functions I have attributed to nuclein and adrenoxidase had all the same general trend, *viz.*, to convert the dead proteid molecule received as food, into living proteid; to maintain its life as long as it was useful to the cell; to break it down when worn and convert it into eliminable waste-products. In brief, the proteid molecule is that *acted upon* in all phases of the vital cycle and essentially, therefore, the focus of vital activity.*

The supply of proteid corresponds quantitatively, of course, with that of the nucleo-proteid granules. There is a suggestive contrast, however, between the nucleus and the rest of the cell, "the former," as stated by Wilson,[193] being characterized by an abundance of nuclein, while the cell-body "is especially rich in proteids and related substances (nucleo-albumins, albumins, globulins and others)." The predilection of the nucleus for a substance "rich in phosphorus" such as nuclein is accounted for by the nature of its function. As pointed out by Claude Bernard, it is "an apparatus for organic synthesis, an instrument calculated to produce, and is the germ of the cell." It receives materials, therefore, and adjusts their components to the needs of the latter.

The evidence so far adduced provides only for a promiscuous distribution to the cell in general of leucocyte granulations and adrenoxidase. How does the nucleus acquire its surplus of nuclein?

That nuclei are mobile in the cell-body has been noted by various investigators. Korschelt observed, moreover, that "there is a definite correlation, on the one hand, between the *position* of the nucleus and the *source* of food supply, on the other hand between the size of the nucleus and the extent of its surface and the elaboration of material by the cell," meaning by the latter its secretory activity. He gives as examples

* The meaning of "proteid," in the light of my views, is that usually attributed to the common proteids, *i.e.*, those that contain carbon, hydrogen, nitrogen, oxygen and sulphur. Although globulins are classed among proteids, because they give some of the reactions peculiar to the latter, their function differs totally from that of common proteid in the cell, including as they do adrenoxidase. Even more confusing, from my standpoint, is to include nucleo-proteid among the proteids, since its nuclein, as do its proteid and adrenoxidase, fulfills an autonomous rôle. The fact also that plasmatic albumins do not, as now believed, supply nutrient materials to the cells—a rôle that I attribute entirely to leucocyte granulations—also imposes the need of a new classification of proteids, since the plasmatic proteids—fibrinogen, for instance—apart from the globulins, are concerned only with the blood's intrinsic functions, coagulation, the maintenance of its own heat, etc.—S.

[193] Wilson: *Loc. cit.*, p. 17.

the silk-glands of various lepidopterous larvæ (Meckel, Zaddach, etc.). "Here," writes Wilson,[194] who cites Korschelt, "the nucleus forms a labyrinthine network by which its surface is brought to a maximum, pointing to an *active exchange* of material between *nucleus* and *cytoplasm*." Again, "in many of the insects," examples of which are given, "the egg-nucleus at first occupies a central position, but as the egg begins to grow, it moves to the periphery on the side turned toward the nutritive cell." By the latter is meant the "*nurse-cell*" which accompanies developing ova in various insects, including certain butterflies, worms, ear-wigs, etc. The nutriment is evidently transferred from the nutritive cell to that nourished, and in the form of granules. Thus, Wilson writes, referring to the eggs of the water-beetle *Dysticus*, in which Korschelt was able to observe the movements and changes of form in the living object: "The eggs here lie in a single series alternating with chambers of nutritive cells. The latter contain granules which are believed by Korschelt to pass *into the egg*, perhaps bodily, perhaps by dissolving and entering in a liquid form. At all events, the egg contains accumulations of *similar granules* which extend inwards in dense masses from the nutritive cells to the germinal vesicle, which they may more or less completely surround." . . . . "The granules could not be traced into the nucleus, but the latter grows rapidly during these changes, proving," says Wilson, "that matter must be absorbed by it, probably in liquid form."

This affords tangible evidence in several directions, (1) that a cell may be nourished by another, and, therefore, that leucocytes can serve as nurse-cells—as they do, we have seen, in *Spongilla;* (2) that the food may be transferred in the form of granules, some, perhaps, in liquid form; (3) that a nucleus is a mobile structure; (4) that it adjusts its position to the source of the food supply; (5) that it is able as an autonomous body to ingest materials suitable for its own nutrition and growth; and (6) that it can transfer materials to the cytoplasm.

The manner in which the nucleus acquires its abundance of nuclein now suggests itself: The nucleus moves wherever granules derived from leucocytes are most prolific, and when

[194] Wilson: *Loc. cit.*, p. 254.

supplied according to its needs, it moves away. Thus, Haberlandt[195] noted that in plants, growth in any part of a cell was always preceded by "a movement of the nucleus to the point of growth," and that after the process was terminated "the nucleus often moves into another part of the cell." That granules may thus enter the nucleus is shown by the fact that bacteria may be drawn into the nucleus of phagocytes as observed by Bail.[196] The same mechanism applies to the adrenoxidase, *i.e.*, the oxychromatin, which, as shown by Heidenhain and others, is also present in the nucleus. Here, the nucleus has merely to move in the part of the cell nearest the capillary from which the latter receives its blood-plasma, to receive, if its functions require it, an unusual supply of adrenoxidase droplets, which, as we have seen, are to be found in the pericellular capillaries.

There is evidently a close functional relationship between the nucleus and the cytoplasm. When a portion of the latter is cut off from the part of the cell containing the nucleus, it may live for a while and move about normally; but, as Wilson says: "Such a mass of protoplasm is, however, devoid of powers of assimilation, growth and repair, and sooner or later, dies." Inasmuch as we have seen in the preceding section that the cytoplasm contained a close network regarded by many investigators as the *living* portion of the cell, it follows that it must be the nucleus which supplies the cell with its *papulum vitæ*. This is sustained by the fact that, as also shown, the network of cytoreticulum is composed of adrenoxidase droplets. It is evidently this substance which the nucleus deals out to the cytoplasm according to its needs.

The manner in which it does so was analyzed in the first volume.[197] I suggested therein that the so-called "nuclear membrane" was in reality a cavity that contained the substance which, though derived from the nucleus, was projected into the body of the cell, and formed its network, its staining properties (iron-hæmatoxylin) being similar to those of the network. Although the function of this "membrane" has remained unknown, the data recorded sustain my interpretation.

[195] Haberlandt: Cited by Wilson, *loc. cit.*, p. 252.
[196] Bail: Berl. klin. Woch., Oct. 11, S. 887, 1897.
[197] *Cf.* vol. i, p. 654.

Thus, both Klein and Van Beneden consider it as similar in structure to the network, while Reinke[198] found that it consisted of "oxychromatin granules like those of the linin network"—a nuclear structure. As oxychromatin is adrenoxidase, the nuclear linin, the "nuclear membrane" and the network of the cytoplasm are all composed of adrenoxidase. This is further confirmed by the fact that in Gulland's plate[199] all three structures are shown to have taken methylene-blue. The rôle of the nucleus in the process now seems clear: It utilizes what adrenoxidase it requires for its own use and feeds the rest into the "nuclear membrane"—the perinuclear vacuole, as I have termed it—whence it is projected into the cytoplasm to form the network. Each thread of this network, according to Van Beneden, Wilson and others, is composed "of a single series of microsomes, like a string of beads." As Hammarsten[200] refers to blood-platelets as "pale, colorless, gummy disks," it could be considered as a string of adrenoxidase disks.

Although the network of the cytoplasm is a living structure, its identity as adrenoxidase accounts only in part for this fact, since its properties, those of a catalytic and oxidizing substance, become manifest, in their relation to the vital process, only when nucleo-proteid is present. Since, as we have seen, nucleo-proteid granulations penetrate directly into the cytoplasm, this feature is also met. Still, how are the adrenoxidase droplets of the network and the nucleo-proteid granules of the cytoplasm brought into contact?

We have repeatedly seen that their mutual affinity is very great. So marked is it, in fact, that the blood-plates have been found combined with nuclein in shed blood. Indeed, they jointly subserve two important functions in this fluid as I have pointed out in the first volume:[201] the maintenance of the blood's temperature to its physiological needs; and fibrin coagulation, adrenoxidase being, we have seen, the fibrin-ferment. During life the blood-platelets and the nucleo-proteid granules are dealt out by their respective cells, the red corpuscles and the leucocytes, as needed by the blood and are promptly dis-

[198] Reinke: Cited by Wilson, *Loc. cit.*, p. 28.
[199] Gulland: *Loc. cit.*
[200] Hammarsten: *Loc. cit.*, p. 186.
[201] *Cf.* vol. i, p. 688 *et seq.*, in the first three editions.

solved. After death, however, or in shed blood, this stage is not reached and the platelets are found either in their normal state (Bizzorero, Hayem, etc.), or in combination with nuclein (Kossel, Lilienfeld, etc.), and called, therefore, "nuclein plates," the latter, though abnormal entities, standing as proof of the mutual affinity of their components. This explains the presence of the close-meshed network in the cytoplasm and also its vital activity, since the affinity of its adrenoxidase for nucleo-proteid causes the granules of the latter to be drawn to the network at once on reaching the periphery of the cell.

Various phenomena that have remained unexplained now appear as normal consequences of the presence of these two bodies in the cell, both nucleus and cytoplasm. Alluding to the labors of van Beneden, Heidenhain, Reinke and Schloter and to his own investigations, Wilson writes[202] in respect to the two kinds of granules: "These two forms graduate into one another." Referring to the nucleus he says: "The chromatic substance is known to undergo very great changes in staining capacity at different periods in the life of the nucleus and is known to vary greatly in bulk." Again,[203] he quotes Heidenhain's statement based on results obtained by physiological chemists and by himself: "Basichromatin and oxychromatin are by no means to be regarded as permanent unchangeable bodies, but may change their color reactions by combining with or giving off phosphorus."

The intracellular process is clearly discernible in the light of these observations: A constant reaction between adrenoxidase and nucleo-proteid granules is going on, the oxygen of the former and the phosphorus of the latter combining incessantly to liberate that heat energy which, as will be shown, is a necessary feature of the life of the cell, or rather, the life of its *proteid*.

How does this apply to the nerve-cell?

We have seen[204] that—from my standpoint—the neuron is not a mere cell, but an organ composed itself of nerve-cells, and that these nerve-cells, as far as the nerve proper is concerned, are the internodal segments—the portions of the nerve

[202] Wilson: *Loc. cit.*, p. 223.
[203] Wilson: *Loc. cit.*, p. 224.
[204] *Cf.* this vol., p. 915 *et seq.*

extending between the nodes of Ranvier. Each of these segments is supplied, like all other cells, with its nucleus, located in the *myelin,* which corresponds, therefore, with the cytoplasm of ordinary cells. This suggests that the myelin must be the seat of the metabolic processes previously referred to. I have not only pointed out that the myelin is not a mere insulating substance, as now taught, but we have seen also that it is capable alone, and before the axis-cylinder is developed in regenerative processes, of transmitting nerve-impulses. Moreover, as stated by Sherrington,[205] "the date at which a nerve fiber completes its development, by acquiring a myelin sheath, indicates the time at which it becomes functionally active." As I interpret this fact, pointed out by Flechsig, it emphasizes the cardinal rôle the myelin plays in the production of the nerve impulse.

A question imposes itself in this connection: How, under these conditions, can "non-medullated" nerves, the fibers of Remak, generate or transmit impulses? Various authorities have held that these diminutive fibers are supplied with myelin as well as the "medullated" nerves. Boveri's[206] researches led him to conclude that they differed in no way from the latter, the axis-cylinder of the fibers of Remak being surrounded by a nucleated myelin sheath. Tuckett,[207] in a comprehensive study of the literature of the subject and after personal investigations, also concludes that "fibers of Remak consist of a nucleated sheath enclosing a core," and refers to the opinion of Ranvier,[208] Axel Key and Retzius,[209] Schiefferdecker[210] and Kölliker[211] that this core or axis-cylinder is composed of bundles of fine fibrils—a view now generally accepted. Moreover, it stains with methylene-blue and acid fuchsin, showing the presence of oxychromatin, *i.e.*, adrenoxidase, and is repeatedly referred to by Tuckett as "granular," though he ascribes this to the action of the stains. It is apparent, therefore, that all nerves have a similar structure, and that the gray color of

[205] Sherrington: Schäfer's "T. B. of Physiol.," vol. ii, p. 792, 1900.
[206] Boveri: Abhand. d. k. bayerisch Akad. d. Wissenschaften zu München, Bd. xv, S. 480, 1885.
[207] Tuckett: Jour. of Physiol., vol. xix, p. 267, 1895-1896.
[208] Ranvier: "Traité technique d'histologie," p. 746, 1875.
[209] Axel Key and Retzius: "Studien in d. Anat. d. Nervens u. d. Bindegew," Bd. ii, S. 159, 1876.
[210] Schiefferdecker: Archiv f. mik. Anat., Bd. xxx, S. 435, 1887.
[211] Kölliker: "Handb. der Gewebel. des Menschen," Bd. ii, S. 30, 1893.

the so-called "non-medullated" fibers is due merely to the fact that their myelin coat is thinner than that of larger nerves.

We have seen that in keeping with all other organs, a neuron is supplied with adrenoxidase, that this substance penetrates into its cell-body through the neuro-fibrils which enter the dendrites, and that they form a very fine network, especially dense around the nucleus. Now, this network is also termed the "cytoreticulum," and, as it takes methylene-blue, it is doubtless the homologue of the network common to all cells. As such, therefore, it is the living portion of the cell in the sense that, being immersed in the cytoplasm or ground-substance, it finds therein and, as in other cells, combines with the nucleo-proteid granules—an important constituent of nervous matter, as we have seen.[212]

Nervous substance contains various bodies which, until recently, were thought to be specific to this substance, viz., the phosphorized fats, which include myelin, protagon, lecithin, etc. Waldemar Koch,[213] however, has found them in other forms of protoplasm, including yeast cells, thus showing that nervous tissue differs only from all other tissues, in that it contains a larger proportion of these bodies. Their rôle is practically unknown. Thus, Halliburton[214] writes: "We know little of these substances from the chemical standpoint, and still less from the physiological." He also says, however,[215] referring to the "long list of substances to consider," and especially to extractives: "We can surmise that they are mostly waste products, as they are elsewhere." This coincides with the conclusion that my views suggest. Indeed, the substances that are brought to nerve-cells by leucocytes are, as elsewhere, proteids, sugars and fats. The proteid (nucleo-proteid) wastes are undoubtedly present: thus, as stated by Halliburton, small quantities of xanthin, hypoxanthin, lactic acid, uric acid and urea have been identified. The *fats* are represented by lecithin, which, in turn, yields fatty acid and glycerine, phosphoric acid and cholin. The *sugars* also appear in the form of galactose, obtained from the cerebrins, etc.

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[212] *Cf.* this vol., p 914.
[213] Waldemar Koch: "Decen. Publications of Chicago Univ.," vol. x, 1902.
[214] Halliburton: "Biochemistry of Muscle and Nerve," p. 68, 1904.
[215] Halliburton: *Ibid.*, p. 61.

All this suggests that the nerve-cell is not so complex a structure as it is now thought to be. Waldemar Koch,[216] in a searching analysis of the question, was led to conclude that "cortical gray matter, free from white fibers, besides containing no cerebrins, also contains no neurokeratin, cholesterin and kephalin or myelin. Gray matter, therefore," adds the author, "has a very simple composition, consisting of a mass of proteids, lecithin and the sulphur compound." As lecithin is a waste product, the constituents are further reduced to the proteids and the sulphur compound.

Now, these bodies include the nucleo-proteid and adrenoxidase we have found in all cells. By "proteids" Koch means Halliburton's three proteids.[217] Two of these are globulins, *i.e.*, fibrinogen (*extra corpore*) compounds. Referring to the third, however, Halliburton states that it is "a nucleo-proteid" which "contains 0.5 per cent. of phosphorus" and "coagulated by heat at 56 to 60°," the identical nucleo-proteid, in other words, that we have found in all tissues. The identity of the sulphur compound suggests itself after the data submitted when the relationship of the adrenal secretion to bronzing was studied. I then showed[218] that sulphur was a constituent of this secretion and therefore of the adrenoxidase circulating in the tissues at large—including, of course, the nervous tissues. Gamgee, in fact, says, referring to hæmoglobin, that "sulphur belongs to the albuminous part of the molecule"—the adrenoxidase—and the presence of this element indicates that "hæmoglobin belongs to the proteid compounds." (Halliburton[219]). The presence of the sulphur compound to which Waldemar Koch refers affords additional proof, therefore, to the effect that adrenoxidase circulates in the nervous system as elsewhere.

We are thus brought to the conclusion that the only appreciable difference between the nerve-cell and all other cells is the presence in the former of a larger proportion of fat. The nucleus contains a network which reacts to stains as does that of cells in general. The cytoplasm shows the same corre-

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[216] Waldemar Koch: Amer. Jour. of Physiol., vol. xi, p. 303, 1904.
[217] Halliburton: *Loc. cit.*, p. 63, 1904.
[218] *Cf.* this vol., p. 835.
[219] Halliburton: Schäfer's "T. B. of Physiol.," vol. i, p. 27, 1898.

spondence. The Nissl granules, which break down into fine dust in chromatolysis, are the homologues of the microsomes we have found in all cells; Halliburton says, in fact, that "microchemical methods have shown that they consist of nucleo-proteid."

The manner in which plasmatic adrenoxidase is supplied to a neuron is characteristic in that (interpreted from my standpoint) it is brought to them by minute capillaries, the neuro-fibrils. The cell-body of the neuron is supplied by fibrils which enter by way of the dendrites; the cells of the nerve proper are also supplied by fibrils, those which form their axis-cylinder, the plasma flowing upward or centripetally, in the minute tubes. But how does the adrenoxidase penetrate into the neural cells proper, *i.e.*, the internodal segments?

In the first volume[220] I submitted evidence showing that what was supposed to be a "supporting framework" in the myelin of each of the internodal segments, was in reality a "thread" which, according to Rezzonico and Golgi, forms a spiral or funnel-like threadwork around the axis-cylinder, and which, according to Tizzoni, communicates with the slits of Lautermann, or hollow canals described by this investigator, von Stilling, McCarthy, Wynn and others. These slits or canals and their threadwork evidently contain adrenoxidase, for they are stained with hæmatoxylin (McCarthy), an "oxychromatin" dye, we have seen, but which does not stain myelin. This is evidently a counterpart of the cytoreticulum we found in all cells, for as stated by Böhm, Davidoff and Huber:[221] "On boiling in ether or alcohol the entire medullary sheath of a nerve-fiber does not dissolve, but a portion remains in the shape of a fine network."

The cells of the nerve proper, therefore, like the cell-body of the neuron, contain their adrenoxidase network, and the meshes of this network bathe in a medium rich in phosphorus and fat. Heat energy is thus continuously liberated to sustain the life of the cell.

The wastes are eliminated through the lymphatic system as they are by other tissue-cells. "Although the nervous sys-

[220] *Cf.* vol. i, p. 535.
[221] Böhm, Davidoff and Huber: "T. B. of Histology," second edition, p. 157, 1905.

tem is not known to be supplied with lymphatic vessels having definite walls, the circulation of lymph within the bundles of nerves is insured," as stated by Berdal,[222] "by the disposition of the intrafascicular connective tissue, the meshes of which represent lymphatic cavities." Such being the case, the plasma, after traversing the networks in the myelin, must either pass out through the neurilemma or at the nodes of Ranvier into the interneural lymphatic spaces. Another lymph-space is present between the bundle and its external covering, Henle's sheath. The cell-body, as is well known, is also supplied with a pericellular lymph-space in which chromatic granules are sometimes found.

How is the nerve-impulse generated and what is its nature?

In the first volume[223] I adduced evidence which had led me to conclude that in all organs all manifestations of activity were due to an influx of oxidizing substance (adrenoxidase) into their cellular elements. We have seen[224] how essential oxygen is to nervous activity and that nervous elements are the seat of active metabolism. The presence of adrenoxidase in the networks of the cell-body, internodal segments and nuclei of a neuron readily accounts for these phenomena and for the waste-products enumerated; it affords also a clear explanation of chromatolysis, etc. That an exacerbation of activity in a neuron is brought about by a process similar to that which prevails in all cells is self-evident.

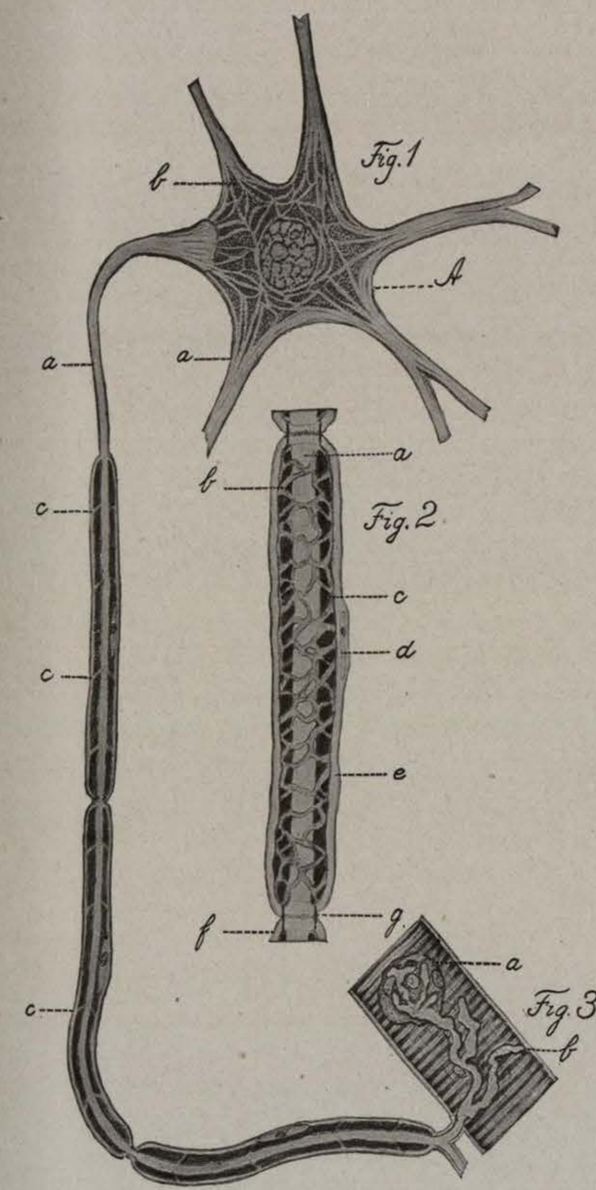
The details of this process again emphasize the need of regarding the neuron, not as a cell, but as an organ. The metabolic activity, chromatolysis and other phenomena indicating work, are practically limited to the cell-body, and yet the avalanche phenomenon and other facts show that the nerve proper is itself a source of nervous energy. On the other hand, a group of neurons—or rather of their cell-bodies—is known to form "centers," capable not only of receiving impulses, but of co-ordinating them and of transmitting the transformed impulses through their neuraxons, the nerves. It becomes a question now whether the cell-body of a neuron is itself the source

[222] Berdal: "Nouveaux éléments d'histologie normale," p. 153, 1894.
[223] *Cf.* vol. i, p. 130, in the first three editions.
[224] *Cf.* this vol., p. 915.

of the nerve-impulse or whether this function falls solely upon its neuraxon or nerve.

The prevailing view that the cell-body initiates nerve-impulses is based upon the fact that electric or mechanical stimulation of a center will awaken peripheral manifestations through the nerves it governs; but this only shows that the cell-bodies forming the center are endowed with a property more or less marked in all cells, *i.e.*, irritability. Again, a cell is not generally endowed with more than one function; and co-ordination, such as that shown by spinal "cells" in a beheaded frog, which will enable the animal to brush off a corrosive substance dropped on its back, is of such high order that it is only because it is a demonstrated fact that any cell or aggregate of cells other than those of the cortex can be regarded as possessing such powers. That in addition to this power, the cell-body is able to generate a nerve-impulse is not only improbable, but as shown below, its own irritability—the same irritability that causes a muscle to contract or a gland to secrete when stimulated—enables it to cause its neuraxon or nerve itself to generate and transmit impulses adjusted as to intensity, rhythm, duration, etc., to the needs of the peripheral organ. Briefly, the cell-body of a neuron is solely, from my viewpoint, a *co-ordinating center*, supplied with a chain of cells, the internodal segments constituting its neuraxon or nerve, and which cells are the source of all the impulses transmitted by the neuron.

The manner in which the cell-body causes its nerve to produce a stream of impulses is relatively simple. We have seen, by the upward flow of tetanotoxin, that the adrenoxidase-laden plasma circulates centripetally in the fibrils forming the axis-cylinder, and that a part of it at least (the rest passing laterally from the axis-cylinder into networks of the internodal segments) flows up the whole length of the nerve, up to the cell-body. At this point, the nerve forms a hillock, the implantation cone, which dips, so to say, in the cell-body's substance, and its fibrils (judging from the showings of Cajal's newer methods) likewise. Now, it is apparent that the *slightest contraction* of the cell-body or of the implantation cone around the bundle of axis-cylinder fibrils must, by compressing them, im-



THE NEURON AS AN ORGAN. *[Sajous.]*

Fig. 1. CELL-BODY OR CHIEF CELL. A, a, fibrils as capillaries for adrenoxidase-plasma; b, Nissl granules, as nucleo-proteid microsomes.

Fig. 2. TRUE NERVE-CELL. a, axis-cylinder fibrils as capillaries for adrenoxidase-plasma; b, network for distribution of plasma throughout myelin; c, myelin; d, cell-nucleus and nucleolus; e, neurilemma; f, tip of next cell; g, Ranvier's node. In cells on neuron: c, slits of Lautermann.

Fig. 3. MUSCULAR TISSUE. a, motor ending; b, terminals of fibrils of axis-cylinder, in which adrenoxidase-plasma (and tetanotoxin) flow upward or centripetally.