rilemma. Indeed, the similarity even extends to the subdivision of the dendritic central canal into fibrils, for Berdal says, referring to the dendrites: "These prolongations seem striated longitudinally as is the cell, and appear to be composed of fascicles of fibrils which are continuous with those of the cellular body." A single structure is missing, however, that which, we have just seen, is represented by the neuroglia in cerebrospinal nervous elements: *i.e.*, the neurilemma. Obviously, the absence of a protective insulating sheath around the cell-body of the neuron and its extensions, considering their functional importance as generators of nervous energy, becomes absolutely incompatible with existing conditions, since the myelin would thus be exposed externally. Indeed, that the cell-body and its dendrites are supplied with an external sheath is shown by the following lines of Berkley's[53]: "Around the body of the cell we find an insulating mass of fluid contained in the pericellular lymph-sac, and as a capsule to the sac there appears a slight condensation of the tissue at this point that would take the place of a retaining membrane. This membrane apparently terminates where the first of the gemmulæ are thrown off from the ascending portion of the primordial process, and likewise at the location where the first buds appear on the basal dendrites. Does the insulating fluid and covering really end at this point? In absolute-alcohol sections of the cortex of the cerebellum taken parallel with the surface and stained with the anilines, particularly the blue-black, it is *quite readily demonstrable* that the thin membrane, which is now *undoubtedly composed of fine glia-filaments,* does not really cease at this point, but becomes attenuated, and continues to ascend *and cover the protoplasmic prolongations* of the cell." This plainly shows that *the cell-body of the neuron and its dendrites are supplied with a covering which is to them what the neurilemma is to nerve-fibers; this covering is similar to that investing these nerve-fibers:* i.e., *a sheath of neuroglia.*

This only affords, however, information concerning the neuroglia supplied to the neuron *per se,* and to the structures which the axons become a short distance below the cell: *i.e.,*

[53] Berkley: *Loc. cit.*, pages 90 and 91.

nerves. But we have still to study an important question: *i.e.,* the identity of the intermediary fibrils of neuroglia—important in the sense that it has a certain bearing upon the concordance between the older views of Gerlach and the modern observations and conclusions of Golgi. Indeed, if the entire cerebrospinal axis is made up (as far as true nervous elements go) of these medullated glia-covered nerve-fibers and dendrites, we may well conclude with Gerlach that nerve-cells are united by an intricate net-work of extremely delicate nerve-fibrils. If, on the other hand, the cell-body, its dendrites, and its axon are alone medullated and glia- or neurilemma- covered, the connection *with the vascular system* being established by *non-medullated fibrils,* I am in accord with Golgi, who denies the existence of any connection through nervous structures between neurons.

That Golgi's view prevails is suggested—provided my own view that fibrils are plasma-channels is accepted—by the following lines by Professor Foster: "The larger part of the gray matter consists, besides a neuroglia supporting the nervous elements, of *nerve-filaments* running in various directions and forming, not a plexus properly so called, but an interlacement of extreme complexity." If the italicized words "nerve-filaments" are converted, in accordance with my view, into *neuroglia-fibrils,* the rest of the quotation will lead us to the solution of the question: "These filaments are, on the one hand, the fine *medullated* fibers spoken of above as being recognized with difficulty, and, on the other hand, *non-medullated* filaments ranging from fairly wide and conspicuous naked axis-cylinders down to fibrils of *extreme tenuity,* the latter arising apparently either from the division of axis-cylinders and nerve-fibers passing into or out of the gray matter or from the continued *branching of the nerve-cells.*"

The solution, it seems to me, lies in the fact that non-medullated fibrils exist at all, and that these range from fairly wide *axis-cylinders* down to fibrils of extreme tenuity, some of which, at least, appear to originate from dendrites. Indeed, this indicates that these non-medullated fibrils (of neuroglia, as stated by Berkley) represent the continuation of the main, or apical, dendrite (or dendrites, for there are often more than one). Since these neuroglia-fibers are deprived of myelin, they cannot serve as sources of nervous energy, and merely represent, therefore, delicate channels through which blood-plasma, obtained by them directly or indirectly from a so-called "terminal" capillary, finds its way to the apical, or main, dendrite. The conclusion which this imposes seems to me self-evident: *A neuron is an autonomous organ as a source of nervous energy, and is supplied with blood-plasma through non-medullated neuroglia-fibrils, which are continuous with the external covering of its apical dendrites.*

Are Apáthy's fibrils, which, in the leech and earthworm, were found by him to penetrate the cell-bodies of neurons, the neuroglia-fibrils just studied? Gerlach, Haller, and others have also referred to the existence of delicate nervous net-works connected with the cells. The mere transformation of these fibrils into plasma-channels has enabled me, we have just seen, to link them with all the other elements of the function studied. In other words, I simply converted the fibrils into neuroglia blood-channels and found them to satisfy the requirements of the latter. Apáthy found that a neuro-fibril passed out of "a process of a nerve-cell": there is no fibril other than the neuroglia-fiber that is continuous with the apical dendrite that this neuro-fibril could represent. The neuro-fibril was found by Apáthy to be composed of "elementary fibrils": we have seen that this is precisely the arrangement within the neuroglia-fibers. He states that in their course "elementary fibrillæ are being given off at short intervals, until finally the neuro-fibril itself may be reduced to a single elementary fibril": I have quoted the statement of Professor Foster's that, as regards the "fibrils of extreme tenuity,"—those we found to act as neuroglia neurilemma,—they arose "apparently from the division of axis-cylinders." Finally, the neuro-fibrils, after freely anastomosing in the cell-body (having entered by way of the dendrite), are stated "to take their exit by way of the axon." This seems to me to indicate clearly, in addition to the evidence adduced in the foregoing pages, that *Apáthy's neuro-fibrils and the various net-works thought to be composed of nerve-fibers by Gerlach, Golgi, B. Haller, and others represent the one and same system of neuroglia-fibrils, some of which contain myelin and blood-plasma and may, therefore, be considered as nerves, while others only contain plasma and are, therefore, blood-channels.*

Under these circumstances, are the above-mentioned investigators not justified in considering the net-works referred to as nervous structures? They would be justified in doing so, did *all* the neuroglia-fibrils contain myelin; but it is the *absence* of this compound in the fibrils that serve as channels for plasma between blood-vessels and the apical dendrites of the neuron which seems to me to neutralize their view. Were there any evidence that a medullated fiber of any kind connects any portion of the cell with another structure capable of converting chemical energy into nervous energy, the question would remain an open one; but such is not the case; the absence of myelin in the neuroglia-fibrils connecting the neuron with the source of its blood-supply seems to point distinctly to the need of its absolute isolation, not only to avoid the promiscuous dispersion of the nervous energy it is able to produce, but also to enable it to store this energy and to direct it in the physiological paths.

The presence of the non-medullated fibers among the cerebro-spinal nervous elements becomes evident when the structural difference between the gray matter and the white matter is interpreted from the standpoint of my view. "Owing to the relative abundance of white refractive medulla," says Professor Foster, "the white matter possesses in fresh specimens a characteristic *opaque* white color; hence the name." . . . "In transverse sections of the cord *nearly the whole* of the white matter appears, under the microscope, to be composed of minute circles, the transverse sections of the longitudinally-disposed fibers." . . . "The *gray* matter, from the relative *scantiness of medulla,* has no such opaque-whiteness, is much more *translucent,* and, in fresh specimens, has a gray or rather *pinkish*-gray color, the reddish tint being due to the presence partly of pigment and partly of blood, for the *blood-vessels* are much more abundant in the gray matter than in the white." That in the cerebral cortex, for instance, these vessels should represent the starting-point of the neuroglia non-medullary fibrils needs hardly to be emphasized. They are now termed "terminal," but their appearance as such is readily accounted for by the fact that here, as in the cord, they are said to be imbedded in neuroglia, whereas, in reality, the latter, composed, as it is, of a mass of diminutive fibrils, is directly *affixed* to the vessel, acting precisely as would a multitude of minute subdivisions of the vessel itself. Each fibril (in which the blood-stream is so slender that it only appears "pinkish" through its translucent covering) is, in fact, a composite counterpart of the ependymal fibril and other neuroglia structures to which I have referred. In other words, *each neuroglia-fibril is affixed to the wall of the vessel either directly or through the intermediary of a neuroglia-cell, and therefrom extends to the main, or apical, dendrite, or dendrites, of some neuron.* In addition, however, this enables me to conclude that *a neuron receives its nutrition and its oxidizing substance directly from the general circulation,* and that *the blood which enters by way of the apical dendrites is distributed to the free dendrites and to the cell-body.*

A question suggests itself in this connection, however, viz.: How does the blood in the collaterals return to the main dendrite to find its way with the latter's blood into the cell-body? This appears to me to find its explanation in the following (already quoted) sentence, in which Berkley describes the cell-body: "Around the body of the cell we find an insulating mass of *fluid* contained in the *pericellular lymph-sac,* and as a capsule to the sac there appears a slight condensation of the tissue at this point, that would take the place of a *retaining membrane.*" The retaining membrane is doubtless the neuroglia covering of the collateral, as it is of the entire cell; underneath, therefore, is the lymph-sac—which I consider as a plasma-sac. But we have seen that Flechsig and Berkley's researches have shown that these "fine branches are furnished with a thin layer of myelin nearly to their termination." That this myelin must, as elsewhere, be supported by the neuroglia covering and in contact with it is evident: a feature which relegates the plasma toward the center, though in contact with the myelin. If we now recall the fact that fibrils have also been discerned even in these delicate collaterals, it becomes a question whether they serve to transmit plasma, centrifugally or centripetally. As

Berkley's experiments have shown that they become the seat of swellings under the influence of poisons, there must be no escape for fluids through their walls; indeed, gemmulation would become impossible were the centrifugal pressure necessary counteracted by the escape of the plasma into lymph-spaces. That the blood returns toward the cell-body and through some of the central fibrils is therefore probable. Under these conditions I can submit, as a working proposition, that *the plasma which enters the collaterals is returned to the apical dendrite, and to the cell-body with the blood of the latter. The blood of the cell-body then passes out through the axon.*

How does the blood leave the axon of the neuron in the substance of the brain and cord? This question plainly resolves itself into the following: How does the blood reach the veins from the axon? "The perivascular lymphatics . . . are especially found in connection with the vessels of the brain" says Gray[54]; "these vessels are inclosed in a sheath which acts as a lymphatic channel, through which the lymph is carried to the subarachnoid and subdural spaces, from which it is returned to the general circulation." This familiar fact would be unexplainable after the views I have advanced concerning the circulation of arterial blood were the return of blood to the veins not the purpose of the lymphatic *sheaths,* for the same authority states that lymphatic *vessels* "have not at present [1901] been demonstrated in the dura mater or the substance of the brain." Again, when we consider that *perineural,* as well as *perivascular,* spaces exist, we are brought to realize that by linking the axon of a neuron to a venule, with a lymphatic space as intermediary, we have the elements of a mechanism which not only utilizes structures that are *known* to be present in the cerebro-spinal axis, but which also satisfy the needs of the function. Finally, if an axon is itself buried (up to the neck of its bulbous terminals) in a perineural sheath, which in turn communicates with a vein through stomata, as is the case in nerves, the blood of the axon is provided with a clear path to the general blood-stream.

That the blood of the neuron is eliminated as it is in other

[54] Gray: *Loc. cit.*

nervous structures—*via* the axon—is evident; but do lymph-spaces connected with *veins* actually receive this blood? Referring to the effects of acute alcoholic poisoning upon the veins, Berkley says: "Changes in the coats of these vessels are similar to those in the arterial system, but aggregations of dying polynuclear corpuscles are more frequent, and are by far the most striking feature both of their contents and surroundings. These aggregations, which may vary from three or four to a dozen or more, are located both *within* and *without* the lumen of the vessel (especially the smaller ones). Within the lumen are collections of white corpuscles filling the interior, and numbers are seen *penetrating the walls.* So vast are the collections in the *perivenous spaces* that the whole cavity is occasionally filled, and backward pressure from the plugs and compression of the vessel from the outside have attained such a height that in a number of instances the vessel's walls have ruptured and *red corpuscles* are intermingled with the white and fill the space completely." These features are well illustrated in the annexed photographs. The center of Fig. 8 shows "polynuclear leucocytes in the perivascular space of a small intermediary vessel compressing its walls," while Fig. 9 shows "leucocytes in the blood in a cross-section of a large vein." The fact that the leucocytes are found in the "perivenous spaces" and "within the lumen of the vessel," coupled with the observation that they are "seen *penetrating* the walls," so clearly point to the process involved that the following conclusion imposes itself: *The blood* (we have seen that even *red* corpuscles are present) *of the axon evidently finds its way into a lymph-space connected with a vein, thence to the general circulation.*

Still, there is a feature of the whole process which requires elucidation. Why should the *veins,* which, of course, communicate with channels through which the blood can be freely evacuated, become *engorged* under the influence of the adrenal stimulation induced by alcohol? Engorgement of the arteries, their capillaries, the neuroglia channels, and the dendrites is a normal consequence of adrenal stimulation; but, the veins being outlets, such is not the case with the venous engorgement. This anomaly is accounted for by the now generally admitted fact that the vessels of the cerebral substance *per se*

Fig. 8

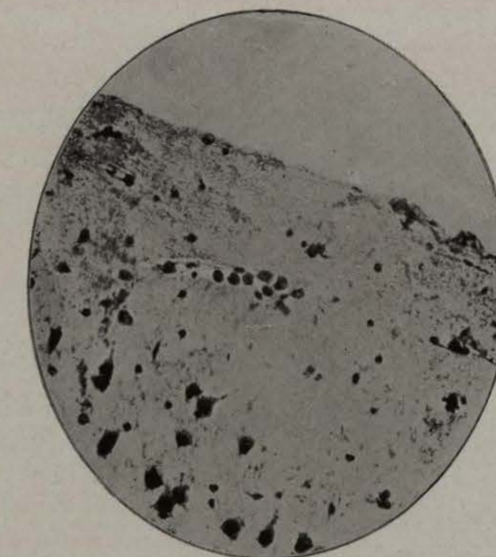
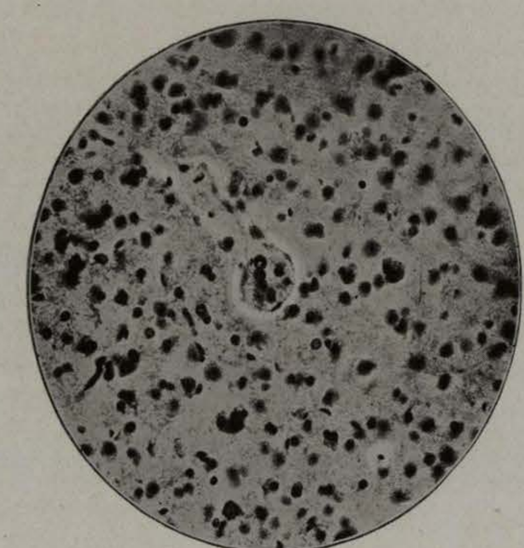


Fig. 9



LEUCOCYTES IN THE PERIVASCULAR SPACES AND IN VESSELS, AS A RESULT OF ACUTE ALCOHOLIC POISONING. *[Berkley.]*

[Johns Hopkins Hospital Reports.]

are not supplied with vasomotor nerves. "Vascular nerves may be found without trouble or difficulty in muscles, glands, etc., by the silver and other stains," writes Berkley, "but in the substance of the encephalon they are never to be seen with similar staining methods; hence it is fairly reasonable to suppose that they are not present in this location and that some other controlling mechanism takes their place. I have most carefully looked for them in many brains, both human and of the lower animals, but have never seen the slightest trace of their presence within the nervous structures. . . . Tuke and Andriezen, who made researches in the same field, have also failed to find them." As I will have occasion to show, this is an extremely important factor in the pathology of all toxæmias, mental and nervous diseases, for it indicates that *any marked rise of blood-pressure due to toxics, drugs, etc., causes vascular engorgement of the vascular channels of the brain-substance simultaneously with the engorgement of the peripheral capillaries of the other parts of the organism.*

Under these conditions contraction of the central vascular trunks through excessive adrenal activity causes not only congestion of the surface, but also of the brain. Strikingly confirmatory of this fact are the following statements of Professor Foster's: "It is argued that, in the absence of vasomotor nerves of their own, the cerebral vessels are wholly, so to speak, in the hands of the general motor system; so that when the blood-pressure is high, owing to a large vasoconstriction in the abdominal viscera, more blood must necessarily pass to the brain, and when, again, the pressure falls, through the opening of the splanchnic flood-gates, less blood necessarily flows along the cerebral vessels." . . . "Again it has been observed that certain drugs have an effect on the volume of the brain quite incommensurate with their effect on the vasomotor system."

If this testimony is sound and the interpretation of the data available is exact,—my conception of the neuron's inherent functions coincides with some of the main conclusions reached by Deiters, Gerlach, Golgi, Forel, and Cajal. In outlining their conclusions, however, I will only refer to those which are directly connected with my views, as a general review would take up too much space.

Deiters (1855) affirmed the prevailing theory—undemonstrated at the time—that the nerve-cell was supplied with two kinds of processes, the protoplasmic and the nervous, the latter constituting the nerve-fiber. Gerlach confirmed the views of Deiters, and showed that the protoplasmic processes subdivided into a fine reticulum, which, he thought, anastomosed with that of other cells. Golgi then demonstrated that, besides the two kinds of processes described by Deiters, there were given off collateral processes which, with the nerve-process, or axis-cylinder, constituted the only truly nervous structures of the cell, the other processes and the cell-body being purely nutritional. The subdivisions of the protoplasmic processes or anastomoses were not, in his opinion, continuations of those of other nerve-cells, either by continuity or through nervous net-works, though some of the protoplasmic extensions were connected with neuroglia-fibers and blood-vessels. Forel contended that the entire cell and its processes were simultaneously functional and nutritional. Ramón y Cajal concluded that net-works of nervous fibrils did not unite the collateral processes, and, these being absolutely free, there could be no continuity of nervous substance between them, contiguity of their extremities alone prevailing.

I need hardly emphasize the fact that Golgi's views are strikingly confirmed by my own; indeed, had this great histologist converted the neuroglia-fibrils connected with blood-vessels into blood-channels, our interpretations would have been similar, though reached from entirely different directions. And I must admit that I consider this striking similarity, apart from the single line of research to which I have devoted all these pages,—*i.e.,* the histological chemistry of the circulation of the nervous system and the manner in which nervous energy is produced,—as a strong indorsement of my own conceptions. While Forel is fully sustained by my analysis when he asserts that all the parts of the neuron are simultaneously functional and nutritional, Golgi is likewise fully sustained when he considers the collaterals and the axon as the truly nervous structures, the others being nutritional. We have seen that the dendrites connected with the neuroglia-fibrils are really blood-channels. True, they are covered with gemmules

and lined with myelin, a feature which shows that they serve for the formation of nervous energy; yet this energy is not utilized in these dendrites, but by the collaterals, in addition to that elaborated by their own myelin. Nor is the greater part of the blood which courses through the main dendrites used by them; it passes into the cell-body: a great center for the *production,* we have seen, of nervous energy, which energy is mainly utilized, not by the cell-body *per se,* but by the dendrites and the axon through which the whole neuron's blood is continuously passing.

Golgi's observation that some of the protoplasmic processes were connected with neuroglia-fibers and blood-vessels furnishes histological proof that my interpretation of the manner in which the neuron is connected with the circulation is based on solid premises. The prevailing ideas, however, as to the nature of *neuroglia* normally suggested that his views included a nervous net-work as intermediary between cells, neuroglia-cells being likewise considered as truly nervous structures. Hence the affirmation of Cajal that collaterals were totally independent of one another, especially if he gave neuroglia-fibers and cells the credit of only being what they are now generally thought to be: *i.e.,* a "peculiar ground-substance," in which the "blood-vessels, the nerve-cells, and nerve-fibers" are "imbedded." The neuron *is* autonomous functionally: *i.e.,* as a nervous organ, *each neuron is connected with the circulation by its own neuroglia blood-channels.* An illustration of the continuity of neuroglia-fibers with the cerebral circulation is afforded by Berkley's experiments with alcohol. "Besides the swellings in the course of the dendrons," says this author, "we must always be on the watch to exclude certain processes of the support neuroglia-cells that traverse long distances of the cortex and exhibit a *pearl-string* swelling in the course of the fiber."

Are nerve-cells contiguous, as thought by Cajal? Berkley states that the great Spanish investigator writes "that the ascending fibers of the cortex, which have a vertical or oblique course through the medullary layers, have their points of contact with the protoplasm of the dendritic structures in the *intervals* between the short transverse processes (gemmulæ)