and the plasma into nervous energy.

THE MINUTE CIRCULATION OF THE CEREBRO-SPINAL SUBSTANCE.—Such a circulation as that I suggest by this title is not thought to exist. Both in the central ganglionic and in the cortical arterial systems the arteries are now believed to be "terminal": *i.e.,* to neither supply nor receive any anastomotic branch. They penetrate the cerebral substance to terminate there. The veins are similarly disposed. Deprived of valves and muscular tissue, they are likewise considered as "terminal" in the sense attributed to that word in respect to the arteries: a normal outcome of the absence of connection with the latter as supposedly indicated by the impediment presented to the injection of fluids in them. And yet, how does the blood, with its corpuscles, find its way from the arteries to the veins? Does it filtrate through the arterial walls, find its way through the lymph-spaces to the venous walls, and reach the sinuses? Of course, we have elsewhere in the organism both the effusion of plasma and the emigration of corpuscles through vascular walls; but this is a process of a different kind, and for which the blood-stream only plays the part of purveyor; it represents the main factor of a reparative and protective function, of which, indeed, the cerebro-spinal system is a prominent beneficiary when need be. There is a wide margin, however, between this process and the mechanism of circulation, which includes channels beginning at the heart and ending in this organ, and having for its purpose, not only to carry oxygen to all parts of the organism, but also to rapidly remove blood as fast as its oxygen-ratio is being reduced. "Terminal" vessels do not satisfy this *sine qua non* of perfect metabolism in the cerebro-spinal system, notwithstanding the presence in the superficial structures of more or less close capillary net-works. Indeed, the very presence of these capillaries seems to me to point to these deeper "terminals" as incongruities.

The marked evidences of engorgement so typically shown by Berkley's illustrations, and to which I have referred, are

characterized by a suggestive feature: *i.e.,* they occur, as far as the neuroglia is concerned, in the elements adjoining the blood-vessels or connected with them. Thus, Berkley writes: "In the silver slides the support elements proper, so far as the stain shows, present *no variations from the control,* but, on the other hand, the *vascular* neuroglia gives indication that alterations are taking place within its structures, and show considerable variations from control preparations. The cell-bodies are larger, the protoplasmic extensions are thick and knotty, and the arms extending *toward neighboring vessels* are more prominent than in the normal." As "the capillaries, like the intermediary vessels, are tortuous and twisted,"—evidences of intense engorgement, further emphasized by the "closely packed" white blood-corpuscles found in the vascular lumen, —it seems but logical that the engorged capillary and the engorged neuroglia-fibers should be continuous; otherwise the latter neuroglia swelling would remain unaccounted for.

Referring to the spinal cord, Berdal[50] states that "the moment the blood-vessels penetrate into the cord they become covered, on a level with the perimedullary neuroglia layer, with a coating of neuroglia, which follows them throughout *all* their ramifications and accompanies them along their *entire* course." Such a coating over cerebral capillaries would readily account for the engorgement of both structures to which we have just referred, since the channel, notwithstanding the alteration in its external aspect owing to the assumption of an extra coat, would, after all, be continuous. That such is the case is sustained by the fact that in what has been termed "chronic ependymitis"—doubtless a condition in which the layer of neuroglia becomes permanently engorged—a marked thickening of the tissue occurs (O. Israel). The increase of blood in the neuroglia-fibers which this morbid condition involves not only coincides with the swellings observed by Berkley after various forms of poisoning, but it is accounted for by the fact that ependymal neuroglia-cells were found by Marchi to send "a central extension which penetrates into the optic thalamus, where it subdivides to become *fixed upon the walls of the blood-*

[50] Berdal: *Loc. cit.,* p. 193.

vessels" (Berdal). This recalls the interesting feature in Fig. 3 of the plate opposite page 550. In the projection-cell represented the extremity of the long and irregularly-swollen apical process is also connected with the wall of what must be a diminutive blood-channel, if plasma is at all the cause of the cellular engorgement. Again, the neuroglia-cell, shown below, copied from an article by Andriezen, to which I will presently refer,[51] may be seen to be directly attached to a vessel. Indeed, we have Golgi's own testimony to the effect that some of the protoplasmic extensions of the nerve-cell are attached to neuroglia-fibers and to blood-vessels.

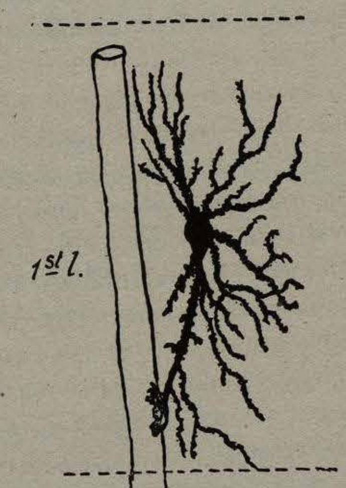

FIG. 1.—"A PROTOPLASMIC GLIA-CELL FROM A HUMAN BRAIN (FIRST LAYER OF CORTEX)." (*Andriezen.*)

The manner in which the neuroglia-cells and their fibers are connected with blood-vessels suggests that they are essentially different structurally, the neuroglia-elements being, not branches or subdivisions of the vascular system, but nervous structures which, at a given time during embryological development, became affixed to the vascular walls. This is sustained by the fact that neuroglia is, like all nervous elements, of epiblastic origin. Again, there is considerable analogy between nerve- and neuroglia- fibers. Foster emphasizes this fact when

[51] Andriezen: Brain, Winter, 1894.

he says: "Since the nerve-filaments, like the neuroglia-fibers, are very fine, and take, like them, an irregular course, it often becomes very difficult in a section to determine exactly which is neuroglia and which are nervous elements."

What is the rôle of the neuroglia and how is it functionally related to the true nervous elements? Suggestive, in this connection, are the following lines of Professor Foster's: "A medullated nerve-fiber of the white matter of the spinal cord resembles a medullated nerve-fiber of a nerve in being composed of an axis-cylinder and a medulla; but it possesses no primitive sheath or neurilemma. This is absent, and, indeed, is not wanted; *the tubular sheath of neuroglia* affords, in the spinal cord (and, as we shall see, in the *central nervous system generally*), the support which in nerves is afforded *by the neurilemma.*"[52] This shows conclusively that for a certain distance, at least, the neuroglia-sheath and the myelin act as coats for the one axis-cylinder: *i.e.*, for the fibrils containing blood-plasma. But we have seen that myelin is not the passive insulating substance that it is now thought to be; if my views are sound, it represents one of the two most important factors of nerve-composition, and, indeed, the main source of nervous energy. In modifying the accepted view concerning its functions, however, I have eliminated its rôle as insulating layer, leaving nothing but the neurilemma, or external, tubular investing sheath, for the protection and insulation of the "battery elements," as it were, the myelin and its oxidizing plasma. It is, therefore, this protective and insulating sheath that the neuroglia replaces in the white substance of the cord and in "the central nervous system generally": *i.e.*, wherever the myelin and its inclosed blood-plasma are present in the cerebro-spinal axis.

We have seen that, according to Barker, and as shown by the researches of Flechsig and Berkley, the dendrites of neurons are furnished with a thin layer of myelin nearly to their termination; while I have shown,—conclusively, I now believe—that their central canal contains blood-plasma. We have precisely, therefore, the structure of a nerve, minus its neu-

[52] All italics are my own.