nerve-fiber being merely rendered opaque, while the connective tissue is destroyed. As the latter is gelatinous, its destruction is easily accounted for, but why should the nerve-fiber be rendered opaque? Evidently non-medullated fiber had been used in the test, for medullated fiber is always opaque, while the non-medullated is translucent. I am led to suspect, in view of my belief that the axis-cylinder of a nerve contains blood-plasma, that it is the latter which became opaque during the boiling process. This is an important feature, for it would mean that neuroglia-fibers also contain plasma.

The identity of neuroglia-fibers as plasma-channels becomes emphasized when the morbid effects of poisons upon them and upon their cells are studied. Berkley[42] found the cell-bodies of the *vascular* neuroglia "larger, the protoplasmic extensions" being "thick and knotty and the arms extending *toward neighboring vessels* more prominent than in the normal." This was noted in slides derived from animals submitted to experimental acute alcoholic poisoning. When we consider that alcohol primarily stimulates the adrenal system with great violence and that the neuroglia closely invests the blood-vessels, it seems permissible to surmise that the thickenings and knots are dilations due to the centrifugal pressure of the plasma derived from the capillaries. Especially does this seem probable when the fact that "capillaries, like the intermediary vessels, are tortuous and twisted" is added to the rest of the evidence. And these alterations, besides an "exceeding abundance of the polynuclear leucocytes in and around the cerebral vessels," etc., are not peculiar to alcohol, for Berkley emphasizes the fact—demonstrated for the first time—that the lesions produced "are very similar to the pathological lesions produced by other more virulent soluble poisons": additional proof that the adrenal system underlies the morbid process. Serum-poisoning was also found to cause great swelling of the bodies of the vascular neuroglia, "thick groups of these swollen cells" surrounding "nearly all the vessels of any size in the gray layers." In ricin poisoning Berkley found the cell-bodies "universally much larger than the control," and "apparently

[42] Berkley: Johns Hopkins Hospital Reports, vol. vi, No. 1.



swollen, even globular in outline." The extensions were also thicker and more nodular. "Are these elements, which belong to the *lymphatic* apparatus," queries the author, "taking up *detritus* from the degenerating protoplasm of the nerve-cells and becoming engorged?" The conclusion that they belonged to the lymphatic system was reached because they were found to contain *lymph,* which, in the language of Johannes Müller, is "blood without its red corpuscles": *i.e., blood-plasma,* and, of course, its due proportion of oxidizing substance.

Evidently then, it is the *plasma* found in the capillaries of cellular elements of all organs which, crowded by excessive back-pressure (due to the marked contraction of the central vascular trunks induced by the poisons), causes the endothelial plates or cells constituting the walls of what Berkley terms the "intermediary vessels" to look, using his words, "as if they had been subjected to *severe strain,*" as their even walls have "many irregular *bulges* in their outlines." That the neuroglia-fibers are the channels through which it is transmitted is also suggested by a remark made in connection with the effects on the gemmules, the retention of which, writes Berkley, "clearly shows that the swelling comes *from within* the substance of the stem and pushes the gemmulæ, which are still adherent, *outwardly* and apart."

Does a direct connection between the neuroglia-fibers and the protoplasmic processes of neurons exist, as suggested by the fact that Apáthy's neuro-fibrils are stated by him to penetrate the cell-bodies—provided his fibrils *are* glia-fibers? To establish this upon a firm basis, the thickening, bulging, etc., found by Berkley upon the vascular neuroglia must also be shown to extend to the processes of the neuron.

Golgi has expressed the opinion that the greater part of the nerve-cell—*i.e.,* the entire structure excepting the axis-cylinder—was concerned with its nutrition: a view which met with considerable dissension. Among the opponents of this interpretation was Forel,[43] who contended that the entire cell was simultaneously endowed with nutritional and functional attributes. This conception was defended by Ramón y Cajal,

[43] Forel: Archiv für Psychiatrie und Nervenheilkunde, vol. 1887.

and seems likewise sustained by our analysis, so far. Indeed, we have seen that the axis-cylinder, if my interpretation is sound, is able, through the presence of its coat of myelin and its plasma-containing fibrils, not only to supply chemical—probably nervous—energy, but also to undergo nutritional metabolism. Can we say the same of the cell-body of the neuron?

We have seen that the fibrils penetrate the nerve-cell, and that various poisons, as shown by Lugaro and Levi, cause them to become "very distinct." Referring to the intracellular distribution of the fibrils, Barker says of Apáthy: "He describes the finer peripheral neuro-fibrils as follows: They are seen to enter the cell-body and passing out to the peripheral part of its protoplasm, there to break up into a complicated plexus composed of anastomosing elementary fibrils in the outer chromatic zone. From this peripheral plexus there pass through the 'inner alveolar' zone radial branches to the internal chromatic zone, in which is to be seen another fine plexus of elementary fibrils, which, anastomosing and converging, finally form the single strong motor neuro-fibril, which passes out of the cell through the very center of its pyriform process. In other animals studied by Apáthy there are cells with definite dendrites entirely separate from the axon and in these the cellulipetal neuro-fibrils *enter by way of the dendrites,* ramify and anastomose freely inside the cell-body, and then, reuniting, *take their exit from the cell by way of the axon.* Similar relations exist in the ganglion-cells of the vertebrates which he has studied thus far."

This strikingly coincides with the course of the plasma-fibrils or capillaries as I interpret it. Indeed, if the fibrils enter the cell, form a plexus therein, and pass out "by the way of the axon": fibril, plexus, and axon represent a continuous channel which must contain plasma, since I have ascertained that the axon contains this fluid. Again we obtain a clear indication as regards the path of the blood-stream: it enters by the dendrites and passes out by way of the axon. It is with the dendrites, therefore, that the vascular neuroglia-fibers found thickened, globular, etc., by Berkley in his poisoned animals must be connected. But this fact suggests that these



structures should likewise present irregular swellings under the influence of the same agencies, and that the axis-cylinder should show less, the intracellular formation of plexuses and anastomoses interposing a barrier to the too free passage of plasma. That such is actually the case is illustrated by the annexed plates by Berkley, which represent the lesions found in the neurons of the poisoned animals to which reference has been made.

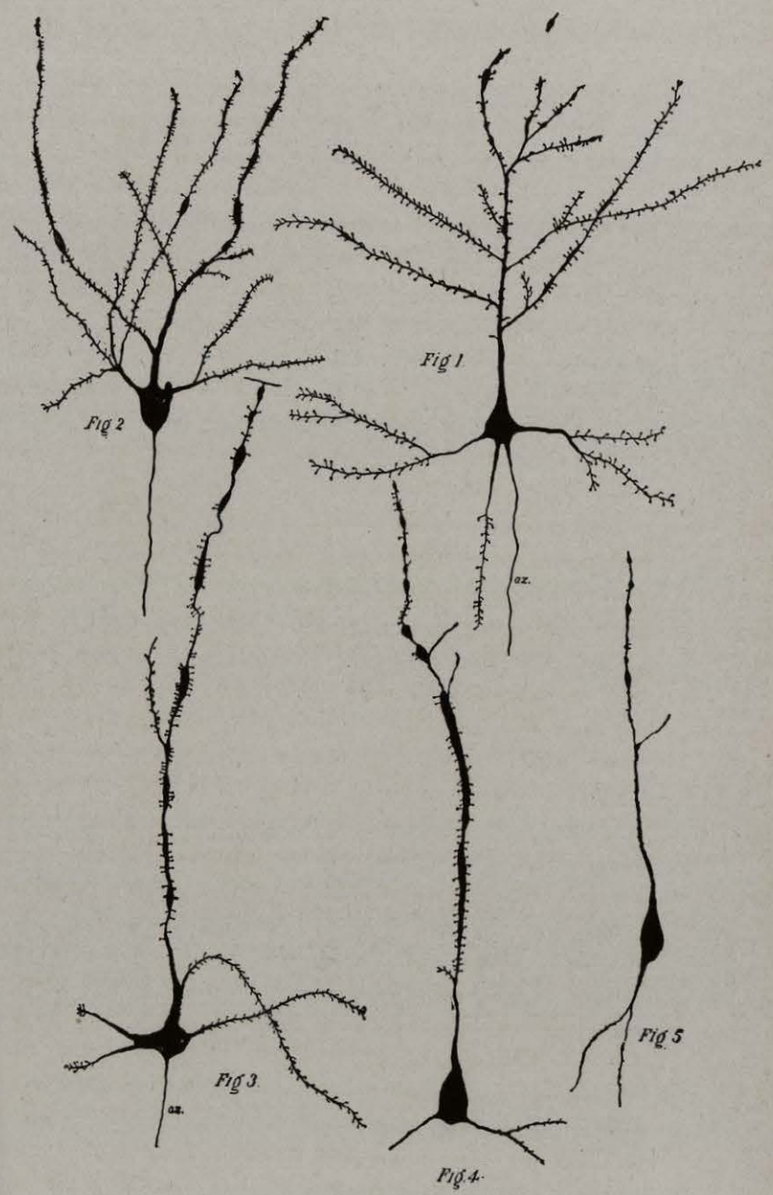
If the protoplasmic processes or dendrites are the first to bear the brunt of the vascular engorgement, the plasma being carried to them through fibrils connected with their tips, these tips or extremities should first show evidence of the expansile pressure. This is well illustrated in Fig. 1, a *"psychical* cell from the second cellular layer of the cortex," which shows, using Berkley's words, "a few pathological tumefactions on the uppermost branches of the apices of the apical dendrite. Otherwise the cell is normal." This cell was selected from a section derived from the brain of an animal poisoned with ricin, death having occurred in thirty-six hours. A feature of importance, however, is that it is the *main,* or apical, dendrite—that giving off the greatest number of subdivisions—which shows the evidences of engorgement; the extremities of the other dendrites are *not* thickened, but they show more or less marked evidences of engorgement as the main trunk is approached. This obviously suggests that the *plasma* penetrates the neuron by way of the main dendrite and that it finds its way into its collaterals cellulipetally; in other words, that, instead of also entering these collateral branches by way of their tips, it is supplied to them by the main trunk—precisely as if it were the main stalk of a plant. Of course, this does not mean that the apices of the collaterals may not subsequently show thickenings; being terminals, they should naturally do so when the pressure exceeds a given limit. This feature is illustrated by Fig. 2, especially by the larger stem of the main trunk. This cell, a projection-cell from the second layer of the cortex, shows the effects of forty-eight hours' ricin poisoning: *i.e.,* of somewhat more prolonged engorgement.

Worthy of special notice, also, is the fact emphasized by Berkley (referring to Fig. 2), that: "there is *now* distinct

diminution of the gemmulæ wherever the swellings are found" —which suggests that these minute ball-tipped projections from all collaterals are structurally similar to them, and that, when the engorgement exceeds in centrifugal pressure the resistance of a given area, the walls of the latter, including the gemmules, are more or less flattened out. Suggestive, likewise, is the fact that all the gemmules stand out boldly in both preparations. As many as thirty-six or forty-eight hours having elapsed before death ensued, the animals were evidently submitted to a primary period of intense stimulation, during which the gemmules were overdistended to such an extent as to cause them to lose their retractile property. Indeed, the sudden cessation of adrenal functions and consequent death must have left the cerebral structures much as if the animals had been suddenly killed.

Of marked interest in Fig. 3 is the presence at the extremity of the main, or apical, dendrite of a section of what appears to me to represent a fiber or capillary from which the neuron with which it is connected might have derived its blood-supply. The fact that it crosses its path suggests that the dendrite itself may be a branch of the vessel. Berkley describes this neuron as follows: "Projection-cell of the long apical process variety, showing numbers of large swellings of the protoplasm of the apical dendrite, thinning of the protoplasm of the stems in the interval between the nodules, and considerable loss of the gemmulæ along the margins. The lateral branches have mainly disappeared. The basal processes are retained intact."

The nodules seem to me also to illustrate the process through which the collateral fibers become detached from the main stem, as shown by the denuded cells represented by Figs. 4 and 5. The thinning of the plasma between the stems would account for the manner in which the lateral branches are detached, viz.: when the apical dendrite becomes sufficiently engorged the plasma ceases to circulate in one or more of the nodules, and the intervening protoplasm, failing to be nourished, disintegrates. That the basal processes should be the last to yield in this cell (corresponding in this with the condition of the same stems in Figs. 1 and 2) seems but normal




LESIONS IN THE NEURONS OF ANIMALS AFTER RICIN POISONING. *[Berkley.]*

[*Johns Hopkins Hospital Reports.*]

when we consider their proximity not only to the cell-body, which contains a large supply of fibrils, but also to the axis-cylinder (*ax.* in the drawings), which is the only centrifugal channel through which the engorged plasma can escape.

A feature of the cells shown by Figs. 1, 2, and 3 which strikingly links them to the adrenal phenomena brought on by toxics in the general organism is the fact that, although they are derived from animals in which the doses of ricin injected were reduced with each animal, the morbid phenomena as exemplified by each cell in turn are correspondingly intensified. In other words, the adult rabbit represented by Fig. 1 was given subcutaneously a dose of 0.5 milligramme, and death occurred in thirty-six hours: the cell only shows apical lesions. The second adult rabbit was given the half of the previous dose, *i.e.*, 0.250 milligramme, and death occurred in forty-eight hours: the entire apical dendrite and two of the collaterals are distinctly involved. The third adult rabbit was given the half of the last dose: *i.e.*, 0.125 milligramme, and death occurred in seventy-two hours; the apical dendrite is markedly studded with thickenings, and all but two of its collaterals have disappeared. It is, perhaps, unnecessary to lay stress upon the fact that this is due to the prolongation of the excessive vascular tension: *i.e.*, of the time during which central vascular contraction caused peripheral capillary engorgement. And this need not be ascribed only to ricin. Berkley emphasizes this assertion when he says: "The poison *ricin*, whose action is in many ways *similar to that of many toxalbumins of bacterial source*, is capable of exerting a deep and extensive degenerative influence on the protoplasm of the nerve-cells of the brain." And this may further be extended to other toxics, for he also says: "Poisoning with alcohol in considerable doses, continued over a moderate time, will produce decided and ascertainable lesions of the nutrient structures and nervous elements of the cerebrum, very similar in character to the pathological lesions produced by other more virulent poisons." We thus have evidence in support of my opinion that *poisons capable of causing congestion of the cerebrospinal and other nervous tissues do so by raising the blood-pressure and by thus driving the adrenoxidase-laden plasma into their neuroglia and neurons.* That the

alterations in the elements of the neuron should be due to the same centrifugal pressure that prevails in the capillaries of all peripheral structures is obvious. Finally, the fact that phenomena witnessed occur under the influence of congestive poisons affords the complemental evidence in favor of my contention that *a neuron is directly connected with the circulation by one or more of its dendrites, which serve as channels for blood-plasma.*

Even the hæmorrhages brought on by excessive pressure, epistaxis, hæmatemesis, hæmaturia, etc., are exemplified in the engorged neuron shown in Figs. 6 and 7, and also from Berkley's series. The observation of Apáthy's, therefore, that his "cellulipetal neuro-fibrils enter by way of the dendrite, ramify and anastomose freely inside the cell-body, and, then reuniting, take their exit from the cell by way of the axon," finds its application if, as interpreted by myself, *his neuro-fibrils are considered as blood-plasma channels.*

Still, the identity of the fibrils in the cell-body as blood-capillaries has so far only been suggested by the fact that they are continuous with the plasma-containing axis-cylinder and fibrils. While this constitutes strong evidence, the fact that they are blood-channels can only be determined by ascertaining the nature of the process in which the plasma takes part. This may probably be done by inquiring into the composition of a neuron's ground-substance.

THE PHYSIOLOGICAL CHEMISTRY OF THE NEURON.—What is the nature of the ground-substance: *i.e.*, that between the fibrils? After reviewing this subdivision of the general subject Barker says: "A neuron is made up, like all other cells, of nucleus and protoplasm. In the latter a centrosome and an attraction-sphere are present; at least it has been demonstrated in a certain number of nerve-cells. The protoplasmic portion of the cell can be roughly divided into a peripheral exoplasmic portion and a central endoplasmic portion. In neurons, as in muscle-cells, though less distinct in the former than in the latter, there is a tendency to a fibrillary structure, the fibrillæ tending to occur in the peripheral exoplasmic portion of both nerve- and muscle- cells rather than in the endoplasmic portion of the protoplasm. In both exo-

*Fig. 6*

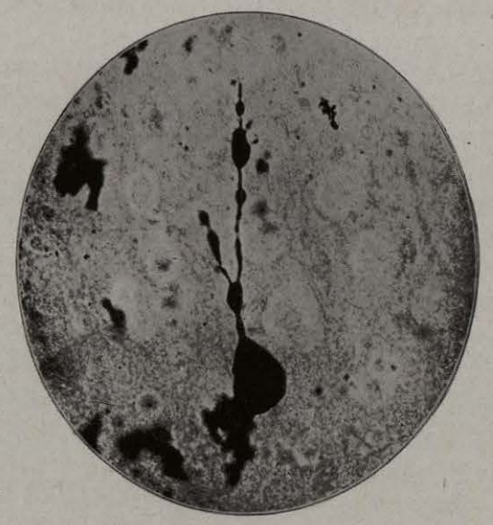


*Fig. 7*

LESIONS IN THE NEURONS OF ANIMALS AFTER RICIN POISONING. *[Berkley.]*

[*Johns Hopkins Hospital Reports.*]

plasm and endoplasm there can be made out in tissues which have been fixed *a more or less homogeneous ground-substance* in which are deposited larger and smaller masses of a granular nature. The ground-substance corresponds in tissues fixed with alcohol and stained by the methods of Nissl and Held to the 'unstainable substance' of Nissl, and the masses of granules to the 'stainable substance' of Nissl and the pigment.

"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: a fact of extreme importance for nerve-anatomy and pathology. The axons appear to be entirely devoid of the 'stainable substance' of Nissl. Whether the stainable substances represent bodies precipitated from solution through the action of reagents or bodies pre-existent, though invisible, first brought into view through the action of fixing or staining reagents in the hardened tissues, in either case they appear to yield the chemical tests *characteristic of the group of nucleo-albumins*. Whether the staining reaction characteristic of the stainable substance depends upon chemical relations or upon purely physical conditions must, for the present, remain undecided.

"The 'unstainable portion' of the cell-body,—that is, the ground-substance,—though probably functionally much more important than the stainable, is not so well understood; its nature and structure are still as obscure as those of protoplasm in general." Still, the link with features previously brought out by our analysis now seems within reach.

Held has maintained that the stainable Nissl bodies represent simply substances precipitated from solution by the action of fixing mixtures; Fischer was led to the same conclusion. Barker says, in this connection, that he repeatedly convinced himself of the *homogeneous* appearance of the protoplasm of the nerve-cell when it is examined immediately after the removal from the living body. That the ground-substance is homogeneous, and that the unstainable portion is a product of dissociation of some of its constituents, are therefore probable. But the stainable portion we have seen has yielded the chemical