to 39° C. In his first experiment, puppies about seven weeks old, sisters from the same litter, were used, the one while somewhat tired, the other after having slept. A careful count of the pyramidal cells of the cortex of the somewhat fatigued puppy gave a proportion of 31.1 per cent. of cells showing varicosity, while cells from the same region of the puppy killed after sleeping was 8.5 per cent. In the former animal 15.9 per cent. of the cells showed much varicosity; in the latter only 0.8 per cent. showed a similar state. In the second experiment the first of two sisters was killed on waking in the morning; the second at night when tired and very sleepy. While it "was difficult to find a single varicosity on the dendrites of the morning puppy, for long distances in the cortex of the evening puppy" it was difficult to find a cell "whose processes" were "not more or less varicose." It is evident that in these instances at least the stain was not alone the source of varicosities, since it was only in the tired puppies that the varicosities were very marked, while in the thoroughly rested animal practically none could be found.

Judging from these experiments, varicosity of the dendrites coincides with a fatigued condition. This corresponds exactly with the experiment of Demoor, previously described, since retraction of the gemmules is accompanied by varicosity; so that fatigue and a large dose of morphine must have produced similar results.

If the staining process alone caused the formation of varicosities in Demoor's experiments,—the same method having been used for all specimens,—how is it that one of the latter showed gemmules (which means absence of varicosities), and that this solitary specimen is precisely from the only animal which had not received morphine? Berkley[25] found that poisoning with alcohol "in considerable doses, continued over a moderate time, will produce decided and ascertainable lesions of the nutrient structures and nervous elements of the cerebrum" very similar in character to the pathological lesions produced by other more virulent soluble poisons. The terminal twigs of the dendrites were also found to have become varicose

[25] Berkley: Brain, Winter, 1895; and Johns Hopkins Hospital Reports, vol. vi, 1897.

or beaded, the gemmules being very scarce or absent. Here, again, is a condition which, as does fatigue, morphine, and, we may add, chloroform, chloral hydrate, and other toxics used by Demoor and others with similar results, all tend in the one direction: *i.e.*, to morbidly reduce functional activity. This is a well-known characteristic of the bromides. In a study of the cortical cells under the influence of poisonous doses of potassium bromide, H. K. Wright[26] says: "If the primal ascending dendron is followed to its visible termination, several ampullous or varicose swellings of varying size are met with," . . . "on the basal processes also varicosities are to be seen; but they are small and, like those of the ascending protoplasmic process, are sharp in outline, and shorn of the lateral projections which obtain on the unaltered part of the extensions. One may be seen on each secondary branch, and ranges in size from a small and *scarcely recognizable* to a *readily obvious* swelling. None of them, however, reach the dimensions of the apical projection and its branches."

If the method of staining is the cause of all this, we are brought to the conclusion that it must be selective as to the parts of the dendrite it affects, and that only functionally-impaired cells are so affected by the stain as to show varicosities. Even then staining methods would furnish precious indications. But it seems clear to me that, while the newer chrome-silver methods still furnish imperfect pictures of the morbid alterations of the neuron, they cannot with justice be said to either cause or prevent the formation or disappearance of gemmules and varicosities; in other words, that they are not artifacts of the Golgi method. The marked tendency of the swellings to locate at the apices, and the gradual reduction of the varices as the cell-body is approached recall, on the other hand, a well-known pathological principle: *i.e.*, that the morbid effects of impaired general nutrition are first felt by terminal structures.

And the painstaking experiments of Weil and Frank do not appear to me in the least to prove their conclusions that "the varicosities must be regarded as artifacts" and that "they

[26] H. K. Wright: Brain, Summer, 1898.

depend for their presence and their amount on the form and method made use of." Demoor employed the same method in each of his *comparative* experiments and his results were not similar, the non-morphinized specimen alone differing from all others. Hubbard used the identical method in both his *comparative* experiments, and likewise obtained results which distinctly showed a marked difference between the rested and fatigued animals. In these and other experiments referred to, the pathogenic agency, including fatigue, was allowed sufficient time to produce alterations in the cortical cells, if *nutrition* has anything to do with the process.

In Weil and Frank's experiments the animals were overwhelmed by the quantity of toxic administered, and death occurred, viewed from my standpoint, by arrest of the adreno-cardiac functions, long before any *marked* action upon the cells could possibly have occurred. The doses of morphine administered were 0.38 and 0.41 gramme (6 and 7 grains), respectively, with death in 15 minutes; of strychnine nitrate, 0.018 gramme ($^1/_3$ grain), death in 20 minutes; of hypertoxic urine, 125 to 150 cubic centimeters (4 to 5 ounces), death in 15 to 25 minutes. That these are overwhelming doses in rabbits is evident. One animal was killed with serum (30 cubic centimeters—1 ounce) in 5 minutes; others with clhoroform inhalations in 10 minutes; one by tracheal clamping in 8 minutes. The rest, six animals, were destroyed instantly by instrumental procedures. In none of these animals was there any distinction established as to whether they had been sleeping, eating, or romping, etc. That some were old and others young in the series of nineteen is probable; as is well known, erethism, especially in such delicate structures, is greatly influenced by age, and a few months in the rabbit represent as many decades in man. The weight of each animal was not recorded in order to establish the relative action of a given dose of the toxic used per pound of animal, though, of course, in the experiments, the large doses used precluded any usefulness on this score.

Finally, the authors themselves will surely admit that "no varicosities," "varicosities," "slightly varicose," and "very slightly varicose," the method of notation utilized by them,

conveys but little exact information. And still, even this sustains a deduction opposite to theirs. Indeed, the short period of time that elapsed between the injection of the toxics in the animals killed in this manner—represented by 108 blocks of slides—must have sufficed to initiate retraction of the gemmules and the formation of varicosities, since only 10.2 per cent. of these blocks show no varicosities. When, on the other hand, the proportion of animals killed instantly by instrumental procedures—93 blocks of slides—is analyzed, over two and a half times as many, *i.e.*, 28 per cent., are found to show *no* varicosities.

But a fair question suggests itself in this connection: Why do the remaining 72 per cent. show any varicosities? Only 14 per cent. of the blocks from the instantly killed animals are recorded as "varicose," the remaining 58 per cent. being entered as "slightly" or "very slightly" varicose. In their explanation of the scope given these terms, the first means "at least some varicosities" and the second as "only very few varicosities." Now, the authors state that "in the first nine cases here recorded the brains were placed in fixing fluids within three to five minutes." Nothing is said of the rest; so that we may infer that the ten other brains were immersed after longer intervals. We have previously seen, when the conversion of myosinogen into myosin was studied, that oxidation processes continued even after death: *i.e.*, until all the oxygen had been utilized. That this must be the case with the brain, which contains one-fifth of the blood of the whole body, and that products of metabolism, especially CO_2, should form in the entire encephalon is evident. It normally follows that we have in this factor a potent cause for the retraction of gemmules and the formation of varicosities.

Indeed, the contrast between the results reached speaks for itself when compared to those of Goddard, who resorted to procedures in which the exact condition at the instant of death were preserved, "the parts of the head falling *instantly* into large culture dishes warmed to 39° C." Even continuation of the normal brain temperature was insured. And what were Goddard's results? "It was difficult to find a single varicosity on the dendrites of the morning puppy,"—*i.e.*, the thoroughly *rested* animal; while in the thoroughly *tired* one "for long distances in the cortex . . . it is difficult to find a cell whose processes are not more or less varicose." That fatigue is the result of an accumulation of products of metabolism and especially CO_2 is generally recognized.

Goddard's procedure appears to me to represent as nearly perfect a one as available staining methods (Cox's and the rapid method show considerable parallelism in Weil and Frank's report, while the mixed and slow methods appear unreliable and contradictory) will allow; *his results, in my opinion, portray the actual changes that are produced in the neuron under the influence of certain poisons and during sleep:* i.e., *when the blood-supply of the brain is reduced.*[27] (See plate p. 1264).

Weil and Frank state that they "are able fully to corroborate the statement of Cajal that normal and toxic material cannot be differentiated by the number of varicosities or of gemmules." The care with which such experiments must be conducted, apart from the method of staining adopted; the need of immediate immersion, and other details to which we have referred, invalidate any opinion that the distinguished Spanish histologist may have expressed on this score, unless he can show that his experimental *physiological* procedures were as perfect as his staining work must have been. Indeed, I must express the belief that the greater part of the physio-histological work done so far in this connection is valueless owing to the absence of the precautions to which I refer.

Again, Ramón y Cajal's conclusions that "the nerve-cells do not move, but on the other hand, that the neuroglia-cells do move" (which underlies his view as to the gemmules and varicosities showing no difference when normal or "toxic"), has been shown by Dercum to embody its own refutation. "Cajal," says the latter author, "points out the fact that the processes of the neuroglia-cells have numerous short arbores-

[27] We wish to particularly emphasize the fact that we are in no way criticis- ing adversely the work of Drs. Weil and Frank. We have nothing but praise to express for these investigators. Much of the searching inquiry to which we are submitting their paper includes the use of features introduced for the first time in the present work, and obviously unknown to them. Indeed, if our views eventually prove to be sound, we will owe much to the counter-evidence Drs. Weil and Frank—and, we may add, Dr. H. Heath Bawden—have published.—S.

cent and plumed collaterals, and he states that in these cells two different phases can be observed: first, a stage of contraction,—that is, a stage in which the cell-processes become shortened; and, secondly, a stage in which the cell is relaxed,—that is, a stage in which the processes of the neuroglia-cells are elongated. He maintains that the processes of the neuroglia-cells represent an insulating and non-conducting material, and that during the stage of relaxation these processes penetrate between the arborizations of the nerve-cells and their protoplasmic processes, and so make difficult or impossible the passage of the nerve-currents; on the other hand, in the stage of contraction the processes of the neuroglia-cells are retracted, and they no longer separate the processes of the nerve-cells, and the latter are thus *permitted to come into contact.*[28] Evidently Ramón y Cajal admits the very thing against which he contends, for if the nerve-cell processes are at one time not in contact and at another are in contact, they must certainly move, and the question before us is self-admitted. It matters not whether the processes of the nerve-cells move little or much, but that they move at all is the question at issue, and this Ramón y Cajal admits, though he makes the movement a purely passive one."[29] To me it appears clear that, since Ramón y Cajal held the nerve-cell to be a passive structure, requiring an independent connecting-link to close the circuit with the adjoinng cell, he must have denied both the gemmules and the varicosities any physiological importance. His opinion, therefore, that normal material cannot be differentiated from toxic material, when applied to the retraction of gemmules and the formation of varicosities, cannot be said to rest upon solid premises, and, for the time being at least, to in no wise affect the question.

In a comprehensive review of the anatomy and physiology of the nervous system, L. F. Barker[30] makes the following remarks: "The physiologist of the present day sees in the func-

[28] We will see farther on that Cajal's observation as to the relaxation and contraction of neuroglia-cell processes is valuable in that it proves that the tips of the gemmules do not transmit nervous energy.—S.

[29] Dercum: University Medical Magazine, April, 1897.

[30] L. F. Barker: New York Medical Journal, May 15 *et seq.*, 1897-98.

tions of the nervous system, even in those which are most complicated, only certain manifestations of energy. Moreover, he believes that in neurons, as in all other cells of the body and as in the world generally, the law of the conservation of energy during transformation holds, and consequently regards the phenomena of irritability, as exhibited by a neuron or by groups of neurons, as the kinetic representative of the potential forces of the cells and their foodstuffs. The metabolic activities and the vital manifestations of the cell are concomitant processes—another example of the inseparable connection which exists between what we term matter and energy. There has been in many quarters a certain amount of hesitancy in accepting the view that the capacities of the nervous system, particularly those of the brain, are dependent directly upon the chemical and physical alterations which are continually going on within its constituents: a hesitancy which, though it has in the past proved a serious obstacle to progress, is happily now fast disappearing. For the plant, all the evidence goes to prove that under the influence of sunlight and heat marked chemical and physical changes take place within it which we recognize in its vital processes. In the animal—be it granivorous, carnivorous, or, like man, omnivorous—it is the chemical energy introduced as food which represents, in the main, the source of the energy of the organism. . . . *The physiologists have been struggling for fifty years or more to gain an insight into the nature of what they call nerve-impulses,* by which is to be understood the occurrences inside axons: for example, at the time when we have good reason to believe that they are functionally extraordinarily active. Their efforts have supplied us with a multitude of data, physical and chemical, interesting enough, no doubt, but which can serve as only the barest prolegomena to an explanation of the essence of the occurrences. If we are so badly informed concerning these elementary and fundamental phenomena we may very well be content to be modest for some time to come in our claims as regards a physiological psychology. It is by no means impossible that in the nervous system forms of energy are concerned which do not exist outside the animal body and which yet remain to be recognized and studied. . . .

Truly, to find out the properties of a single neuron would be a task appalling enough; but, when we remember that of the millions of neurons in one individual perhaps no two are just alike, the quest would seem hopeless. But instead of burying ourselves in pessimistic reflections, or being discouraged by what is at present unattainable, by what may perhaps forever remain to us unknowable, we may profitably turn to the consideration of some of the points which lie more within our ken. One point, self-evident enough when one's attention is directed to it, but which often appears to have been overlooked in connection with the neurons, is the unremitting character of their activity. With a metabolism as complicated as that occurring within the nerve-units it is inconceivable that there can be any period in which alterations in chemical structure, and consequently energy transformation, are not going on. From moment to moment, throughout all the hours of the day and night, analytical and synthetic processes are taking place, associated with the alterations in physical forces which necessarily accompany these changes. In common with everything that lives, the neurons know no absolute repose. As I have said, in speaking of their metabolism, periods of extravagant activity may alternate with periods of more economic change, but total rest is inconsonant with continuance of existence. We are forced to believe that what we ordinarily speak of as the passage of a nerve-impulse represents, as it were, *a stormy process in the nerve-fiber,* and that just as absence of a storm does not mean absence of weather, there are in all probability minor alterations—currents, if you will—passing to or fro or *passing to and fro in a given nerve-fiber in the intervals* between the more violent excitations."

The words that I have italicized will doubtless recall some of the more prominent features previously emphasized in respect to the relative nervous processes involved in the functions of the various organs reviewed. I have termed "passive" that form of energy continuously transmitted to tissues and vessel-walls. A quiet and steady flow of blood into the cellular structures, sustained by the tonic contraction of the arteries, and a stream of nervous impulses to the tissues coinciding in rhythm, perhaps, with that sent to the vessels, suffice to insure nutrition and to hold the structures thus supplied ready for active work. What is the source of *this* energy?

If the posterior pituitary reinforces the flux of impulses when functional activity is demanded, passive energy would seem to require another source, and as the lower, or middle, brain and the cord are included in the "sphere of influence" of this organ, the hemispheres are the only parts of the encephalon that can supply the need. But they do not. Removal of the hemispheres, we have seen, does not impair muscular activity; a frog can jump, a pigeon can fly, etc., and, after a short period of shock-paralysis immediately after the operations, movements return—evidence that their nutritional metabolism, incited and regulated by nervous impulses, continues. Evidently, therefore, the hemispheres have nothing to do with the process; they are solely the seat of the "mind," and constitute an organ among the rest, itself supplied with vasomotor nerves (Obersteiner, Gulland, Huber, Hürthle, Cavazzani, François-Franck, *et al.*), and probably with its own nutritional nerve-system. We are, therefore, brought back to the posterior pituitary as the only organ capable of satisfying the needs of the situation: *i.e.*, as the only source of passive energy.

This suggests that metabolism may suffice, through the agency of the blood's oxidizing substance, to sustain physiological activity during the intervals between "stormy processes of the nerve-fiber"; but this is promptly shown to be a wrong interpretation when the effects of section below the medulla are recalled. As all the arteries of the organism are immediately relaxed, a continuous stream of impulses must have served to hold the vessels in tonic contraction: evidence that passive nervous energy is a factor to be reckoned with. Thus, the fact that all co-ordinated muscular movements continue after removal of the hemispheres relegates to the lower brain the function of supplying active energy—and, obviously, passive energy likewise, the need of the latter being shown by division of the medulla. Indeed, *passive* energy may well be described as passing to and fro in a given nerve-fiber in the intervals between the more violent excitations, while *active* energy can as fittingly be likened to "a stormy process in the nerve-fiber": both ascribable, it now seems likely, to the one organ, the posterior pituitary body.

To establish the functions of the posterior pituitary within its proper physiological limits, however, it is necessary to ascertain how nervous elements in general and neurons in particular are nourished, since it is upon the degree of perfection with which the nutritive processes are carried on by the blood that the functional integrity of these structures depends.

The fact that a *general* nutritional process prevails, of which the adrenal system is the primary motive agency, I have shown; but it finds further support in the following statements of Professor Barker's—which, of course, but emphasize a generally known fact—that, "in the absence of substances in the body derived from the thyroid gland, the nervous system undergoes very important and serious metabolic modifications, evidenced by the remarkable nervous and mental phenomena with which all are now familiar. On restoring these substances to the body by the administration of a thyroid extract the symptoms may sometimes be made to disappear. It is likely, however, that the neurons find their staple foods in the main nutritive constituents of the blood as derived from the food digested in the stomach and intestines and purified by the lymph-glands and liver."

I have, I believe, satisfactorily shown that the thyroid secretion incidentally sustains the activity of the anterior pituitary body, and therefore of the entire adrenal system, by pouring its secretion into the blood. The functions of the digestive organs we have also reviewed. Among the latter, however, are two upon which I laid considerable stress,—*i.e.*, the spleen and pancreas,—and I called attention to the great importance of trypsin—the splenopancreatic ferment—in the conversion of albuminoid substances, and especially of their toxic derivatives, into benign products. These albuminoid substances, we have seen, then pass through the liver, and, after traversing the cardiopulmonary circuit are distributed broadcast throughout the organism. There is a feature which I kept in abeyance, however,—though a well-known one,—since at the time its true weight would not have asserted itself: *i.e.*, the fact that *albuminoids include nucleins derived from the animal and vegetable* *cells ingested with food, which nucleins contain at least 3 per cent. of phosphorus.* We can now realize how great is the physiological rôle of the pancreas and of the spleen in the organism.

Indeed, the functions of these two organs may be said to constitute one of the pillars upon which the vital functions rest. As a constituent of calcium phosphate, phosphorus is found in the bones, teeth, cartilage, and other tissues; in the blood, milk, etc., in quantities which bespeak of its functional prominence, since calcium phosphate is represented by nearly six *pounds* among the organism's constituents. Sodium phosphate—which gives the blood, lymph, and other body-fluids their alkalinity and fluidity, and the potassium and magnesium phosphates, which fulfill much the same rôle, obviously find in phosphorus their main dynamic attributes. But it is when we reach the nervous system that the functional worth of this element reaches its highest mark.

How are nervous structures—neurons, axis-cylinders, sheaths, etc.—adequately supplied with blood-plasma, their oxidizing substance, their phosphorus, etc.?

THE PHYSIOLOGICAL CHEMISTRY OF NERVES.—The functions of myelin, or white substance of Schwann—a jelly-like homogeneous and transparent material which surrounds the axis-cylinder of nerves, and is only separated from it by a thin protoplasmic film—may be said to be unknown. It is a fatty substance, blackened by osmic acid, and which, after death, coagulates and becomes opaque, loses its homogeneity, etc. Myelin is now universally considered as a protective coat: a function which the overlying neurilemma already fulfills. Is myelin fatty in the true sense of the word? Examined chemically in quantities, a very large proportion of dried nerve-substance—about one-half, according to some observers—consists of a peculiar body: *cholesterin.* This body is not a fat, but an alcohol; like glycerin, however, which is also an alcohol, it forms compounds with fatty acids. "Though we do not know definitely the chemical condition in which cholesterin exists during life in the medulla," says Professor Foster, "it is more than probable that it exists in some combination with some of the really fatty bodies also present in the medulla, and not in a free isolated state." . . . "Besides cholesterin, 'white' nervous matter contains a less, but still considerable, quantity of complex fat whose nature is disputed. According to some authorities rather less than half this complex fat consists of a peculiar body, *lecithin,* which we have already seen to be present also in blood-corpuscles and in muscle. Lecithin contains the radical of stearic acid (or of oleic, or of palmitic acid), associated, not—as in ordinary fats—with simple glycerin, but with the more complex glycerin-phosphoric acid, and further combined with a nitrogenous body, *neurin,* an ammonia compound of some considerable complexity; it is therefore of remarkable nature, since, though a fat, it contains both nitrogen and phosphorus." Cholesterin ($C_{26}H_{44}O$), lecithin ($C_{44}H_{90}NPO_9$), and neurin ($C_5H_{15}NO_2$), as shown by the formulæ, are all oxygen-containing bodies. May this supposed coating and insolating material, myelin, not be to the nerve what myosinogen is to muscle?

Cholesterin, we have seen, is associated with hepatic functions. "It is singular," says Professor Foster, "that, besides being present in such large quantities in nervous tissue, and to a small extent in other tissues and in blood, cholesterin is a normal constituent of bile." I have previously referred to the fact that this alcohol, the only one which occurs in the body in a free state, combines with glycocholic acid in the formation of bile, and is thus eliminated by the liver. This view sustains that of Austin Flint, who looked upon cholesterin as an excrementitious product derived from the nervous system: *i.e.,* the result of nerve-metabolism. Cholesterin is present in abundance in the white substance of the cerebro-spinal axis, as well as in the myelin, or white substance of Schwann, in nerves. We have seen, however, that the elimination of excrementitious products by the liver is carried out by the combination of various agencies: mainly glycocholic and taurocholic acids derived from cholic acid through an oxidation process in which the oxidizing substance plays the predominating rôle. That an oxidation process also occurs in a nerve during functional activity is suggested by the following lines of Mathias Duval: "Direct experimentation has shown that the functionating nerve is the seat of *increased combustion;* this