nal system, and, as such the primary source of certain excito-motor impulses now believed to arise in the bulb.

Of course this conception conflicts with the prevailing view that the pituitary body is the source of an internal secretion; but there is ground for the belief that some leading investigators are not convinced of the existence of the latter. Swale Vincent, we have seen, finds it "extremely difficult to imagine how such a structure," referring to the posterior lobe, "can be regarded as a secreting gland." In a very recent paper, E. A. Schäfer,[15] though a partisan of the secretion theory, concedes that "some functions of the organ might be conceived to be carried out through the ageney of nerves." Nothing so far published has, in my opinion, raised the secretion theory beyond the level of a plausible assumption. (See also page 173 in the present volume.)

If, however, the posterior pituitary holds the important relation to the nervous system I believe it does, its influence in the pathogenesis of general neuroses must be very great. No disease having so far been associated with the *posterior* lobe, it may prove profitable to seek among the symptoms of typical disease of the *anterior* lobe what signs might be assigned to implication of the posterior, with which it is intimately blended.

Acromegaly, which may be attended by irregularity of the reflexes, paræsthesias, localized pains, vasomotor neuroses, paraplegia, etc., and known to be due solely to lesions of the pituitary, suggests itself as a profitable field of study in this connection.

It is interesting to note, in this connection, that quite a number of exceptionally able clinicians—von Recklinghausen, for instance—have considered acromegaly as a trophic neurosis, the organic disease of the pituitary being deemed secondary. That the various theories adduced also bear upon *nutrition* of the nervous elements is significant as testimony in favor of my view. Indeed, the clinical signs that point to impaired nervous action are numerous, and are present in practically all cases of acromegaly when the anterior lobe has become sufficiently enlarged or functionally disordered to involve the posterior lobe, either directly by pressure, continuity of tissue, etc., or indirectly by overstimulating the adrenals, or, in the later stages, by causing insufficiency of these organs.

[15] Schäfer: Proceedings of the Royal Society of Medicine, May, 1913.

In a previous chapter I have, on good grounds, I believe, ascribed to overactivity of the adrenals the stage of "erethism," and to insufficiency of these glands that of "cachexia." But, if we ask *how* these states are produced by the adrenals, the answer which would not have been available before now seems to be within our reach.

I have previously referred to the vicious circle that obtains in acromegaly. Though primarily located in the anterior pituitary, the lesion probably gives rise to no untoward symptom until well advanced: *i.e.*, until pressure occurs either upon its own structure by the pathological elements or upon the posterior pituitary. Even slight pressure upon the whole organ, as shown by de Cyon,[16] gives rise to marked general symptoms. But if the posterior pituitary is also considered as a factor in the production of the symptomatic phenomena, as a source of nervous energy, we not only have the vascular erethism of suprarenal overactivity, but distinct evidence of *nervous* erethism besides. This is well illustrated by the following *quoted* lines, *i.e.*, Gauthier's definition of the erethic stage of acromegaly as given by Hinsdale[17]: "The phenomena of *erethism* which characterizes the *first stage* embraces, first, a painful *hyperæsthesia*, which manifests itself in headaches and rheumatic pains; second, an hypertrophy of the muscular fibers which may give to patients a muscular power greater than usual; third, palpitation of the heart accompanying the hypertrophy of that organ; and, finally, the polyphagia and polyuria which may be considered to be connected with an erethic state of the respective organs." Everything here points to overactivity. But these are only the milder manifestations. Tamburini, for instance, describes a case in which "the mental symptoms, on account of which the patient was sent to the asylum, began to show themselves only a year before her admission. They consisted chiefly in delusions of suspicion accompanied by threats and acts of violence. The patient presented, in a marked degree, the bodily changes characteristic of acromegaly. While in the asylum she was confused, resistive,

[16] De Cyon: Archives de Physiologie, July, 1898.
[17] Hinsdale: *Loc. cit.*, p. 30.

and suicidal, and refused her food. . . . Only the anterior lobe was involved, the posterior presenting no change either in volume or structure." This typifies the irritability or stimulation induced by pressure without organic change.

The phenomena produced are of another kind when both organs are involved in the morbid process, as appears to be the case in the following instance reported by Johnston and Monro[18]: The patient, a woman, "was taciturn and intellectually obtuse, and her memory was bad. Her utterance was thick and indistinct, as if her tongue were too big for her mouth. Her gait was slow and shuffling; her expression partly melancholic, partly demented. . . . The skin of the face is of a dull-yellowish tint; the mucous surfaces are pale. . . . Hearing is somewhat impaired. Reflexes are diminished. The subject of these notes remained in hospital for about four weeks. She scarcely ever spoke, took no interest in anything, and slept about sixteen hours daily. . . . She was readmitted in September—blind, more deaf, more drowsy, very feeble in muscular power. She could no longer rise without assistance. Control over the sphincters was lost. . . . Paralyzed. For a couple of months before death there was a discharge of clear fluid from the nose. . . . The pituitary body is represented by a large, red mass, almost diffluent—much softer than brain-substance." The entire organ being destroyed, the posterior lobe had obviously followed the fate of its mate.

In a case described by Pirie[19] the history of the nervous symptoms is very clearly defined, though the author was unfortunately unable to obtain an autopsy. "The disease first manifested itself in 1886, when menstruation finally ceased. Pains and paræsthesia of the arms and legs were felt, and the patient noticed that her hands and feet were getting larger and more awkward. . . . Along with the development of physical symptoms a peculiar alteration of mental condition took place. Attacks of narcolepsy overcame her, she became sluggish and irritable, and she suffered much from the *ennui* of life. . . . Breathlessness on the slightest exertion ap-

[18] Johnston and Monro: Glasgow Medical Journal, August, 1898.
[19] Pirie: London Lancet, Oct. 5, 1901.

peared, and ultimately the muscle weariness so gained upon her that she had to take entirely to bed. . . . Sensory disturbances are marked. Shooting pains in combination with paræsthesia, tingling, and numbness are complained of in the arms and legs. Neuralgic pains are felt also in various parts of the body, viz.: the face, chest, back and loins. A remarkable perversion of thermic sensibility is found in the lower limbs and over the front of the abdomen and chest up to about the level of the fourth rib, the patient having no sensation of heat in these regions. . . . Sternberg remarks particularly on the occurrence of pain and paræsthesia as valuable signs for diagnosis in the early stages of the disease; they are probably due, he considers, to changes in the cutaneous nerves."

In a previous chapter I remarked: "Whether the mental symptoms are ascribable to the cerebral hyperæmia or to the impairment of certain functions of the pituitary itself, or to both, it is as yet impossible to say." It now seems evident that *both* organs are involved in the pathogenic process. If the far-reaching meaning of this fact is apprehended, it seems clear that there lies hidden under the whole fabric—of which we only now see the outline—a truth of overwhelming importance to us physicians: *i.e.,* the fact that *it is not alone in acromegaly that the typical signs of impaired function of the posterior pituitary appear, but in other syndromes directly ascribable to the adrenal system: i.e., myxœdema, cretinism, exophthalmic goiter, and Addison's disease, which include in their aggregate the majority of organic changes of a morbid kind to which the system is liable, besides nervous phenomena.*

This may be briefly illustrated by further quotations from Dr. Pirie's excellent paper, entirely devoted to the one case. As regards the *muscular system,* the author states that "muscular atrophy is a prominent feature, affecting the thenar, hypothenar, and interossei muscles of the hands, the forearm- and arm-muscles, the calf- and thigh-muscles, and also the glutei," and refers to Duchesnau,[20] "who has made a special study of the atrophy of muscles in acromegaly. So marked is it in some cases that it has been mistaken for syringomyelia,

[20] Duchesnau: Thèse de Lyon, 1891.

progressive muscular atrophy, or amyotrophic lateral sclerosis; it has also been mistaken for Charcot's cervical pachymeningitis hypertrophica and for erythromelalgia." Referring to the *skin,* Pirie says: "Its chromatogenous functions are disturbed, much as in rheumatoid arthritis. Small freckles are frequent; patches of a yellowish bronzing occur also on the face, the chest, and the insides of the thighs. (Motais describes a bronzing such as occurs in Addison's disease.) Numerous small warts are present. (Mollusca fibrosa are described in many cases and xanthoma-like tumors by Dallemagne.) The patient suffers from a brownish seborrhœa, especially troublesome in the scalp. The hair is thick and coarse and stands straight upward. There is a scanty beard and moustache. Profuse perspirations are constantly complained of. The heart is dilated. There is tachycardia, the heart beating about 98 to the minute. A soft, systolic, basic murmur is heard at times. Palpitations and fainting fits occur very often. Dyspnœa is marked, and asthmatic-like attacks occur, during which the patient has to sit up in bed and fight for her breath." . . . "The *soft parts* are remarkably changed as well *as the bones.* The scalp is much thickened, as is also the skin of the face. . . . In addition to the kyphosis there is a compensatory lumbar lordosis and also a certain degree of scoliosis. The clavicles are enormously hypertrophied. The ribs are thickened and expanded, the costal cartilages feel bony, and there are nodular projections resembling the 'rachitic chaplet' at the junctions of the ribs and their cartilages." . . . "With regard to the *organs of special senses,* the skin of the eyelids is thickened and puffy. The lacrymal glands are hypertrophied. Increased lacrymation occurs at times, and I have noticed a colloid-like secretion between the eyelids." . . . "There is amblyopia, nearly complete in the left eye, and color-vision for blues and yellows is defective. Bitemporal hemianopsia is present. The pupils contract in accommodation and react to light, though very sluggishly in the case of the left eye. With the ophthalmoscope optic atrophy is found." . . . "She suffered much at this time from polydipsia and *glycosuria,* and for over twelve months there was an almost constant dribbling of saliva from the mouth. . . . The

thyroid was greatly enlarged, but under treatment with thyroid substance it diminished much in size." We have seen how dependent the organism is upon the integrity of the suprarenal system when infectious diseases develop.

I can fully agree with Harlow Brooks[21] when he says: "It is quite natural to expect pronounced abnormalities in the various portions of the nervous system in a disease which exhibits so many neurological symptoms"; and his statement that "examinations of the nerve-tissues have shown quite *extensive* and *general* changes" further sustains my deductions. Evidence of this kind, garnered from all sides long before the feature it serves to support is thought of, appears to me of the strongest kind. I again prefer to use the author's own words, therefore, rather than my own, when he reviews the pathology of the disease, and which seems to me to portray *in parvo* the main landmarks of neurological pathology. I have only omitted those of the author's own estimates that do not bear directly upon my subject and what text was not purely descriptive:—

"*Peripheral Nerves.*—The trunks of the peripheral nerves are, for the most part, enlarged; this is directly due to an increase in the connective tissue of the endoneurium and perineurium. Often the sheaths of the nerve-trunks also show considerable thickening. This general connective-tissue hyperplasia frequently so encroaches on the nerve-fibers as to destroy them, and degenerated nerve-fibers are quite commonly found some of which may show complete axis-cylinder destruction (Arnold, Comini). These conditions may persist throughout the entire nerve-trunk, extending even into the nerve-roots. (Arnold, Duchesneau.)

"*Ganglia.*—In the posterior-root ganglia, also, we find the connective-tissue elements greatly increased, so that even macroscopically the ganglia are often considerably enlarged. Microscopically the ganglionic cells are sometimes pressed upon and atrophied (Marie, Marinesco). Arnold reports that he found vacuoles in the nerve-cells. In Cases I and II of the author's, the alterations in the ganglion-cells were slight.

[21] Harlow Brooks: Archives of Neurology and Psychopathology, vol. i, No. 4, 1898, p. 592.

"It is difficult to determine whether the nerve-cell lesions are secondary, perhaps directly dependent on the connective-tissue hyperplasia about the cells and fibers, or are primarily due to defective nutrition of the ganglion-cell bodies. Perhaps these ganglionic changes are wholly, or in greater part, responsible for the degenerations and atrophies which take place in the muscles of the voluntary system.

"*Sympathetic Ganglia.*—The changes in the sympathetic ganglia and trunks have been made the subject of special study by several very prominent investigators, among whom are Marie, Marinesco, and Arnold, and have been looked upon by many as factors of an etiological nature. Finding, as we do, such pronounced change in the blood-vessels, it does not seem at all strange that lesions in the sympathetic ganglia should be present; but a view intimating a dependence or relation of the vascular changes to the lesions in the sympathetic system is not in accordance with our own ideas expressed at the close of this paragraph. In general, the changes in the sympathetic ganglia are very similar to those already described in the ganglia and trunks of the cerebro-spinal system. In some cases the size of the ganglia is considerably increased (Arnold, Marie, Marinesco), and, microscopically, the connective-tissue web is thickened and proliferating. The ganglion-cells are often reported as exhibiting evidences of degeneration." . . . "Arnold has found vacuolization; not infrequently considerable deposits of pigment are seen within the cytoplasm. But, as in Case II, the ganglion-cells may be normal; the Nissl bodies are present in normal arrangement, volume, and shape, and show no deviations in their staining reactions; and the pigmentary deposit is not abnormally abundant. The sympathetic ganglia in the case reported by Gauthier were also normal. It is advisable, at this point, to call attention to the fact that the interstitial hyperplasia is by no means a lesion characteristic of the sympathetic system, but is simply an extension of the general process so often alluded to. The growth of connective tissue in the sympathetic may depend in part on lesions in the walls of the vessels; or both may be referable to the common factor of deranged nutrition.

"*Cord and Medulla.*—The pathological findings in both

the cord and medulla differ greatly. Virchow, and also Fritsche and Klebs, have reported hypertrophy of the medulla. The spinal cord was enlarged in the case reported by Linsmayer. Many observers have reported various degenerations in the cord. Baruch's case was associated with symptoms of syringomyelia; Debierre gives a case with diseased posterior columns, while Arnold, Dallemagne, and Tamburini have found at autopsy irregular degenerated areas in the cord, affecting, however, no special place with any degree of constancy."

That the trophic changes in the nerve-tissues explain several of the neurological and myological symptoms in acromegaly is obvious, but these occur in *advanced* cases, *i.e.*, when such morbid changes have had time to occur. The signs which point to the posterior lobe as the seat of an important center—in keeping with physiological data enumerated on page 510—occur during the *early* or erethic stage, viz., the painful hyperæsthesias in the extremities, the tingling, numbness, the vasomotor neuroses and the palpitation. Their presence is explained by the marked rise of blood-pressure produced by irritation of the pituitary body proper, observed by Cyon, and confirmed by Masay, and by the long-recognized identity of the posterior pituitary as the *neural lobe, its histology and nervous connections.*

Pending additional evidence in this direction the nature of the process through which the pituitary influences the nervous system requires study.

THE HISTOLOGY AND PHYSIOLOGICAL CHEMISTRY OF THE NEURON.

We are first brought to inquire into the relationship between the modern conception of the structural composition of the cerebro-spinal axis and the views I have submitted. Granted, therefore, that the posterior pituitary body is the seat of a process through which chemical energy is converted into nervous energy, and that this constitutes the nervous impulses which the cerebro-spinal axis transmits to the various organs, how do the nerve-elements utilize this energy when functionally active?

I refer, of course, to Waldeyer's neuron as the morphological unit of the cerebro-spinal axis, and the processes of

which are not in contact, but sufficiently close, one to the other, as to make it possible, when required, for a nerve-impulse to cross the interval between them. These facts have been satisfactorily established by modern methods, especially through the labors of Golgi and Ramón y Cajal. But the manner in which the gap between the processes is closed—*i.e.*, how the impulse passes from the terminal brush of the axon of one nervous element to the dendrites of the next—is still to be determined. It has been suggested, however, that the processes behave, in a limited manner, as do the pseudopodia of the amœba, and that by a slight extension the interval between the processes is closed. When the processes are not in contact they are said to be in a state of "retraction." Much as such a function would facilitate and shorten our analytical work could incontrovertible experimental facts be adduced to sustain it, we are brought, by a review of the literature of the subject, to recognize that such facts are not available. Indeed, the majority of physiologists and neuro-histologists now consider the question of "amœboid movements of the neuron" in the light of a working hypothesis.

There is one feature of the investigations in this direction which may serve to throw more light upon the whole question if one of the more prominent deductions submitted by me in the present work is taken into consideration: *i.e.*, the fact that certain drugs cause overactivity or insufficiency of the adrenals.

Much of the physiological work done in connection with the neuron includes the administration of various toxics,—strychnine, chloroform, morphine, etc.,—and amœboid movements or other active manifestations of the protoplasmic processes are thus ascribed to the action of the drugs upon the neurons *per se,* whereas, in the light of my views, the changes of form witnessed should be ascribed to increased or reduced blood-supply when toxic doses are given. To illustrate my meaning I will give in outline an experiment which represents one of the key-stones of the entire theory, that of Demoor. Before doing this, however, it may, perhaps, be well to state that I will consider the terms *"neuron"* as applying to the complete nerve-cell, including processes; *"neuraxon"*

to the (usually) single and long process which extends along the center of the nerve-fiber, and is then called "axis-cylinder; "*dendrites*" to the cell's many processes—some of which end in many branches or tufts—other than the neuraxon. With Foster and Sherrington we will consider that neuraxons carry impulses *away* from the cell, while dendrites transmit impulses *into* the cell. Two other prominent morphological features are the "*gemmules*"—minute projections all along the dendrites—and their terminal twigs, which recall those on the stems of the moss-rose, and the *varicose*, or irregular, swellings that may be observed in the course of the dendrites or their terminal twigs.

The experiment of Demoor was briefly as follows: He *killed* a dog by injections of morphine; a second dog was given morphine for some time, then killed by cutting the medulla; a third was trephined. The next day a piece of the left hemisphere of the latter dog was removed; the animal being then morphinized, another piece—but of the right hemisphere this time—was removed. Portions of the hemispheres of the two killed dogs having also been removed, all specimens were treated in precisely the same manner. The cellular changes were found to be similar in all specimens taken from the morphinized animals: their gemmules had disappeared. Alone of the series the piece removed before morphine had been given was covered with regularly distributed gemmules. Now the fact I wish to emphasize is this: while this experiment is thought by its author to show that the retraction of the gemmules constitutes the inactive state, as induced by morphine through the *local* action this drug is now thought to have upon nerve-cells, the retraction of the gemmules is due to general vasoconstriction of all arterioles, *including those of the adrenals*, by a direct action of the morphine upon the sympathetic center. (See page 1272.) We thus have, instead of a purely local effect, an example of the general physiological process through which the neuron passes from the active to the passive state, the circulation of oxidizing substance in the neuron being thus inhibited.

Again, the same structures treated by different methods have been found to yield different results. Thus, H. H. Bawden[22] found that "all material treated according to the slow method of Golgi shows, as a rule, an almost absolute freedom from varicosities; varicose cells occasionally occur." The mixed method and the rapid were found to yield practically the same results when the dendrites had taken the stain: the gemmules were almost invariably present and regular. In some sections almost every dendrite was varicose; in others hardly any. All these results were similar whether normal or "toxic" material was used, and the author concludes that "it is impossible for an unprejudiced observer to differentiate or distinguish between the two kinds of material." Lugaro,[23] who has upheld the retraction theory, also reached the conclusion that "imperfect fixation is very largely, though not entirely, responsible for the formation of varicosities and the disappearance of gemmules." Weil and Frank summarize what a review of the literature of the subject shows, when they say: "The findings have been in almost every case positive, although there are occasionally records of negative results and even contradictions,—as, for example, between the investigations of Demoor and of Soukhanoff on the effects of chloroform. . . . Retraction of the gemmulæ and coincident swelling of the dendrites form the essential features of every description."

Judging from the foregoing estimates as to the effects of stains upon dendrites, these phenomena are to be considered as artifacts: *i.e.*, as artificially produced changes. Under these conditions, it is clear that the latter should appear, irrespective of the condition of the animal at the time of its death: *i.e.*, whether under the influence of toxics as stated, fatigue, etc.

That prevailing views in this connection are erroneous is my firm belief after a critical analysis of available experimental evidence. Particularly instructive and valuable in this connection are the experiments of H. H. Goddard,[24] which consisted "in cutting through the entire head of the animal at a single blow with a very thin sharp knife, the parts of the head falling instantly into large dishes of Cox's solution warmed

[22] H. H. Bawden: Journal of Comparative Neurology, May, 1900.
[23] Lugaro: Rivista di patol. nerv. e ment, vol. iii, 1898.
[24] H. H. Goddard: Jour. of Compar. Neurol., Nov., 1898.