

around which the ascending fibers twine." In other words, the tips, or extremities, of the axon of one neuron, instead of being in contact with the tip of the gemmule, touch the intervals between gemmules. "Such a discharge of the nerve-forces from cell to cell taking place at hundreds of indefinite points," continues Berkley, "could not fail to produce stimuli that would be more often aberrant than direct, and, in all likelihood, such an arrangement would produce the utmost confusion of thought and motion, a veritable inco-ordination of the cerebral functions, which would reduce direct cerebration to a nullity." This point seems to me to be well taken, and the identical argument prevails as regards contiguity, for if, as I believe, myelin and the oxidizing substance are constantly in contact in the neuron,—*i.e.*, the cell-body, dendrites, and axon,—nervous energy is continuously being formed, and promiscuous contact with the dendrites of other cells would give rise to the untoward effects enumerated. In the light of my views, therefore, continuous contiguity between neurons through their dendrites or axons does not appear possible.

How do neurons transfer their nervous energy to other neurons? Berkley states that it is "more than probable that it is only at the free bulbous terminations of the nerve-filaments [axons] that we have naked protoplasm, and from this uncovered nervous substance the dynamic forces, generated in the corpora of the nerve-cells, are discharged, through contiguity, on to the protoplasmic substance of other cells. Thus, in contradistinction to the hypothesis of Cajal," continues the author, "we have only comparatively few points at which the nervous forces may discharge themselves from axons to the protoplasm of other cells, and these are seated at definite points on the terminal arborizations of the nerve-filaments, for otherwise what would be the necessity of a terminal apparatus were the nerve-conductors free to discharge their dynamic forces at any point at which they came in contact with the substance of a dendron?"

It seems to me that the feature to ascertain in this connection is the character of the functions of the gemmules. Why do these little projections of the dendritic walls become erect during the cerebral congestion induced by poisons? Are they

really intended to receive discharges of nervous energy from the bulbous tips of axons? They outnumber the axonal end-organs out of all proportion. Indeed, their multiplicity around all the stems excepting the axon hardly points to them as terminals endowed with such important functions as those attributed to them. Again, Berkley states that "the twigs of the dendrites and the fibers touch each other frequently and in a manner that appears to be perfectly indifferent for the different kinds of nervous substance, receptive and projective." Such promiscuousness plainly testifies, it seems to me, against the identity of the substances in contact being exposed surfaces capable of transmitting to each other a stream of nervous impulses.

In the light of my views, however, a function perfectly in keeping with the experiments of Goddard in puppies, of Demoor with morphine, of Berkley with alcohol, ricin, serum, etc., suggests itself. We have seen that during functional activity the gemmules project, while during inactivity they recede. If we now connect these facts with the presence in the gemmules of a thin layer of myelin immediately under their external or limiting covering, and concede that the latter and the myelin take part in the formation of each gemmule, it will become evident that during the erethic state the surface of myelin exposed to the action of the oxidizing substance of the plasma will be greatly increased and the proportion of nervous energy produced correspondingly augmented. Retraction of the gemmules, on the other hand, by emptying them of their plasma, will normally cause diminution of energy-production, the myelin of the main channel sufficing to sustain nutritional functions during sleep, for instance, when the gemmules are retracted. We have what seems to me a counterpart of these minute structures in the muscle-cell, the myosinogen of the latter being replaced by the myelin. We have also, in the processes outlined, an *active* and a *passive* functional stage in keeping with other organs. All this so thoroughly coincides with the various attributes which the gemmules have been shown by various investigators to possess, that I feel warranted in concluding that *the gemmules are peripheral extensions of the dendritic walls having for their purpose to increase, when erect, the area of*

myelin exposed to the action of the oxidizing substance of the plasma, and thus to render the dendrite functionally active: i.e., able to transmit or receive nervous impulses. When the gemmules are retracted or collapsed, therefore, functional activity is in abeyance, as during sleep, anaesthesia, etc.: i.e., they are unable to transmit or receive impulses.

This tends to show that none of the gemmules serve *per se* to transmit impulses, and that the dendritic tips must alone be endowed with this function. That such is the case seems to me suggested by Fig. 2 on the plate opposite page 550, which exemplifies the condition of a dendron before the engorgement induced by ricin has become far advanced: *i.e.*, at a time when the dendron's lumen has not as yet become completely blocked. The two central dendrites may be seen to terminate with bulbous tips, while the remaining gemmules immediately adjoining the latter are not apparently enlarged. This would point to the enlarged extremity as a dissimilar structure in respect to the gemmules, a terminal organ as it were. Again, the gemmules and terminal organ would have presented a certain degree of resemblance under the influence of the engorgement under the action of poisons, had they been similar; their appearance, on the contrary, suggests dissimilarity. Berkley states that, "so far as the end-apparatus of the collaterals from the psychical cells is concerned, the terminations of the intermediary cells, the fibers entering from the medullated masses, all have the same end-apparatus, which consists solely of a simple freely terminating *bulbous ending*, situated upon the *extremity* of the finest branches of the nerve-fibers." As he then refers to figures in one of his illustrations which represent axons supplied with bulbar extremities, I infer that it is to the dendritic terminals that he alludes, and not to those of the gemmules, as a broad application of his preceding paragraphs might suggest. If the bulbous terminals of the entire dendrite as well as the axon are referred to, the quoted lines afford additional evidence tending to show that the dendritic extremities alone transmit or receive impulses. Indeed, in the article in which chronic alcoholic poisoning is studied, Berkley remarks: "The process of tumefaction *always* appears to begin at or near the fine extremity of the dendron, be it the

extremity of the main apical process or one of its *collateral* branches, and not infrequently the *extreme termination* of the dendron, is seen to be somewhat swollen *when no other portion of the cell is involved.*"⁵⁵ He also states that "in his description of the mode of ending of the *collaterals* of the great pyramidal cells" Cajal "describes their finest branches as terminating freely by a *nodosity.*" All these facts seem to me to warrant the conclusion that *each of the collateral dendrites of a neuron and each axon, or subdivision of the latter, is supplied with a bulbous end-organ.*

How is an axonal end-organ of one neuron functionally related to that of a dendrite of another neuron? Berkley, alluding to the subdivisions of the axon, each of which is supplied with its bulbous end-organ, says: "These spherical apparatuses are closely adjusted against the bulbous tips of the gemmules, at times the approximation being so close that the impression is given of actual contact, though it should be remembered that the slightest overlapping will produce the same effect; and, on the whole, it is more probable that there is no actual contact, but that the *axonal discharges* of the stimuli overleap the infinitesimal distance between bulb and gemmule." For the reasons adduced, I do not think that the gemmules serve for the reception of impulses. These reasons also suggest that each axonal end-organ can only discharge its stream of impulses into the bulbous *terminal* of a neighboring dendrite, which bulbous terminal would, under these circumstances, present some analogy with the end-bulb of Krause, and, indeed, with several peripheral sensory organs. I have also submitted reasons that seem to me to offset the assertion that the end-organs actually touch. Indeed, that an "infinitesimal distance" between the efferent axonal end-organ and the efferent dendritic end-organ exists seems to be the only conclusion warranted by the histological picture, as described by Berkley. It seems to me, in other words, that *each of the bulbous end-organs of an axon, though apparently in contact with the end-organ of one of the dendrites of a neighboring neuron, may be separated from it by an infinitesimal distance.*

⁵⁵ All italics are my own.

The bearing of this arrangement, as an element of function, asserts itself when the stress we have laid upon the *vibratory* character of a nervous impulse is recalled. When studying the nature of the functional activity of muscles, I had occasion to say, referring to the governing action of motor nerves: "As the vibratory rhythm of the impulse and that of the muscle always correspond, any variation of rhythm by the brain-center correspondingly modifies the muscular contraction." If we now analyze what this vibratory rhythm means when the dendritic end-bulb and the axonal end-bulb are separated by an infinitesimal distance, but one answer appears to suggest itself: *i.e.*, that there can be no flow of impulses from one to the other. But we must not lose sight of the fact that the contradictory histological pictures described by Cajal and Berkley are those of *non-living* cellular elements, and that death may leave the two end-bulbs juxtaposed, as seen by Cajal, or separated by an "infinitesimal distance," as seen by Berkley. Thus, each histologist is right in his way as regards dead tissue. But what of living structures? Cajal and Berkley will again assist us in reaching a deduction in this connection, for *each* investigator furnishes one-half of the main physical function involved: *i.e.*, *vibration, which means rapidly alternating juxtaposition and separation of the bulbous end-organs.*

The rapidity with which the gap between the two terminals is opened and closed—*i.e.*, the *rhythm*—regulates, we have seen, functional activity. But can we conclude from this that non-activity of an organ means cessation of vibration of the bulbous end-organs involved in the function? We have seen that the nutritional processes of all tissues are continuous, nervous energy being supplied to the cellular elements as long as life lasts. Forel, as stated, was led by his admirable investigations to the conclusion that "living muscle appears to be so organized that without nervous stimulation it can live as little as the tropical animal can without warmth or the rose without water." This applies to all living tissues: a feature of the problem which necessarily implicates the continuous *development* of nervous energy and, as a consequence, an unceasing vibration of the end-organs. It seems to me, therefore, that, *inasmuch as the nutritional processes of the organism require a continuous*

supply of nervous energy, all the systemic axonal and dendritic end-organs are in a state of constant vibration.

Analyzing muscular contractility, I stated that: "The impulse-wave [and the blood supplied the cell] simply sets the muscle-elements to a given vibratory rhythm, and they retain this whatever be the intensity of the exertion required. . . . This may aptly be compared to the manner in which a note on a violin is made loud or soft. The power with which the string is pressed upon with the moving bow modifies the intensity of the sound; but the note remains the same. This means that its pitch does not vary, and if, for example, the lower C is given, we will know that the sound-wave of that note represents two hundred and sixty-one vibrations per second. So may the *impulse-wave* transmitted by the brain through a 'motor' nerve be represented by a fixed number of vibrations. Retraction, the muscle being then most tense, is therefore characterized by the greatest number of vibrations." If this interpretation is sound, it is likewise applicable to the "to-and-fro" motions of the bulbous terminals which constitute vibration, the number of these motions within a given time representing a given intensity. Any modification of the number of these to-and-fro motions within a given time, therefore, correspondingly modifies the intensity of the resulting vibratory impulse-wave, *the PASSIVE state of function (that during which cell-nutrition alone occurs) being represented by the lowest number of vibrations, the ACTIVE stage (during which the function is in full sway) by the highest number of vibrations compatible with normal health.*

Still, in accordance with my views, this applies to the impulses transmitted by the posterior pituitary body, since this organ, directly and through its extension in the cord, governs the passive stage of function and incites the cellular elements, both through the terminal vasomotors and the net-works distributed to the cells themselves, to higher activity when the active stage becomes necessary. Can we say the same of the independent hemispheres? This carries us back to the circulation of the brain, for the question involves another: *i.e.*, whether the cerebro-spinal functions, active and passive, are carried out in a manner similar to that of all other organs.

I am now able to state that they are, for the neuroglia-fibrils of the substance of the brain and cord represent their blood-supply, just as the cellular capillary net-work of any other organ represents its blood-supply.

Indeed, we must not overlook the fact that, while the neuroglia-fibrils representing the capillary supply of the cerebro-spinal substance are not supplied with vasomotor nerves, the peripheral vessels connected with the organ are, thus furnishing it with what might be described as an *extrinsic* supply. This extrinsic system would thus be represented by the pial vessels, which, as shown by Andriezen,⁵⁶ are supplied with vasomotor nerves. "We find," writes this investigator, "that it is possible to stain the vasomotor nerves with Golgi's method. Starting from the carotid and vertebral plexuses we can trace them no farther than the circle of Willis by anatomical dissection (using a lens). Do nerves accompany the cerebral arteries as they go off from the circle of Willis; and, if so, how far; and what is their ultimate distribution? Our observations on the kitten's brain show that bundles of nerve-fibers accompany the middle cerebral artery (the one specially chosen for our study) and its branches in the pia. These fibers run in tortuous and zigzag fashion, and in the finer pial branches they can be seen to form a very fine (non-anastomotic) plexus of fibrils lying between the outer and the muscular coats. From this *perimuscular* plexus terminal fibrils issue which, running a short distance along the muscular layer either longitudinally, transversely, or obliquely, end in small spherules: little ovoid bulb-like arrangements abutting against the muscular elements (cells). We have succeeded in tracing these terminals and their distribution to the finest pial cells, but no farther. The intracortical continuations of the pial vessels have constantly failed to give us the least evidence of this perimuscular plexus, which therefore—so far as our investigations go—we are compelled at present to imagine as *stopping with the pial branches*, and *not* continued along the intracortical vascular branches."⁵⁷ This evidence, added to the facts already outlined concerning the pericerebral vascular supply, seems to

⁵⁶ Andriezen: Brain, Winter, 1894.

⁵⁷ The word "not" is alone italicized by Dr. Andriezen.

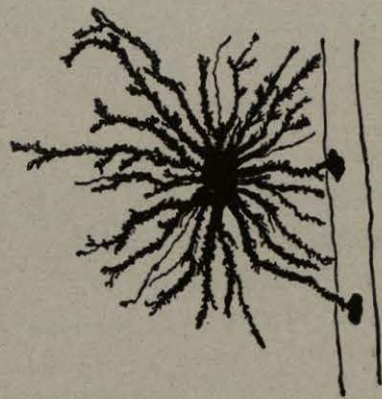
me plainly to indicate that *the cerebral circulation is governed, as is that of the arterioles of the body at large* (by the posterior pituitary body, as we shall see, pages 982 and 1259), *through the vasoconstrictor nerves of the pial vessels, which are terminals of the sympathetic system.*

This only furnishes us, however, the functional mechanism of the *passive* stage. In other words, the nervous energy developed owing to the presence of a given proportion of adrenoxidase (brought into contact with the myelin through the tonic vascular contraction insured by the general motor system) only causes the entire brain to create the nervous energy which, as we have seen, is essential to its own life. But how is the *active* stage incited in any one part of the cerebrum?

As is well known, groups of individual muscles may be caused to contract simultaneously, while some of the muscles which enter into the formation of these groups may be replaced by others. This is well exemplified by the mechanism of piano-playing: the index, thumb, and little finger, to form one chord; the annular and thumb to form the next, etc. Tracing this mechanism back to the structure which *incites* and *governs* the muscular adduction and abduction through which the keys are struck and released, we are brought back to a neuron. But how is the *neuron* incited to activity? In other words, how is the increased speed of blood through its myelinated dendrites, cell-body, and axon incited and governed? Can we ascribe this all-important function to the posterior pituitary body? We have seen that removal of the hemispheres did not prevent muscular action; a frog can swim, a pigeon fly, etc., and, indeed, continue to live a considerable time—months—if carefully fed, notwithstanding the absence of its hemispheres. This suggests that, while the posterior pituitary body either directly or indirectly incites and governs the functional activity of all organs, exception should be made of *the brain*, though it governs the circulation of this organ.

Still, the cellular elements of all organs are supplied with a net-work of terminal *nerves*, and it is through the intermediary in this net-work that its functional metabolism is governed by the posterior pituitary. How is the same function fulfilled in the hemispheres: *i.e.*, how are its cells, the

neurons, "incited and governed?" Are they also supplied with a net-work of fibrils which receives impulses from the posterior pituitary body? There is no evidence available to suggest that such is the case, and the functional relationship with the latter through the vasomotor supply of the pial vessels is the only link between the two organs that existing data permit us to accept. If, therefore, a regulative mechanism exists, it must be one connected with the vascular system, and so disposed as to enable it to govern the circulation through one or more neurons simultaneously. It must supply its own nervous energy, for we have seen that Andriezen found the vasomotor



"A PROTOPLASMIC NEUROGLIA-CELL FROM THE HUMAN BRAIN (FOURTH LAYER OF CORTEX) SHOWING TWO EXPANDED CONICAL DISK-LIKE ATTACHMENTS TO A VESSEL." (Andriezen.)

nerves to distinctly terminate upon the muscular coats of the pial vessels; indeed, it must be as autonomous an organ as is the neuron itself.

Such an organ we have, it seems to me, in the neuroglia-cell shown in the above illustration, which Andriezen has named the "protoplasmic neuroglia-cell," and describes as follows⁵⁸: "The protoplasmic glia-cell has a distinct cell-body, which is irregularly oval, frequently pyriform. Its various protoplasmic processes are of moderate length; they exhibit *great variations of caliber*, some being stout and coarse and others exceedingly fine. These processes are also *dendritic*: a thing never seen in the stellate cells. A most striking feature is the shaggy

⁵⁸ Andriezen: British Medical Journal, July 29, 1893.

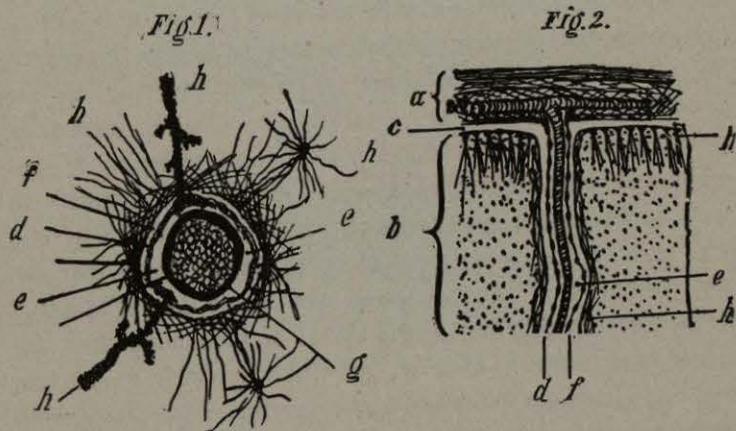
granular contour, as if a fine moss constituted the protoplasmic processes. . . . Further, by one or more of their *coarser* processes the protoplasmic cells are attached to the perivascular sheaths. The figure [on the opposite page] shows the cell with two such vascular processes, each *attached to the vessel* by a conical disk-like expansion ('foot')."

These characteristics of this cell speak clearly in favor of my view that neuroglia-cells and fibrils are channels for blood. Bearing directly upon the question in point, however, is the fact that this cell, as indicated by its gemmules and its dendritic appearance, must be supplied with myelin. The association of this myelin with the blood-plasma in transit at this point—*i.e.*, so close to the blood-vessel—seems suggestive, for, if the illustration is closely examined, dendrites are not alone found around the cell, but also fibrils, which start from various parts of these dendrites. That these protoplasmic neuroglia-cells are directly connected with the blood-vessels so as to admit plasma is demonstrated by the fact that they also take part in the engorgement of neuroglia structures that follow poisoning. "The bodies of the *mossy* neuroglia-cells," writes Berkley, alluding to the effects of ricin poisoning, "are larger than normal, rounded, sometimes globular in outline, and the tentacles are thickened and knotty. There are general evidences that these structures of the *lymphatic* system are undergoing modifications of a pathological nature." I have already stated that this "lymph" was, according to my view, its next o' kin: *i.e.*, *blood-plasma*.

Referring to the paper from which I have just quoted, Andriezen remarks⁵⁹: "We also stated at the time that the evidence of staining with Golgi's method shows us a system of lymph-spaces surrounding the cell-body and its branches. Careful and fresh observation confirm us in this opinion, viz.: that there is an *exceedingly fine system of canaliculi and lymph-spaces* surrounding the body, and dendritic processes of the protoplasmic glia-cell, and directly continuous with the perivascular lymph-spaces." If the annexed sketches by Andriezen are now examined and *interpreted from my standpoint*, addi-

⁵⁹ Andriezen: Brain, Winter, 1894.

tional testimony in favor of my conception of the whole mechanism of brain-function will appear. Indeed, the *canaliculi* are evidently the openings into the neuroglia-fibrils. But these microscopical channels, which are often one-sixth the size of a blood-corpuscle, would soon be blocked were the latter allowed to reach them. There is interposed between them, therefore, a lymphatic membrane, similar to the one which, as we have seen, forms the lymph-space from which veins start. Here, however, a double purpose is served, as shown in the sketch. It forms two cavities: the one surrounds the blood-vessel, and



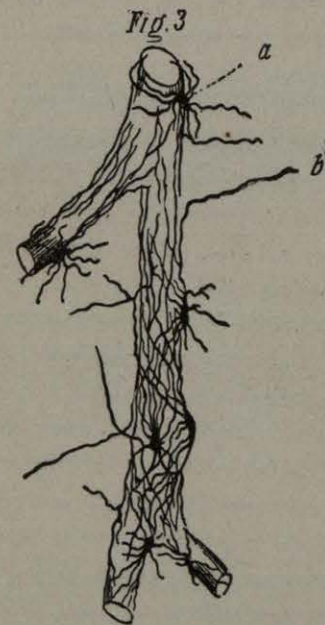
RELATIONSHIP OF THE VASCULAR AND LYMPH CHANNELS IN THE BRAIN. (Andriezen.)

a, Pia-arachnoid. *b*, Brain-substance. *c*, Epicerebral space. *d*, Adventitial sheath. *e*, Intra-adventitial space. *f*, Extra-adventitial space. (According to my view, these are all blood-channels: The blood arrives in pial artery (*g*), and escapes through the walls of the latter into the "intra-adventitial" space (*e*). Part of the plasma of this blood passes through sheath *d* into the "extra-adventitial" space (*f*) and enters neuroglia-fibers and cells (*h, h, h*), and then passes into the apical dendrites of neurons; the rest of the plasma and all corpuscles return to the veins by way of the "intra-adventitial" space at *e*.—S.)

represents the channel connected with the venous system, to which all corpuscles return; the other, or external, space receives only the blood-plasma which has passed through the membrane. The latter, being mainly composed of endothelial plates, is therefore phagocytic and bactericidal, and thus admits into the neuroglia canaliculi not only plasma relieved of all its

cellular elements, but also aseptitized adrenoxidase-laden plasma. The outside of a vessel covered with a neuroglia-ridden sheath is shown in Fig. 3.

The two kinds of neuroglia-cells may be seen to take part in the formation of the external net-work of fibrils in the illustration on page 586. It is here, it seems to me, that the governing attribute of the "protoplasmic neuroglia-cell" shows itself, as suggested by the dendritic appearance of its exten-



BLOOD-VESSEL OF THE HUMAN BRAIN, SHOWING SEVERAL NEUROGLIA FIBER-CELLS SURROUNDING IT AND FORMING A FELT-WORK (PERIVASCULAR SYSTEM). (Andriezen.)

a, An encircling cell. *b*, Perpendicular neuroglia-fiber entering the sheath at right angles from a distant (extrinsic) cell.

sions. Indeed, Ranvier has been led to conclude that the other variety of neuroglia (stellate) cell is not much more than a mass of aggregated fibrils in transit, the latter passing through them without forming part of the cellular structure. Still, as it contains a nucleus, it may possess a regulative action. The larger cell, however, imposes itself as an organ of a very active kind—capable probably of playing in the brain the part that the vagus plays in various organs: *i.e.*, to incite