This applies likewise to *nucleo-proteid*, the presence of which in nerve-cells was shown in the preceding section. Interesting in this connection is a remark of Halliburton's brought out by Baumstark,[133] who referred to "the *chief proteid matter* in nervous tissue as resembling casein." "There is a certain amount of truth in this," says Halliburton, "for it is a nucleo-proteid." This is true of brain-cells as well. Levene[134] found that "the nucleo-compound of the brain was a true nucleo-proteid."

Although the presence of *ferments* in nervous tissues has not been determined specifically, it is a necessary factor in the biochemical processes of which nerve-cells and their prolongations, dendrites and axis-cylinders, are known to be the seat. Thus, Halliburton[135] found fresh nervous tissues invariably alkaline; and that on exposure they rapidly became acid. He ascribed this change to lactic acid, stating, however, that Müller and Gschleiden had concluded that it was due to *fermentation* lactic acid. We have a counterpart of this process in the formation of lactic acid in muscles, the sarcolactic acid. The lactic acid formed in milk may also be elaborated, as in muscles, irrespective of any bacterial action. Thus Babcock and Russell[136] found that, notwithstanding the total absence of bacterial influence, insured by careful sterilization, casein was steadily being digested. Their experiments led to the conclusion that this was due to a ferment which they classed among the trypsins. If, now, Baumstark's observation that the "chief proteid matter in nervous tissue" resembles casein, and Halliburton's remark that this casein-like body is nucleo-proteid, are taken into account, and the casein-like nucleo-proteid given the position it occupies in milk as a substance which is being digested by the trypsin (considered elsewhere as a hydrolytic triad), we have evidence to the effect that catabolism is not only a feature of nervous tissue metabolism, but also that it corresponds with that of all other cells. Briefly, I showed in a preceding section,[137] that leucocytes supply nucleo-proteid granules

[133] Baumstark: Zeit. f. physiol., Chemie, Bd. ix, S. 145, 1889.
[134] Levene: Arch. of Neurol. and Psycho-Path., vol. ii, Nos. 1-2, p. 3, 1899.
[135] Halliburton: *Loc. cit.*, p. 82.
[136] Babcock and Russell: Annual Rep. of Agricul. Exp. Sta., Univ. of Wisc., 1897.
[137] *Cf.* this vol., p. 902 *et seq.*

to nerve-cells as well as to other cellular elements; we now find that, as in all other cells, it is nucleo-proteid which is broken down by the action of a ferment.

That nerve-cells must be the seat of metabolism as well as other kinds of cells imposes itself as a logical conclusion. Soury,[138] in his comprehensive treatise, says in this connection: "On the whole, the metabolic processes in the spinal ganglia are most active. Levi[139] found therein a quantity of granules greater than in any other nervous element in the organism. It is evident that the quantity of these intracellular exchange products affords a criterion as to the metabolic activity of a nervous element. Ranvier has pointed out the great vascular wealth of the spinal ganglia of mammals. It is, in fact, probable that not only in the spinal ganglia, but also in *nerve-cells in general*, the metabolic processes are very active." He adduces as evidence to this effect "besides the abundant vascularization of all the centers and nerves of the organism, the fact that of all the elements of the body, the nerve-cell is that which bears the least well a diminution of oxygen."

Cytology and pathology furnish direct evidence in this direction:—

The predominant rôle of chromatin in the vital functions of cells have caused it to be regarded by cytologists as the cellular living substance, that which is being constantly disintegrated and replaced concomitantly by new matter. This applies likewise, as is well known, to the chromatin of nerve-cells. Now, Halliburton,[140] alluding to chromatolysis of the Nissl granules, writes: "It occurs in various abnormal states and under the influence of certain poisons, and its occurrence indicates a diminution of the *vital interaction* between the highly phosphorized nucleus and the surrounding protoplasm. Chromatolysis alone, however, is not indicative of cell destruction, and the cell may recover its functions later when the abnormal condition passes off." It is evidently the nucleo-proteid which is thus reduced, and—as inferred—replaced; for, as stated by the same author with reference to the "fine dust-like particles" into

[138] Soury: "Système nerveux central," Tome ii, Paris, 1889.
[139] Levi: Riv. di patol. nerv. e ment., p. 169 *et seq.*, 1896.
[140] Halliburton: *Loc. cit.*, p. 87.

which the granules are reduced, "micro-chemical methods have shown that they consist of nucleo-proteid."

The nerve-cell differs from the typical cell described by zoölogists in one particular—a feature which assumes a normal aspect in the light of the foregoing evidence, viz., that its nutrition and its reproduction are not solely under the domain of the cell-body, at least in young animals.

"Many experiments have shown," says Verworn,[141] "that protoplasm is incapable of self-preservation without the cell-nucleus, and the nucleus similarly incapable without the protoplasm." If, for example, *Stentor Roeselii*, a trumpet-shaped infusorian, be cut so that one piece will contain protoplasm and nucleus, and the other only protoplasm, "the former continues to live and represents a complete cell, while the other, possessing no longer the individuality of a cell, invariably perishes." As stated by Wilson, the latter ceases to assimilate or grow, and is devoid of the power of repair. This is thought by physiologists to apply to nerve-cells; thus Stewart[142] writes: "Nerve-fibers are 'bound in the bundle of life' with the nerve-cells from which their axis-cylinders arise: the connection between cell and axon once severed, the nerve-fiber dies inevitably." That this can no longer be taken as a guiding-principle, however, is shown by the following facts.

"The question of the possibility of autoregeneration of the distal end of a divided nerve which has been prevented from uniting with its central end is one of great interest," wrote Barker recently.[143] "Bethe has repeated the earlier experiments of Philippeaux and Vulpian, and asserts that in young animals autoregeneration takes place, the Schwann cells, uniting end to end, building the new nerve-fibers and producing not only new axons, but actually new myelin sheaths and neurofibrils. Bethe's experiments have been confirmed by Ballance and Stewart in England, van Gehuchten in Belgium, Barfurth[144] in Germany, and recently by Raimann." The facts that, as we have seen, axis-cylinders receive blood-plasma by way of their *peripheral* nerve-endings, and that the nerve-substance, including the myelin, receives nucleo-proteid granules through the intermediary of leucocytes, readily account for this phenomenon, every nerve-segment, whether above or below the section, being nourished as if it were an ordinary tissue-cell.

[141] Verworn: *Loc. cit.*, p. 60.
[142] Stewart: *Loc. cit.*, p. 605.
[143] Barker: N. Y. Med. Jour., Apr. 7. 1906.
[144] Barfurth: Anat. Anzeiger, Jena, Bd. xxvii, Suppl., S. 160, 1905.

Barker says also, however, that the validity of the experiments referred to above "has been denied by Munzer and by Langley and Anderson,[145] the latter asserting that if anastomosis with other nerves in the limb and all possibility of outgrowth from the central stump be prevented no autoregeneration occurs." In the light of my views these experiments impair in no way the observations of Philippeaux and Vulpian, Bethe and their followers. The process of regeneration being intimately bound up with that of nutrition, the anastomotic branches of the divided nerve may subserve important rôles in this function, both direct and indirect. Under these conditions division of these branches cannot but prevent the reparative process. This applies as well to the prevention of outgrowth from the central stump. If this outgrowth happens to be a feature of the regenerative process, the latter including a simultaneous development of both stumps, artificial prevention of the outgrowth of one of them must inevitably invalidate the process of repair. Interpreted from my standpoint, therefore, the experimental procedures of Munzer and of Langley and Anderson merely rendered the autoregeneration of the divided nerve impossible by impairing the mechanism upon which it depends.

The importance of this feature of the problem lies in the fact that the regeneration of the peripheral stump has been, and is now, regarded, even by the supporters of the neuron theory, as a serious obstacle. In the light of my views, it contributes additional evidence to the effect that a neuron is nourished throughout its entire length, and serves, with other available testimony, to raise the neuron to a higher position than it now occupies, since it emphasizes the fact that it is not merely a cell, but a structure composed of *many cells*, and therefore an *organ*—traversed, like all other organs, by blood channels.

Many investigators, Capobianco and Fragnito, Paladino, Fischer, Hill, Bechterew, van Gieson, Sachs, Nissl and others have urged this view to offset Waldeyer's conception of the

[145] Langley and Anderson: Jour. of Physiol., vol. xxxi, p. 418, 1904.

neuron as a cell or unit, the tendency being even to drop the term "neuron."[146] I can see no practical advantage in this; Waldeyer's term is so generally accepted that a new term would merely introduce another source of confusion.

That a nerve, including the various structures which constitute a neuron, is built of cells fused end to end, is sustained by considerable evidence. Apáthy, Bethe, Rosenheim and Benda, Wynn and other histologists hold that the neuro-fibrils are differentiated from these neuroblasts or formative cells, while the rest of the cell becomes a sponge-like reticulum destined to hold the fatty substance (casein-like, to recall a former comparison), the myelin. Many embryologists, including Hertwig, Beard and Balfour, besides Apáthy and Bethe, contend that the peripheral nerves are developed from migrated neuroblasts, the end-result being that described by histologists. Physiology adduces the "avalanche" phenomenon observed by Pflüger, *i.e.*, increase of the intensity of the impulse throughout the length of the nerve, and as the segments increase in number. Durante[147] strongly urges this view, and states that it explains the presence of normal nerve trunks in embryos in which the central nervous system is absent. This author also points out—the contribution of pathology to the question—that during Wallerian degeneration each segment breaks down as a separate entity, and that in peripheral neuritis the lesions may be strictly localized in a single segment. Finally Barker, referring to the recent investigations of Capobianco and Fragnito,[148] Pighini[149] and La Pegna,[150] writes: "This pluricellular or catenary explanation of the origin of the peripheral fibers has been extended even to the dendrites and the nerve-cell of the central organs, certain Italian investigators especially asserting that the rows of cells fuse inside the central system to give rise to them, their nuclei gradually disappearing."

While all this may be said fairly to apply to the formation of myelin-sheaths, the conclusion that the development of the axis-cylinder is also a product of the sheath-cells is only infer-

[146] Durante: Le bulletin Médical, Aug. 23, p. 733, 1905.
[147] Durante: *Ibid.*, p. 47.
[148] Capobianco and Fragnito: Annali di Neurologia, vol. xvii, 1899.
[149] Pighini: Bibliogr. Anat., Paris and Nancy, T. xvi, p. 74-105.
[150] La Pegna: Annali di Neuroligia, vol. xxii, 1904.

ential. As stated by Böhm, Davidoff and Huber,[151] "the segmental structure of nerve-fibers would seem to give the impression that they are formed by a number of cells fused end to end;" but they refer to their description of the ganglion cells and their processes as showing that "this can be the case only so far as the nerve-sheaths are concerned." All the testimony submitted in this section as to the circulation of the plasma (the freedom with which tetanus toxins ascend to the nerve-cell, the end-to-end circulation of methylene-blue, etc.) in the axis-cylinder points in the same direction. Barker recalls "the embryologic researches of His, which taught that the *axis-cylinder* of a nerve-fiber represents the outgrowth from a single nerve-cell" and that "the studies of Golgi's preparations of young embryos confirmed in the most striking way the opinion of His." He mentions also the recent experiments of R. G. Harrison,[152] which conclusively showed that "naked, non-nucleated fibers which could be traced as such all the way from the spinal cord to the extreme ventral part of the musculature" had developed from the anterior horns "in the entire absence of sheath cells."

As interpreted from my standpoint, these fibers are, of course, plasma channels (the rôle I have ascribed to them as axis-cylinders or neuro-fibrils), and not as Barker calls them "motor-nerves," nor even as Apáthy terms them "conductors." In fact, as is well known, and as Stewart says, the nerve-impulse "passes *over the nerve* with a measurable velocity." Evidence to the effect that the axis-cylinder is not a conductor is also available in Durante's paper—though this observer was not aware, of course, of the identity of the fibers as neural capillaries: "A normal nerve," writes this clinician, "is endowed with two essential physiological properties, *conductibility* (the property of transmitting the nerve-impulse) and *excitability* (that of transforming exogenous vibrations into vibrations capable of being transmitted along nerve-paths). In the course of regeneration, fifteen or twenty days after section and immediate suture of a motor trunk, the voluntary movements recur, although electric excitation of the peripheral end gives no result

[151] Böhm, Davidhoff and Huber: "T. B. of Histology," p. 160, 1905.
[152] R. G. Harrison: Sitzungsber. d. Niederrhein Gesellsch. Nat. u. Heilk., 1904.

(Duchenne). Then, indirect currents applied upon the central end [the sutured stump] provoke contractions, while no result is obtained by exciting the scar or the peripheral end (Erb). The peripheral end is thus a conductor before being excitable. At this stage, as Howell and Hubert, Weiss, etc., have been able to observe, this peripheral end is still composed of imperfectly differentiated embryonic protoplasmic tubes. These and other facts tend to show that the protoplasm of *neuroblasts*, even when undifferentiated, can *alone* transmit, at least partly, nervous impulses, and this *in the absence of the axis-cylinder* which has been considered as the conductor par excellence."

This evidence, backed by all the data previously adduced, speaks for itself. Referring to the function of the myelin-sheath, Howell[153] states (1905) that "nothing that is certain can be said upon this point." In the first volume[154] I pointed out that it did not act as a mere insulating material as now believed, this rôle being probably fulfilled by the keratin neurilemma, and that it—the myelin, or white substance of Schwann—was the active agency in the elaboration of the nerve-impulse. We now see that the true nervous matter is the product of a chain of neuroblasts which, at a given time, surrounds the axis-cylinder, forming the so-called myelin-sheath, and that it is this structure which, in the absence of the axis-cylinder, transmits nerve-impulses. The "avalanche" phenomenon affording proof that the latter increase in activity with the length of a nerve, it is plain that each neuroblast must contribute nerve energy to the sum total produced. The neuroblast being a segment of the myelin, it follows that I did not err four years ago in considering the latter as the source of the nerve-impulse.

The identity of the nerve-cells composing a neuraxon or nerve now suggests itself. The so-called myelin-sheath is subdivided, as is well known, at intervals varying from 80 to 900 μ by constrictions, the nodes of Ranvier, through which the axis-cylinder passes. Each segment thus formed is a *cell* supplied, like all other cells, with a nucleus. This, in the light of my views, is the only true nerve-cell—the cell-body and its dendrites being the sensorium of the whole structure—while the

[153] Howell: *Loc. cit.*, p. 73.
[154] *Cf.* vol. i, p. 543.

neuron assumes the rank of an organ, just as a sweat-gland is an organ.

Briefly, this evidence has served to show (1) *that a neuron is not a cell, but an organ composed of many cells;* (2) *that like all other cells of the body, the cells composing a neuron contain adrenoxidase, nucleo-proteid, and a trypsin-like ferment;* (3) *that the axis-cylinders are the extension in the nerve of the neuro-fibrils which enter the dendrites from above and form a meshwork in the cell-body* (*the main cell of the neuron*) *and around its nucleus;* (4) *that the neuro-fibrils, including the network in the cell-body and the axis-cylinders, are not, as now believed, conductors, but capillaries which supply adrenoxidase-laden plasma to the cells of the neuron;* (5) *that the myelin is not, as now believed, a mere insulating material, but the seat of the metabolic processes to which the formation of the nerve-impulse is due.*

Other phases of the question as a whole must be studied before the process through which the nerve-impulse is produced, and the nature of the impulse, can itself be analyzed.

THE GRANULATIONS OF LEUCOCYTES AS LIVING SUBSTANCE.

The sponge, as we have seen, is to a certain extent a counterpart of the cell-aggregates which constitute many highly differentiated organs, both as to structure and as to the manner in which their existence as living organisms is maintained. Its channels are traversed, as shown by Robert Grant, in 1820, by water currents (propelled by ciliated collar-cells), which enter by minute pores and leave by larger apical apertures. As stated by Professor Minchin,[155] the animal receives in this way "a supply of oxygen for respiration." If we compare these minute afferent pores with the permeable walls of our capillaries and the efferent apertures of the sponge with our lymph-vessels, substituting for the water currents our plasma currents (which become lymph currents in the lymphatic spaces), considerable analogy between the irrigating process of the sponge and that of our tissues will appear. Just as a sponge is "a city of cells," with canals coursing between them, so are our tissues "cities of cells" with canals, our intercellular spaces, the

[155] Minchin: Ray Lankester's "Treatise on Zoölogy," Pt. ii, 1900.

lymph-streams, simply replacing the sea-water streams. Indeed, Loisel[156] has compared the mesoglœa of sponges to lymph. This striking analogy applies even to the porous walls in which the colonies are encased, since our tissue-cells are likewise enclosed in porous connective tissue. A group of sponge-cells may thus be said to exemplify the tissue-cells in one of our lymph spaces. Finally, the excurrent canals, as the analogues of the lymphatic capillaries, serve similarly as a drainage system for these cavities. "By the outgoing current," writes Minchin,[157] referring to sponges in general, "the waste products of metabolism are removed from the body."

The manner in which the tissue-cells of these lowly animals are nourished corresponds also—in the light of my views—with that of our own tissues, Fiedler's "Nährzellen," *i.e.*, nourishing-cells or *trophocytes*, being, as their name indicates, recognized by naturalists as food-bearers, while their granules find their counterpart in "excessively minute" cells referred to by Minchin, which "often occur in nests as if they had originated from the breaking up of larger cells," *i.e.*, the wandering cells or leucocytes. That these cells can supply their granulations as nutritive particles, is also rendered evident by the observations of zoölogists. Minchin,[158] referring to the researches of Maas,[159] writes: "In *Spongilla* each ovum becomes surrounded by a follicle formed of the parenchyma, amongst which a certain number of trophocytes work their way. The trophocytes are concerned with the *nutrition* of the ovum. . . . The nutriment received *from the trophocytes* being worked up into *yolk granules*." We will see presently that the nutrition is but a prototype of the mode of nutrition of all cells.

The rôle of these trophocytes exemplifies the general function carried on by leucocytes in the nutrition of cellular elements in the higher organisms, as I interpret it, the parenchymatous follicles representing a "city of cells" in our lymph spaces. The conversion of the nutriment into yolk granules is ascribed by Maas, however, to an intrinsic process in the recipient, *i.e.*, the ovum; but as we have seen, there is ample evidence to show that the leucocytes themselves convert food-stuffs into assimil-

[156] Loisel: Jour. de l'Anat. et de la Physiol., vol. xxxiv, pp. 1-187, 1898.
[157] Minchin: *Loc. cit.*
[158] Minchin: *Loc. cit.*, p. 61.
[159] Maas: Anat. Anzeiger, Bd. xvi, Nu. 12, S. 290, 1899.

able end-products, their granulations. Again, I have referred to these cells as "tissue-builders;" even this cardinal function is exemplified by their rôle in the sponge. Professor Minchin, for example, states that "archæocytes," the name given to these wandering cells when they assume the rôle of germ-cells, "are capable of giving rise again as sexual cells, to *the whole organism*, or, in the gemmules, to any form of tissue."

The function that leucocytes can fulfill in this connection, *i.e.*, as tissue-builders and germ-cells, is of far-reaching importance. It affords (1) a clue to the manner in which the leucocyte granulations penetrate tissue-cells to carry on their functions therein, and (2) proof that they—the leucocyte granulations—are living organisms in the sense that spermatozoa are living cells.

A spermatozoön, in fact, differs but little from a leucocyte granulation. "The head of the spermatozoön represents the nucleus," writes Howell,[160] "and contains the valuable chromatin material." We have seen that the phosphorus-laden nuclein is the active agent of the granulations. The same physiologist says:[161] "These heads consist entirely of nuclear material." . . . "Miescher, in investigations upon the spermatozoa of salmon, discovered that the heads are composed essentially of an organic combination of phosphoric acid, since designated as nucleic acid, united with a basic albuminous body, protamin. This view has been confirmed and extended by later observers, especially Kossel and his pupils."[162] Inasmuch as protamin is a proteid, the head of a spermatozoön may be said to be composed, like a leucocyte granulation, of nucleo-proteid. Again, as likewise shown by Kossel, the quantity of alloxuric bases is considerable only in blood rich in leucocytes. "In such blood," says Hammarsten,[163] "Kossel found 1.04 per mille nuclein bases against only traces in the normal blood." Now, Howell, alluding to the nucleic acid in the spermatozoa of the salmon, states that "on decomposition by hydrolysis it yields at first some of the purin bases (adenin, guanin) . . ." etc. Even the minuteness of the leucocyte granulation is a known characteristic of the head of the spermatozoon.

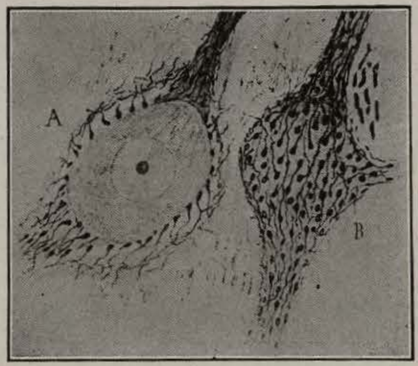
[160] Howell: *Loc. cit.*, p. 850.
[161] Howell: *Loc. cit.*, p. 862.
[162] Burian: Ergebnisse der Physiol., Bd. iii, Hft. 1, 1904.
[163] Hammarsten: *Loc. cit.*, p. 131.

This analogy between the head of the spermatazoön and the leucocytic granulation as to their biochemistry is certainly striking. It extends also to the motility of the organisms. As observed by Stokes and Wegefarth, Sangree, Gulland, Bail and Leo Loeb,[164] the granulations actually leave the leucocyte and show considerable agitation. Sangree[165] saw fifty or sixty granulations leave a leucocyte at a time, with considerable velocity; some moving away oscillating while others in masses "would move in one direction, wave this way and that, and finally return to the central body"—the cell.

Stokes and Wegefarth write to illustrate their motility of these granulations, when exposed to a temperature approximating that of the body: "At times the granular leucocytes become actively amœboid, and the granules *within* the neutrophile exhibit a characteristic activity which might be compared to the swarming of bees around a hive. The number of fine granules free in the plasma is perceptibly increased. The eosinophilic granulations also show a less vigorous tremulous motion, and both varieties follow the changes in the direction of the pseudopodia, the protoplasm being thrown out first, and the granules following. The characteristic dancing motion of the granules in the neutrophilic leucocyte can be brought out very plainly by simply mixing the drop of blood with an equal amount of distilled water containing 1 per cent. of alcohol. The granules become very active and present a characteristic picture."

The granulations of leucocytes are thus similar to spermatozoa in chemical composition, staining properties; like these organisms they are motile—the motions in both being vibratile—and they are capable of becoming chromosomes in the process of reproduction. They are practically tailless spermatozoa such as those of myriapods, and when "they work their way" into the tissues, and enter cells in aggregated masses (as in the cell-body of neurons), recall the spermatophores of certain urodeles. The penetration of the granulations into tissue-cells thus becomes a normal feature of the process of nutrition; they enter the cell as a spermatozoön enters an ovum. In my opinion Auerbach's "terminal buttons" are naught else than such granulations, as shown in the annexed plate.

[164] *Cf.* this vol., p. 887.
[165] Sangree: Medical Bulletin, Jan., 1898.



LEUCOCYTE GRANULATIONS IN THE ACT OF PENETRATING THE CELL-BODY OF A NEURON. *[Sajous.]*

Now regarded as the "terminal button of Auerbach." Two large funicular cells of the spinal cord of the adult rabbit. After Ramon y Cajal, 1903.

(*Barker.*)