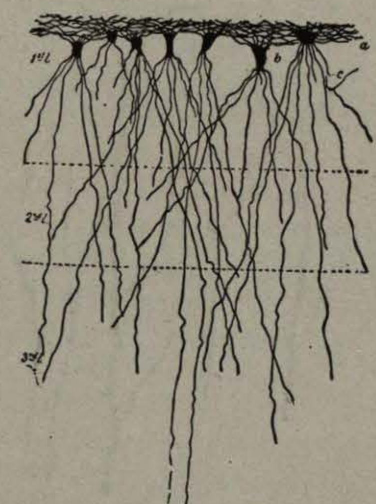
active function and govern it in the neurons with which it is connected, either directly or through the intermediary of other neurons. The connection with the latter would not be established by continuous fibers, but through their end-bulbs, the axonal of the one to the dendritic of the other, etc., in order to allow of the transmission of *vibratory* impulses. Referring to these larger "protoplasmic" ganglia cells, Andriezen writes: "They occur abundantly throughout the gray matter, in all the layers of the cortex, but are rare in the white substance." Indeed, according to my views, the latter is a mass of axis-cylinders coming from the upper strata, and surrounded by their myelin, wherein energy increases with distance: a true "avalanche"—using Pflüger's expression—of nervous force toward the lower cerebral structures.

The predominating function of both varieties of neuroglia-cell asserts itself, however, when the characteristics of the cortical layers are reviewed. The first, or molecular, layer contains but few nerve-cells, according to Andriezen. Its proximity to the pial vessels normally suggests that, if glia-cells are intermediaries between these vessels and the brain-substance's circulation, they should occur in large quantities in this region. "Its outermost, or superficial, region is formed of a system of neuroglia fiber-cells," says Andriezen, and by means of the annexed illustration, among others, he emphasizes the varied directions and the length their extensions may assume. But if the illustration on page 586 is examined, the manner in which these cells (according to my interpretation) are supplied with plasma may be easily understood. As shown therein, the pial vessel dips into the brain-substance, surrounded by its lymphatic membrane in such a manner, we have seen, as to form two spaces, the internal of which is for the blood and corpuscles to be returned by the veins to the general circulation; the other, or external space, being that in which the plasma for the neuroglia-cells passes after penetrating the lymphatic membrane, in order to reach the neuroglia-fibrils. This affords a supply to both kinds of cells, which are seen to line the plasma-containing space. That both are intimately connected with the circulation appears to me beyond doubt; that the mossy, or protoplasmic, cell is endowed

with some function other than as a mere distributing center is as likely; that this function should be to regulate the circulation in the neurons, or groups of neurons with which it is connected (as shown by the effects of poisons upon all structures thus connected), is strongly suggested by the fact that, while the need of such a regulative system is evident, there is no discernible or known organ or system of organs, directly connected with the pial blood-vessels, other than these cells to which this important function could be ascribed. The following conclusions, therefore, seem to me warranted:—

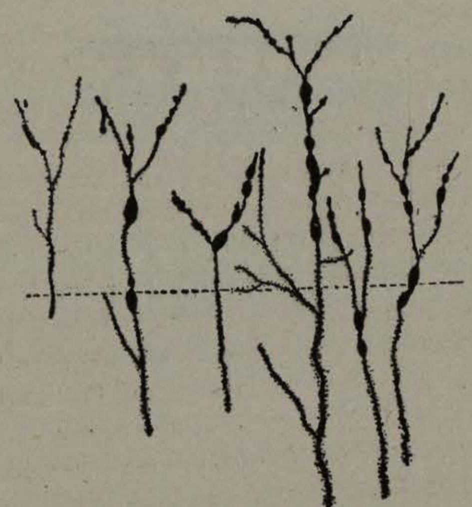


SEVEN CAUDATE NEUROGLIA FIBER-CELLS FROM THE HUMAN BRAIN-CORTEX (FIRST LAYER). (*Andriezen.*)

a, Tangential fiber-system. *b*, Cell-bodies. *c*, Descending fiber-system. The dotted line shows the limit between the first and second and the second and third layers.

The neuroglia-cells are the intermediaries between the general circulation and the capillary system (neuroglia-fibrils) of the brain-substance. The smooth stellate cell seems only to serve for the equable distribution of the blood-plasma to the neurons, while the mossy, or protoplasmic, cell presents the attributes of an organ to which the function of inciting a group of neurons to action by activating its blood-supply and of governing the quantity of nervous energy produced in these neurons can be ascribed.

Judging from the admirable histological work of Andriezen and Berkley, the engorgement caused by poisons affects the three upper layers of the cortex most markedly. The bead-like swellings of the first-layer dendrites are well shown in the annexed illustration, the lesions being those found in alcoholic insanity. The second layer and third layer are represented by the plate opposite page 550, reproduced from Berkley's article, ricin poisoning, as previously stated, having been the cause of the cerebral engorgement. The cells of the last, or fourth (polymorphous), layer are not shown, but the fact that



TERMINAL TUFTS AND ENDINGS OF THE PROTOPLASMIC APICAL PROCESSES IN THE FIRST LAYER (HUMAN BRAIN-CORTEX). (*Andriezen.*)

Showing bead-like and moniliform swellings, coalescence of fine miliary granules in place, and loss of fine granulation in the most affected parts. The dotted line marks the limit between the first and second layers. Alcoholic insanity.

Marchi found that the ependymal neuroglia-cells sent a central extension to the optic thalamus, where it divided and became attached to the blood-vessels, shows that the circulatory mechanism I have described applies to the entire cerebro-spinal system. Briefly, *the cerebro-spinal system is built up of neurons supplied with adrenoxidase-laden blood-plasma through the intermediary of protoplasmic neuroglia-cells, which regulate the volume of this fluid admitted into the neurons and, thereby, their functional activity.*

THE POSTERIOR PITUITARY BODY AS THE SOMATIC CENTER OF THE NERVOUS SYSTEM.

Howell,[60] in the course of experiments which led him to conclude that "the infundibular lobe of the hypophysis (the posterior pituitary) is, in all probability, not a rudimentary organ, but a structure that has some important physiological activity," found, as I have already stated, that "the extracts of the glandular lobe (the anterior pituitary) have little or no perceptible effect when injected alone. Extracts of the small infundibular lobe, on the contrary, have a distinct and remarkable effect upon the heart-rate and blood-pressure, an effect which resembles, in some respects, and differs, in others, from that shown by suprarenal extracts."

We have seen in our previous analysis of these observations that the symptoms produced were those of suprarenal overactivity, and that the extract acted as did adrenal extract; the heart-beat was "not only slowed, but considerably augmented in force," says Howell, "as shown by tracings taken with a Hürthle manometer," etc. When both vagi were cut or a little atropine was given, the slowing of the heart was less marked. The result of vagal section is evident. As to the atropine, it prevented the slowing because, when added to the pituitary extract, it modifies its action, by inhibiting the functions of the adrenals as it does those of other glands. But an interesting query imposes itself in this connection: The extract having at first stimulated the activity of the adrenals, how did the latter, through the increased oxidizing substance, bring about increased vagal action? The answer is easily reached: the posterior pituitary being also increasingly supplied with oxidizing substance, its activity is likewise increased. This emphasizes an important feature: *i.e.,* that *the posterior pituitary is* functionally stimulated, as is any other organ, by the oxidizing substance in the blood passing through it. Indeed, the nerve-fibers which Berkley found to accompany the arteries suggest the presence of a functional arrangement similar to that of any organ, while

[60] Howell: "Transactions of Congress of American Physicians and Surgeons," vol. iv, p. 83, 1897.

the presence of so many neuroglia-cells at the apex—*i.e.*, where the posterior pituitary meets the infundibulum—indicates that the neurons which they supply are the seat of marked functional activity.

The feature brought out by Howell's experiments, however, is that the posterior lobe (including the *pars intermedia* as recently shown by Herring[60a]) contains an active agency. This harmonizes with my views, since, as we have seen, the anterior lobe is, to a certain degree, passive in that it is stimulated to an inordinate degree only when toxics are present in the blood, while its normal activity is sustained by the secretion of the thyroid gland. Though the purpose of both organs is similar, therefore,—the conversion of chemical energy into nervous energy,—the manner in which this is done is not similar. Indeed, in the posterior lobe, the exciting agency is, as just stated, precisely as it is in any organ: *i.e.*, oxygen. The posterior pituitary must, therefore, become physiologically active through the same chemico-physical process that prevails elsewhere in the body.

Indeed, we have seen that the posterior lobe is, in reality, but an aggregate of neurons—and a precious aggregate it must be, ensconced, as it is, in a bony cradle and resting on a pillow of blood, to preserve it against shocks or traumatisms! That, like all neurons, this aggregate depends mainly upon a phosphorus-containing ground-substance has been shown. I will recall that Cyon,[61] in the course of a large number of experiments (since confirmed by Masay, see pages 983 to 989), observed that: "1. Any, even slight, pressure upon the hypophysis (*i.e.*, both organs) immediately gives rise to a sudden variation of blood-pressure and to a notable reduction in the beats of the heart, the strength of which is at the same time considerably increased. 2. Electrical stimulation of the hypophysis, even with extremely weak currents, produces exactly the same phenomena as does mechanical pressure, but in a much more intense manner. 3. Extract of hypophysis, injected into the veins of an animal, produces upon the heart and upon blood-pressure effects that are analogous to those caused by electrical and

[60a] Herring: Quarterly Journ. of Exper. Physiol., vol. i, p. 281, 1908.
[61] De Cyon: Archives de Physiologie, July, 1898.

mechanical stimulation of this organ." I have pointed out that this pituitary extract does not prove the existence of a secretion at all, and that its action was due to the presence in the organ—as in all sympathetic structures, of chromaffine, *i.e.*, of adrenal substance. Indeed, Oliver and Schäfer in 1895 found that pituitary extract could be boiled without destroying its action—a property which a ferment such as the adrenal principle possesses alone. This added to the chromaffine and adrenalin reactions and the fact that the effects of pituitary extract are precisely those of adrenal extract shows the fallaciousness of the secretion doctrine. Conversely the facts reviewed the presence of phosphorus, noted by Rossbach, and the effects of direct stimulation, plainly show that *the posterior pituitary, being mainly composed of neurons and their protoplasmic extensions, is the seat of reactions similar to those that prevail in other nerve centers.*

The intrinsic processes upon which the physiological functions of neurons and nerves depend seem to me to be represented in the foregoing pages, but I have still to account for the "stormy processes in the nerve-fiber" to which Barker refers: *i.e.*, the exacerbations through which *passive* functions become *active*. Can we attribute these to the cells in the several centers? "Notwithstanding almost infinite minor variations in form," says Professor Barker, "the neurons in the most different parts of the nervous system present surprisingly similar general external morphological characteristics." We have seen, by the details furnished by the histological studies of Berkley, that such is not the case with the neurons in the posterior pituitary. Indeed, there are in this organ *ten* cells, exclusive of four of the neuroglia type that differ in morphological characteristics, each of which receives from Berkley a separate description. Not only do all the axons of the cells in this lobe point upward, but the diversity of cellular shapes is beautifully illustrated in the plate opposite page 594, a transverse vertical section of the infundibular region.

We have seen that above the infundibulum—*i.e.*, in the structures of the third ventricle—he found "varieties of ependymal neuroglia-cells, previously supposed to have entirely disappeared from the central nervous system," etc., and which were thought to be confined to "reptiles, amphibia, and fishes." The physiological rôle I have ascribed to neuroglia-cells and fibers further emphasizes the importance of these structures and of the marked nutritional activity of which they are the seat. As a complement of this I showed that Andriezen traced a direct nervous connection in all classes of vertebrates between the "posterior lobe of the pituitary," on the one hand, and "the olfactory center" and the "bulbo-spinal centers," on the other.

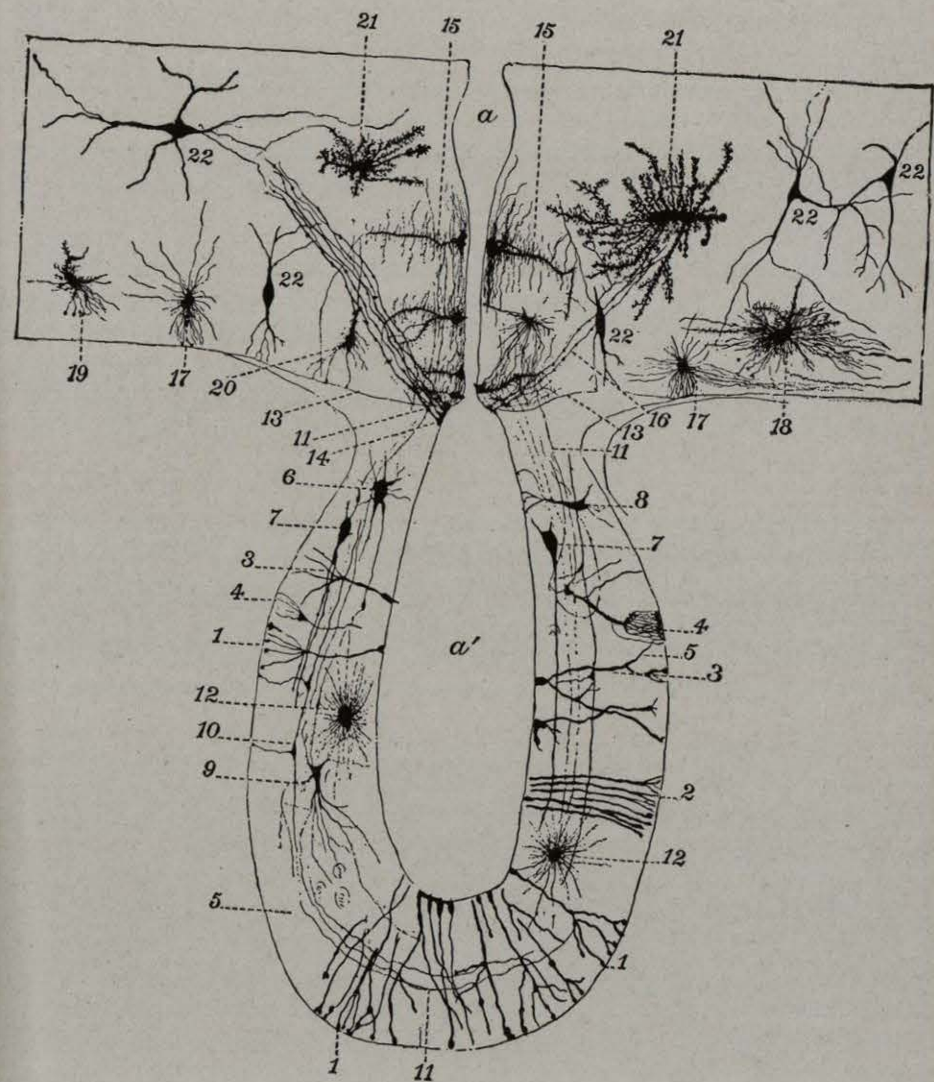
When these facts and others reviewed are placed side by side with the adduced evidence (1) that the middle brain is the seat of a nervous mechanism through which highly differen-

TRANSVERSE VERTICAL SECTION OF THE INFUNDIBULAR REGION.

a, Lumen of ventricle. *a′*, Lumen of infundibulum. 1, Primary forms of ependymal neuroglia, the processes extending from a cell-like body at the edge of the ventricular cavity to the subpial limit. 2, Coarser and less ramified variety of ependymal cell. 3, Coarser ependymal cells, branching within the inner half of the infundibular wall. 4, Portions of ependymal cells with tufted subpial branchings. 5, Unstained nerve-cells. 6, Pyramidal cells with long, fine processes. 8, Transversely lying cells of small size with knobbed extremities. 9, Pyramidal cells with large numbers of apical processes. 10, Probable axis-cylinder extension of pyramidal cells with thickenings, and rectangular extensions to the subpial limit. 11, Nerve-fibers passing from the infundibular wall into the tissues along the border of the ventricle. 12, Burr-like cells of the infundibular wall. 13, Line of the floor of the brain. 14, Long-rayed ependymal cells of the juncture of the ventricular and infundibular cavities. 15, 15, Fir-tree ependymal cells of various sizes and forms lining the border of the ventricle. A few of them are seen to have rounded knobs adjusted against the pial limit of the basis cerebri. 16, Neuroglia cell approximating the short-rayed type of Golgi. 17, 17, Sustentacular glia-cells of the inferior border of the tuber cinereum. 18, 19, Glia-cells with numerous long and stout hairy processes from the bodies, and thicker projections, probably transition forms between the sustentacular cells and cells of later development. 20, Probable nerve-cell resembling some of the glia-cells. 21, 21, Large mossy cells situated at some distance from the ventricular border. 22, 22, Nerve-cells of different forms. (*Berkley.*)

tiated afferent impulses meet with response, and (2) that the structures to which Berkley and Andriezen refer are contained precisely in the central gray matter which Foster considers as "perhaps in point of origin the oldest part of the brain" and which "seems to serve chiefly as a bed for the development of the nuclei of the cranial nerves," it seems clear to me that the posterior pituitary body is *a general center in which active functions are incited and governed in response to afferent impulses.*

A neuron, we have seen, presents the attributes of other organs; that the analogy includes the functional limits of these



SEMIDIAGRAMMATIC TRANSVERSE VERTICAL SECTION OF THE INFUNDIBULAR REGION OF THE BRAIN. [*Berkley.*]

[*Brain.*]

organs is very probable. Under these circumstances and taking the digestive system as example, a group of neurons constituting the origin of a nerve would be able automatically to continue its *passive* functions between meals. But just as the onset of digestion, the active functional state of the stomach, involves an increase of the volume of blood supplied to its muscular and secretory elements, through vasodilator impulses, *so would a nerve-center, when required to assume the active phase of its functions receive more blood (adrenoxidase-laden plasma) through arterial vascular elements governed by the posterior pituitary.*

Professor Foster's reference to the central gray matter as a bed "for the development of the nuclei of the cranial nerves" suggests that the posterior pituitary might possibly supply energy for all cranial nerves. The complex origins and connections of the optic nerve would, under these conditions, convert the posterior pituitary into a source of energy, pure and simple, for general distribution. Ample evidence to this effect is submitted in the second volume.

This does not apply to the anterior lobe, however, although its *pars intermedia* governs the adrenals. Berkley says, of the anterior pituitary: "No nerve-*cells* are to be found in the substance of the organ, and all nerves belonging to it appear to be derived from branches of the carotid plexus." This indicates that nervous energy supplied by this organ to the adrenal system, while produced through the intermediary of the layer of sensitive cells in the partition between the two lobes (see page 960 for its description), is due to a *stimulating* influence other than that which prevails in the posterior lobe. In other words, while the iodine in organic combination in the thyroid secretion is the *normal* stimulus of the sensitive cell-layer,—and one of the many stimuli to which it responds,—the posterior lobe is made up of many types of neurons which depend upon the lecithin formed between their protoplasmic partitions for their functional activity.

The organs differ markedly and significantly in one respect, therefore: *i.e.*, in the fact that, while the whole of the anterior lobe is devoted to the one purpose of energizing the suprarenal center, the posterior is an aggregate of many centers. This indicates, it seems to me, that if the organ were a general source of energy for the whole bed of cranial nerves, irrespective of the individuality and purpose of each nerve, it would have been similar in general construction to its mate, the anterior lobe. That it tends to suggest that each group of neurons in the posterior pituitary body is a highly specialized center for a single class of nerves. Indeed, this is experimentally, though indirectly, sustained by Andreizen's researches. He could not have traced a direct nervous connection with the olfactory bulb and with the cerebro-spinal axis had the organ been a center for the production of energy intended to be diffused promiscuously in the central gray matter.

Again, the connection between the posterior lobe and the nervous system cannot be limited to the cranial nerves, since we have seen how intimate is the functional relationship in which afferent impulses obtain, between the middle brain and the entire motor system. Were the cranial nerves alone involved, the skeletal muscles would have to be omitted from the list of structures under the organ's control. As we have seen, removal of the middle brain abolishes all "bodily movements," as Foster puts it, "carried out by means of co-ordinate motor impulses, influenced, arranged, and governed by coincident sensory or afferent impulses."

Yet, how can the posterior lobe influence organs with which it has no anatomical connection? Thus, the most prominent motor paths, the pyramidal tracts, arise, in the cortex, from the upper two-thirds of the central convolutions, pass down behind the knee of the internal capsule, and then penetrate the middle third of the pes cerebri, then the pons and the medulla, and finally pass down the cord. Where is the connection with the posterior pituitary? When the tracts "emerge from the pons," says Edinger,[62] "their fibers form two large bundles in the ventral portion of the medulla,"—*i.e.*, in the regions of the middle brain,—where, as we have seen, not only all nerves endowed entirely or in part with motor properties—the second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, and twelfth pairs—are represented either by their nuclei or by communicating roots, but also where *all nerves acquire certain vasoconstrictor*, i.e., *sympathetic properties.*

It becomes a question as to the manner in which the cerebrum is itself functionally governed, in so far as its somatic functions are concerned. In the light of the foregoing facts we are brought to the eminently logical conclusion that, in order to insure perfect co-ordination of the functional activity in all organs, a single structure is entrusted by Nature with this all-important rôle, *i.e.*, the posterior pituitary. *The cerebrum, as the organ of Mind, differs in no way from other organs*, from my viewpoint: *its circulation is also governed by the pituitary body* during its active and passive state: wake and sleep. I have previously referred to the fact that the medulla is only a transmitting center: a general station to which impulses from various directions arrive by the cord from below, by the commissures from the encephalic structures, and establish junctions with the several paths with which they are related. "The encephalon is a very complicated system of large and small continents of gray or central nervous substance," says Professor Duval, "communicating one with another and with the medulla by numerous commissures."

We have seen how absolutely independent of motor functions the hemispheres are, though volitional attributes enable them to *utilize* the motor system. Indeed, the experimental evidence adduced on this score is incontrovertible. But the same distinguished physiologist says: "The nerve-cells of the cord form in this organ a continuous central gray mass, extending from one extremity of the organ to the other. But, if the anatomist locates the superior limit of the cord on a level with the occipito-atloidian articulation, for the physiologist the cord extends into the interior of the cranium; it reaches to the aqueduct of Sylvius (the true origin of the motor oculi communis and patheticus) and even on a level with the third ventricle—the gray substance of the walls of this ventricle." We have seen that he also referred to its reaching up to the *sella turcica*. That it is *within* this bony structure that the main center of this vast mechanism—with its extensions and terminals, including the vasomotor fibers—lies, has been sufficiently emphasized. I feel, therefore, that I have good

[62] Edinger: *Loc. cit.*