pillars of the vital process itself.* By the use of strychnine, digitalis, coca, etc., we greatly stimulate functional activity, but the judicious adjunction to them of substances which actually take part in function, such as phosphorus, iron, appropriate foods, etc., we supply besides, the building material.* It is as such that phosphorus is especially beneficial in *neurasthenia* due to overwork, anxiety, mental strain and sexual excesses. Here, it actually replaces missing materials.* In *anæmia*, the addition of phosphorus to iron will render the latter effective where before it was useless, because the improvement of the oxygenizing power of the blood requires a corresponding increase of available nuclein.* In *impaired nutrition* following exhausting diseases, such as influenza, typhoid, typhus, intermittent fevers, etc., the same indication prevails. This applies likewise to debility following *prolonged lactation, overwork, shock, sorrow,* etc. In the disorders which are thought to be normal results of old age, such as *loss of memory, mental torpor, insomnia,* etc., an inadequate supply of phosphorus, iron and iodine, is the pathogenic factor, and these agents will often serve to prolong a useful life. In the depraved condition to which *morphinomania* and *chronic alcoholism* finally drive the patient, the judicious use of phosphorus after cessation of the habit is conquered, not only hastens recovery, but tends to prevent its recurrence by enhancing the nutrition and conductivity of all nerves.* Finally, the value of phosphorus in *rickets* and *osteomalacia* is generally recognized.

* *Author's conclusion.*

CHAPTER XX.

THE INTERNAL SECRETIONS IN THEIR RELATION TO PHARMACODYNAMICS (*Continued*).

THE SYMPATHETIC CENTER AS THE SLEEP CENTER.

Bradbury, in his Croonian Lecture,[1] stated eight years ago, that "notwithstanding the brilliant and laborious researches of physiologists and neurologists during recent years, the phenomenon of sleep is still enveloped in mystery"—a conclusion which is still applicable. The reason for this is plain in view of the fact pointed out by myself in the first volume, that this function is intimately connected with the circulation of oxidizing substance (adrenoxidase) *in* the neurons and their dendrites, that sleep is due to a diminution of this substance in these elements, and that the adrenal system is intimately connected with this process. To overlook this intrinsic nervous circulation and the ductless glands in this connection is to perpetuate the "mystery" to which Bradbury refers. And this applies not only to the mechanism of sleep, but also to a widespread source of suffering, insomnia, and, moreover, to the action of hypnotics and anæsthetics.

A diminution of adrenoxidase in the nervous elements referred to entails a corresponding reduction of metabolic activity and other phenomena connected therewith. Howell[2] wrote recently: "The central and most important fact of sleep is the partial or complete loss of consciousness, and this phenomenon may be referred directly to a lessened metabolic activity in the brain tissue, presumably in the cortex cerebri." Again, "the physiological oxidations are also decreased, as shown by the diminished output of carbon dioxide." A fall of blood-pressure is also present, as shown by Tarchanoff[3] in dogs and by Brush and Fayerweather[4] in man.

[1] Bradbury: Lancet, June 24, 1899.
[2] Howell: "T. B. of Physiol.," p. 238, 1905.
[3] Tarchanoff: Arch. ital. de biol., vol. xxi, p. 318, 1894.
[4] Brush and Fayerweather: Amer. Jour. of Physiol., vol. v, p. 199, 1901.

The manner in which hypometabolism produces sleep and the process through which lowered oxygenation of the cortex is produced are left unexplained by the prevailing interpretations. In the first volume, I filled both these gaps. In the first place, I showed that the adrenoxidase-laden plasma which circulates in all parts of the neuron sustained the vital process in this organ as it does in all cells,[5] and submitted the conclusion[6] that the thornlike processes which project from the dendrites[7] and other parts of a neuron, *i.e.,* the gemmules, were "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 [adrenoxidase] of the plasma, and thus to render the dendrite functionally active, *i.e.,* able to transmit or receive nervous impulses;" and also that when the gemmules are retracted or collapsed, "functional activity is in abeyance, as during *sleep,* anæsthesia, etc." Additional evidence has been submitted in the present volume as to the rôle of adrenoxidase and myelin in all nerve-cells, and to the effect that they jointly liberated nerve-energy, *i.e.,* the impulse. The manner in which sleep follows thus becomes plain: the *intrinsic* metabolism of all nervous elements, including those of the cortex, is itself reduced.

The introduction of adrenoxidase and myelin as the joint source of functional activity harmonizes with a theory to which Bradbury refers as follows: "The most fascinating of them all is what Duval has termed the histological theory of sleep: This seems to have been propounded in its most rudimentary state by Rabl-Rückhard, who suggested that an assumed amœboid motion of the neurons, and especially the dendritic processes, would account for various psychological phenomena. Thus sleep might be explained by a *retraction of these processes* and consequent *inability of nervous impulses to pass from one neuron to another.* The same theory was elaborated independently by Lépine and Duval. Lépine thinks this isolation of the individual neurons may be due to some chemical modification of the cellular protoplasm, and he also states that the theory explains the extraordinary suddenness with

[5] *Cf.* vol. i, pp. 518 to 590 incl.
[6] *Cf.* vol. i, p. 577.
[7] *Cf.* vol. i, plate opposite p. 550.

which a state of wakefulness passes into one of sleep. Duval goes so far as to explain the action of medicaments on this theory, and he draws comparisons between the action of drugs on the terminal dendritic processes and the effect of curare on motor nerve-endings. This is surely hypothetical" . . . . quite as much so, I would add, as the assumed action of curare (administered internally) on nerve-endings, as emphasized in the preceding chapter.

The manner in which adrenoxidase and myelin take part in the transmission of impulses from neuron to neuron, suggests itself when the effect of intrinsic metabolic activity on its gemmules is taken into account. Ràmon y Cajal,[8] who states that the dendrites are covered with a "protective sheath of great tenuity" (which I assimilate to the myelin sheath of nerves, and a factor in the elaboration of nervous energy as stated above), advanced the view that impulses were transmitted by the gemmules which project through this sheath. As previously stated, however, and for reasons submitted in the first volume, I ascribe a different function to these thornlike projections, viz., to extend the area of myelin exposed to the action of adrenoxidase and local metabolic activity. The structures which I regard as intermediaries for the transmission of impulses, afferent or efferent, are the tips of the dendrites and the branches (and collaterals) given off by the axons or axis-cylinders of neurons, to which Berkley[9] refers as a "bulbous ending situated upon the extremity of the finest branches of the nerve-fibers." Since he says of the latter: "The researches of Flechsig, as well as my own, have shown that these fine branches are furnished with a thin layer of myelin nearly to their termination," and as they likewise take methylene blue and other stains showing the presence of adrenoxidase, the bulbous tips referred to are, as well as those of the dendrites and their thorns or gemmules, subject to erection during activity as distinguished from rest, *i.e.,* sleep.

Now, whether with Cajal we regard the gemmules as the structures which receive impulses from these bulblike axon terminals, or with Berkley, that the latter transfer them to the

[8] Ramon y Cajal: Cited by Bradbury: *Loc. cit.*
[9] Berkley: Johns Hopkins Hosp. Reports, vol. vi, p. 89, 1897.

dendrites between the gemmules, or with me, that the bulbous tips of the dendrites (as in nerve-terminals in the Pacinian corpuscles, in the end-bulb of Krause, etc.) receive the impulses from the knobbed axon-terminals or offshoots from dendrites, the mechanism of transmission is the same, provided another conclusion embodied in the first volume (in accord with Berkley's previous observation) be accepted, namely: that these end-organs do not actually touch each other, as believed by some, but that they are separated by[10] an infinitesimal distance. Now, as I interpret the process, during active metabolism, *i.e.*, during waking hours, this infinitesimal distance is preserved, because *both dendritic and axonal terminals are erect.* The functions of the brain are active, owing to the ability of these terminals to *touch and separate with great rapidity,* i.e., *to vibrate rhythmically* according to the nature of the stimulus transmitted, whether it be connected with motility, sensibility or thought. Conversely, during lowered metabolism the bulbous terminals recede and are then separated sufficiently to prevent vibratory contact and inhibit function. Motility, sensibility and thought are then in abeyance, *i.e.*, in the state of rest or sleep.

Thus it is that lowered metabolism can, in the light of my views, produce sleep.

Another factor is required in this connection, however, to account for the mechanical erection of the gemmules and the bulbous tips, namely, an increase of blood-pressure. The anæmia of the cerebral structures observed in exposed areas and other facts have caused Howell[11] to suggest a theory which has deservedly received considerable attention, the "vasomotor" theory. The reduction of blood affords the necessary factor for the recession of the bulbous tips during sleep, and their erection during wakefulness. While he explains this phenomenon by variations in the cutaneous circulation, Leonard Hill[12] accounts for it by dilation of the vessels of the splanchnic area, a condition which, we have now seen repeatedly, causes recession of blood from the periphery—and from the brain, according to Hill. The *manner* in which this vasodilation is brought about, however, is left obscure by these investigators. And yet, a fully established factor of the problem clearly accounts for it, viz., lessened metabolic activity, which, as previously stated, affects the cardiac muscle and the vascular muscle fibers, two conditions which entail vascular relaxation.

[10] *Cf.* vol. i, p. 579.
[11] Howell: Jour. of Exper. Med., vol. ii, No. 3, 1897.
[12] Leonard Hill: "The Physiol. and Pathol. of the Cerebral Circulation," London, 1896.

That this brings the original cause of sleep down to the organs which regulate metabolism is self-evident. In the first volume, I ascribed[13] retraction of the gemmules to "suprarenal insufficiency." By stating[14] therein that "when the gemmules are retracted or collapsed, functional activity is in abeyance as during sleep . . . . ," I indicated that sleep was to be ascribed primarily to a deficiency of adrenal secretion, *i.e.*, of adrenoxidase. This relegates us to the adrenal center in the pituitary body.

Salmon has recently[15] suggested that the internal secretion of the pituitary body produces sleep. All the evidence extant indicates, however, that this organ enhances oxidation; it fails, therefore, to support such a theory. Again, I have called attention to the fact that in the higher vertebrates the pituitary body was not a secretory organ, its secretory functions having been taken up by its offshoots, the adrenals.

Quite in keeping with the prevailing knowledge concerning the rôle of hypometabolism in sleep, and my own view that *depression* (and not overactivity, as Salmon believes) of the functions of the adrenal center, is the important fact pointed out by Lorand,[16] that degeneration of the thyroid gland causes a tendency to sleep. He observed that dogs deprived of their thyroid slept almost all the time, that the loudest noises failed to awake them, and adduces other facts in support of his opinion. Recalling the researches of Magnus Levy, Thiele, Nehring and others to the effect that the thyroid gland regulates metabolism, Lorand ascribes the influence of degeneration of this organ on sleep to a corresponding depression of general metabolism. The manner in which this process is carried out is fully explained by the functions I had attributed to

[13] *Cf.* vol. i, p. 520.
[14] *Cf.* vol. i, p. 578.
[15] Salmon: Trans. 15th Congress of Intern. Med., Genoa, Oct., 1905.
[16] Lorand: Verhandl. d. Congr. Innere Med., Bd. xxii, S. 395, 1905.

the thyroid secretion in the first volume, viz., to stimulate the adrenal center of the pituitary body, and through it the adrenals, whose secretion becomes converted into adrenoxidase in the lungs. It is plain that under these conditions and as Lorand has shown, any degenerative disorder of the thyroid should depress the adrenal center, inhibit the formation of adrenoxidase and metabolism, and provoke sleep.

Interpreted from my standpoint, however, this does not represent the process which prevails in normal or *physiological* sleep. It is sleep due to a pathological condition. The thyroid, as a gland, can not be a governing organ: as is the case with the adrenals and all other glands, its secretory activity is regulated by a nerve-center.

In a preceding chapter[17] I pointed out that it was by inhibiting the functions of the pituitary body and of the thyroid gland that Cyon's depressor nerve produced general vasodilation, at first of the vessels of the splanchnic area and then the vessels of the peripheral structures. The main conditions of Howell's vasomotor theory and Hill's observations are thus met. The manner in which metabolism is depressed during sleep is now self-evident: the proportions of thyroidase, which sensitizes all cells, and of adrenoxidase, which incites and sustains metabolism, being reduced, the blood's energizing properties are brought down to the physiological limit which normal sleep requires. This entails just sufficient lowering of the blood-pressure to reduce the tension in the axons and dendrites of all neurons, not only of the cortex, but of the entire nervous system. Indeed, sleep does not mean repose of the cortex alone, but of the whole cerebro-spinal system. Goltz's dog, for instance, which lived eighteen months after its cerebrum had been removed, slept as do normal animals, even going through the preliminary circular movements peculiar to dogs.

This clearly indicates that the center which causes constriction of the vessels of the pituitary and thyroid lies below the brain, and, in the light of the evidence I have adduced, that it is to the neural lobes of the pituitary that we must ascribe this function. This organ, we have seen, sends fibers to the great-cell nucleus in the third ventricle, which nucleus,

[17] *Cf.* this volume, p. 1125.

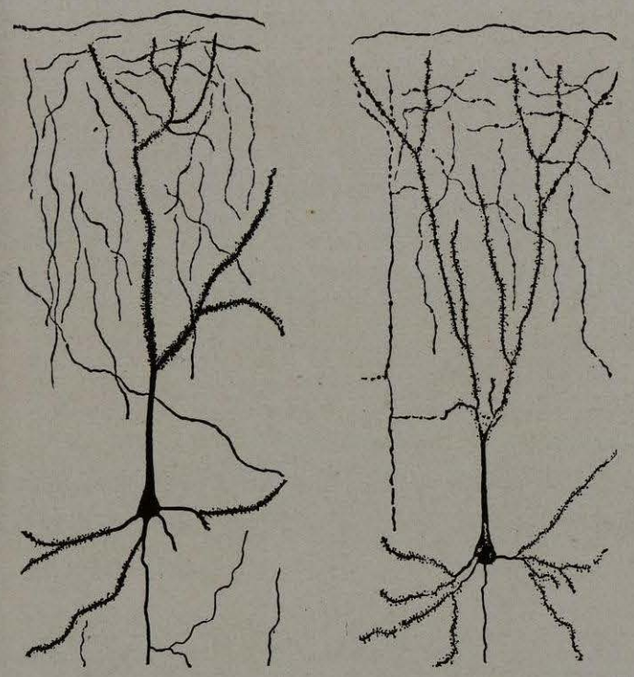

Fig. 1. *Fig. 2.*

BRAIN-CELLS OF MARMOT. FIG. 1, WHILE AWAKE; FIG. 2, WHILE ASLEEP. *[Querton.]*

Shows neuron dilated by adrenoxidase-laden plasma in Fig. 1, and the same cell depleted of plasma during sleep, in Fig. 2. (Sajous.)

in turn, sends fine fibers—those peculiar to the *sympathetic* system, as previously shown—to the medulla and cord, and to the anterior pituitary. Now Cyon found that the constrictor fibers distributed to the thyroidal arteries were derived from the cervical sympathetic; while Berkley specifies that the nervous supply of the anterior lobe is also of sympathetic origin. I have already submitted considerable evidence to the effect that the sympathetic was the vasoconstrictor of all arterioles. We are furnished here not only with additional testimony to this effect, but we are brought to realize that it is the sympathetic center in the posterior pituitary which, by inhibiting the circulation of the thyroid and of the anterior pituitary (including its test-organ and the adrenal center with which it is linked), causes sleep.

This evidence sustained by the data previously adduced seems to me to warrant the following conclusions: (1) *sleep is brought on by the sympathetic center;* (2) *by sending constrictor impulses to the arterioles of the anterior pituitary body (including its test-organ, which governs the adrenals) and also to the arterioles of the thyroid gland, this center lowers the metabolic activity of the body at large;* (3) *metabolism being also lessened in the cardiac and vascular muscular fibers, general vasodilation follows;* (4) *as this in turn entails augmentation of the blood circulating in the splanchnic area and other deep vessels, a corresponding volume of blood is withdrawn from the peripheral organs, including the cerebro-spinal system.* (5) *In the brain this lessened metabolic activity and diminution of adrenoxidase-laden plasma jointly provoke unconsciousness by inhibiting the functional activity of the neurons, which take part in all psychical processes;* (6) *in the spinal and peripheral nervous systems the same two conditions cause depression of sensibility, including that of the spinal motor cells which convert sensory impulses into motor stimuli.*

Hypnotism.—This condition is generally associated with sleep, but in the light of my views—to which only a brief allusion can be made here—it is a morbid process. Many theories have been advanced as to its nature; all, naturally, ascribing the phenomenon to some functional aberration of the cerebral cortex. That this does not account for the hypnotic state is

indicated by the fact that, as shown by Verworn,[18] animals deprived of their hemispheres can be hypnotized. Landois[19] also writes: "Hens (also after removal of the cerebrum) assume a rigid position if an object be suddenly placed in front of the eye, or a straw be placed over the beak." . . . . This rigidity occurs in the human subject, and may be brought about in many ways which affect the lower animals similarly. This indicates that it is upon structures below the brain that the hypnogenic influence is exercised.

In the first volume[20] I referred to the posterior pituitary as the *sensorium commune,* and pointed out in the preceding[21] chapter, in connection with the meaning of "idiosyncrasy," that the sympathetic center stood foremost in this connection. Considerable evidence has already shown that this center governs the caliber of the arterioles, and that marked constriction inhibits function by reducing the volume of blood distributed to the peripheral capillaries. We have seen also that their dilation reduces the blood-supply. Evidence to the effect that such a condition prevails during hypnotic sleep is afforded by the pallor of the skin and mucous membranes, and the fact, noted plethysmographically by Walden,[22] that the arm and hand show a marked diminution in volume.

If we take into account the mechanical means capable of inducing hypnosis in man and animals: fixing intently a bright object, or revolving mirrors held a short distance from the face; a sudden flash, such as that of an electric spark; a stern command to go to sleep; the noise of a gong, etc., it becomes plain that a shock, strain of the ocular muscles entailing reflex sequences, etc., underlie the genesis of the hypnotic state. Its production by pressure upon hysterogenic zones also betokens reflex action through a center capable of influencing the vessels of the body at large, and, in the light of the foregoing evidence, those vessels which influence sleep. This indicates that the most sensitive center of the posterior pituitary, *the sympathetic center, is the source of the vasomotor impulses through which hypnotism is provoked,* and that the kindred

[18] Verworn: "Die sogen. Hypnose der Thiere," 1898.
[19] Landois: *Loc. cit.*, p. 780, 1905.
[20] *Cf.* vol. i, p. 598.
[21] *Cf.* vol. i, p. 598.
[22] Walden: Amer. Jour. of Physiol., vol. iv, p. 124, 1900.

states: *somnambulism, lethargy and catalepsy, are due to a corresponding process, likewise under the influence of the sympathetic center.*

EXCESS OF ADRENOXIDASE IN NERVOUS ELEMENTS AS A CAUSE OF PAIN.

Stewart,[23] in a brief review, writes: "Pain has been defined as 'the prayer of a nerve for pure blood.' The idea is not only true as poetry, but, with certain deductions and limitations, true as physiology. That is to say, pain, as a rule, is a sign that something has gone wrong with the bodily machinery; freedom from pain is the normal state of the healthy body. Physiologically, pain acts as a danger-signal; it points out the seat of the mischief." While the latter fact is true, and it is self-evident also that pain is an abnormal phenomenon, the connection between these two facts on the one hand, and the assertion that pain is "the prayer of a nerve for pure blood," is not clear. In truth, this conception, as I view it, is a most misleading one. Even in disorders such as gout, rheumatism, neuralgia, etc., in which the pain might be ascribed to the local action of noxious substances, the administration of an analgesic, morphine, for example, will subdue or even entirely remove the pain. It is evidently not the poison which causes suffering, since the analgesic certainly does not promote its destruction or removal. The pain must be subdued through some other mechanism.

Again, as stated by Howell,[24] "pain is probably the sense that is most widely distributed in the body. It is present throughout the skin, and under certain conditions may be aroused by stimulation of sensory nerves in the various visceral regions, and indeed in all of the membranes of the body. Our knowledge of the physiological properties of the end-organs and nerves mediating this sense is chiefly limited to the skin, and for cutaneous pain at least, the evidence, as stated above, is very strongly in favor of the view that there exists a special set of fibers which have a specific energy for pain. All recent observers agree that the pain sense has a punctiform distribution in the skin, the pain-points being even more numerous than

[23] Stewart: "Manual of Physiol.," fourth edition, p. 855, 1900.
[24] Howell: *Loc. cit.*, p. 262, 1905.

the pressure-points." Briefly, pain is generated by a special neural mechanism possessing specific nerve-terminals, and occurs when, from some cause, these nerve-endings are stimulated. These causes, as is well known, are numerous, and when pain is due to traumatism, pressure, etc., it is readi y accounted for by excitation of these sensory endings and the transmission of pain-impulses to the central nervous system.

Here, however, we meet with an obstacle. How and by what organ are pain and its location perceived? Stewart states that "the precise mechanism of the localization is unknown. But," he adds, "we must *suppose* that each peripheral area is 'represented' in the brain, so that the afferent impulses from it affect particularly the related cerebral area. The brain therefore, so to speak, associates excitation of a given cerebral area with stimulation of the corresponding peripheral area, and thus not only recognizes the quality and quantity of the resultant sensation, but also localizes it." We have seen, however, that this supposition is not based upon a solid foundation. Goltz's dog, for instance,[25] which lived eighteen months after being deprived of its hemispheres, not only felt pain, but kept one of its paws, which had been hurt accidentally, raised from the ground until the injury had healed.

Referring to the same animal, Schäfer[26] writes: "It reacted promptly and consequentially to tactile impressions. When its skin was pinched it gave vent to its discomfort by snarling or barking just as a normal dog might do, and attempted to get away from the hand which was the source of discomfort, or, failing to do this, would turn round and bite at it, but in a clumsy manner and often without coming near it. If its feet were placed in cold water, they were quickly withdrawn." Again: "The rabbit, after removal of the hemispheres, in a few minutes sits up and begins to move about in an apparently normal manner. Its reflex excitability is increased. If the foot is pressed, it will kick and struggle violently." Striking in this connection is the behavior of the brainless frog. "If placed in a vessel of water the temperature of which is gradually raised," writes Ferrier,[27] "it will not

[25] *Cf.* this volume, p. 970.
[26] Schäfer: "T. B. of Physiol.," vol. ii, p. 702, 1900.
[27] Ferrier: "Functions of the Brain," second edition, p. 109, London, 1886.

quietly submit to be boiled like a frog which has only its *medulla* and *cord,* but will leap out as soon as the bath becomes uncomfortably hot."

These examples show clearly that it is not the brain which perceives pain or even its location, since, by limping on three legs, Goltz's brainless dog showed not only that it felt it, but that it located it in the raised limb. The location of the perceptive region is pointed out, moreover, by the behavior of the frog. Not any more than the hemispheres can the medulla oblongata or spinal cord be said to perceive pain, since the presence of these organs will not cause the frog to escape from the hot water; it is evidently a region *above* the medulla and *below* the brain. It is not due to the corpora striata or the optic thalami, for Schäfer, who quotes Ferrier, states that they "were included in the removal." This brings us once more to the only structure to which any such function can be attributed: the posterior pituitary. Indeed, in the sixteenth chapter[28] I submitted the conclusions, sustained by considerable evidence, that "the cortex is not the organ through which any of the cutaneous and internal sensations are perceived," and that "these sensations, which include pain, heat, cold, pressure (constituting touch), hunger, thirst, and the muscle and spatial senses, are perceived by and through the neural or posterior lobe of the pituitary."

Returning to the production of pain, we have seen that, aside from the traumatic or mechanical causes, the purity of the blood can hardly be granted the dominant position in the process that the poetical conception quoted above has earned for it. On the other hand, we have ample proof to the effect that an *excess* of blood in a given region can provoke suffering, and that its intensity varies with the degree of local congestion. Evidence to this effect need not be produced. It becomes a question whether *all pains* other than those due to traumatism are not due to local congestion. In neuralgia, for instance, even in the anæmic, pathological anatomy points to the presence of a neuritis either in the nerve itself or in the ganglion from which it originates. In *tic douloureux* such lesions are practically always found. The fact that, as I have shown, adren-

[28] *Cf.* this volume, p. 1007.