Croonian Lecture.—*The Principles of the Minute Structure of the Nervous System as revealed by Recent Investigations.*

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(Lecture delivered May 14,—MS. received June 15, 1908.)

When the flattering invitation to deliver this year's Croonian Lecture before your far-famed Royal Society reached me, I first of all felt considerable hesitation as to whether I should be able to discharge so honourable a task.

The very choice, out of the field of my investigations, of a subject which should be suitable for lecturing to you about, presented a very real difficulty. During the past 20 years I have been working principally in three departments of scientific research—*the Nervous System of Vertebrata and Invertebrata, Physical Anthropology in Sweden,* and *the Spermia of Animals of all Orders.*

By far the most interesting of these subjects is the first, dealing as it does with the chief organ in nature, that of the psychical functions. Upon this subject, of the minute structure of the nervous system, there has been a great deal of light thrown during the last two decades by the histological researches of a number of scientists, of whom may be specially mentioned the eminent Italian and Spanish neurologists Camillo Golgi and Ramôn Cajal.

The subject, however, has two real drawbacks: on the one hand it is exceedingly complicated, especially as several of its results are still under debate; and on the other it has already, in 1894, been treated of in a Croonian Lecture by Professor Cajal. Since his lecture, however, 14 years ago, the discoveries made in this department of science have been very numerous, many of them due to the researches of Cajal himself. At last I came to the conclusion that I might on this occasion continue and bring up to date the review of the subject which he then gave you.

In pursuing this intention I have, however, been obliged here and there to glance back at work done prior to 1894, and also to speak of some aspects of the subjects upon which my predecessor only touched very lightly. I conclude that it is in accordance with the idea of these lectures that the lecturer may also mention some of his own researches. And I hope that you will pardon me for expressing my opinion more definitely in certain particulars, seeing that I have arrived at a conviction of my own respecting them, which is based upon investigations which I have myself carried out. I regard this as

unavoidable when the field of research in question consists of so much unbroken ground and such important problems are still not solved. It will all the same be necessary for me to limit my attention to a few of the most interesting chapters in this wonderful and fascinating department of biology.

The scientific investigation of the histology and physiology of the central nervous system, above all of the brain, is surely one of the most difficult problems presented to human intelligence to solve. With good reason Emil Dubois Reymond's famous ejaculation: "ignorabimus," may be applicable here.

"E pur si muove." How rapidly has our physiological knowledge of the localisation of the *motor* and *sensory centres* in the brain—since Fritsch and Hitzig first showed their existence by experimental proof—gone forwards step by step, owing principally to the brilliant discoveries of the English investigators Sir Victor Horsley, Schäfer, Beevor, Ferrier, Sherrington, and still others.

It is indeed true that the proverb, "There is nothing quite new under the sun," is not without an illustration here, too, for one cannot but be astounded to find that, as far back as the year 1744, the Swedish polyhistor and scientist, Emanuel Swedenborg, was able, in his famous work 'Œconomia Regni Animalis,' with his prophetic vision to set up as a goal for the science of physiology of the brain the following standard: "Experientiæ est et temporis, ut investigetur qui gyrus et qui serpens tumulus in cerebro hunc aut illum musculum ut correspondentem suum in corpore respiciat," and "Ergo inquirendum venit, qui tori corticei his aut illis musculis in corpore correspondent: quod fieri non potest nisi per experientiam in vivis animalibus, per punctiones, sectiones et compressiones plurium, perque inde in corporis musculis redundantes effectus." As we see, this is nothing short of a full programme in the experimental physiology of the brain which this marvellous man here lays before us, and we are yet again amazed to read his clearly worded statement, that the muscles of the lower extremities have their centre at the top of the cerebral cortex, the muscles of the abdomen and thorax in the central portions of the cerebrum, those of the head and face at the bottom, "nam videntur ordine inverso sibi correspondere." It has been my purpose in quoting these theses of Swedenborg's to point out that grand scientific discoveries, of which our own age is rightly proud, may have been not only vaguely guessed at, but actually set forth in clear and definite terms by one or another brilliant enquiring mind of an earlier age. The theses cited are drawn up with such precision by Swedenborg that they cannot possibly be based on divination only, but must rest upon a real

grasp of natural phenomena as well as on actual experiments and dissecting work.

A more thorough knowledge of the minute structure of the brain and the whole nervous system was essential, if the physiology of those organs was to advance. To that end the perfecting of the microscope was a *conditio sine quâ non.* Earlier anatomists, *e.g.,* Leeuwenhoek and Malpighi, had paved the way, it is true, to our present results, but did not proceed far themselves. In accord with the last-named great Italian scientist (Malpighi), Emanuel Swedenborg, though, put forward a remarkable theory regarding the composition of the cerebral cortex, which he—in opposition to so many anatomists of that day—definitely declared to be the seat of the psychical phenomena.

Not until during the last century was it possible to get nearer the solution of this the most difficult problem of histology. It had by degrees been discovered that the nerve-tissues consist of nerve-cells in several different forms, and of nerve-fibres with and without myelin sheaths. It was also found out that the nerve-fibres are processes of the nerve-cells. The attempt was made to devise methods for tracing the nerve-fibres in their several courses, partly by hardening and staining them, partly by effecting their degeneration along certain paths, partly by studying the gradual development of their myelin sheaths in the embryo. By means of such researches scientists, before the close of the seventies, had arrived at the point of being able to establish theories concerning the minute construction of the nervous system in general. But, alas! how hypothetical, how uncertain these theories for the greater part were! I have still a clear remembrance of the hesitation and reluctance which I felt year after year, from 1877 onwards, in lecturing, as professor of histology, about this subject to my classes of students. I did not myself believe in a good deal of what I was constrained to teach them in accordance with the then accepted doctrines of science concerning the structure of the central nervous system. As a result of the investigations which I conducted in conjunction with Axel Key in the years 1869 to 1876, into the lymphatic spaces, and the structure of the brain, and the rest of the nervous system, I had arrived at the conviction that the abstract theories then held by men of science as to the construction of that system must be incorrect and were inconclusive.

It was at this period the Italian scientist Camillo Golgi made his invention for staining chrome-hardened nerve tissue with silver solution, by which the nerve-cells were selectively dyed brown. At first his communication, which was published in some smaller Italian journals with a very limited circulation in other countries, attracted very little notice, but on the appearance in 1885

of his great work, "Sulla Fina Anatomia degli Organi Centrali del Sistema Nervoso," men of science were surprised at this invention and its results.

Now, von Kölliker, myself, and others repeated this method, but, though we carefully followed Golgi's directions, the results were not really satisfactory.

I then began working by the new method of P. Ehrlich, which he published in 1886, and which consisted in staining living nerve tissue methylene blue.

Golgi's chrome-silver method had, however, in the inventor's own hands, yielded a series of fundamentally important results, which are already mentioned in the Croonian Lecture of Cajal. Of these the following may be specially mentioned here also. The occurrence in the central organ of two types of nerve cells, those whose axis-cylinder process does not branch and come to an end until after a long course, and those whose processes, after a short course, branch copiously, and come to an end in the central organ; further, the discovery of fine collateral branches emerging out of the axis-cylinder processes in the central organs; a more exact knowledge of the forms of the cells in the cortex of the cerebrum and the cerebellum, and more especially also in the gyrus hippocampi; the investigation of the different types and methods of ramification of the dendrites, and an enquiry into the structure of bulbi olfactorii. Golgi had become convinced that in the grey substance of the spinal cord there exists an exceedingly extensive and delicate network, which he considered was due to anastomosing of the collateral branches, and not, as Gerlach before supposed, to the anastomosing of the dendrites.

During the next following years, however, Golgi's method did not yield any very remarkable results; the scientists who used it did not obtain any real success with it.

Ehrlich's methylene method, on the other hand, was tried and valued in some places, especially in Kazan by Arnstein, Dogiel, and Smirnow, and in Stockholm by myself. In the higher animals, the vertebrata, the method could be well applied to the peripheral nervous system, but to the central one only with the utmost difficulty. I then determined to try and find some *lower* animals which admitted of having their whole nervous system, or, at any rate, the principal parts of it stained, so that by experimenting with them one might obtain a comprehensive idea of their entire construction. At last, in 1890, I found, with a certain modification, that the method gave excellent pictures in the ganglions of the ordinary crawfish (Astacus). A general survey was obtianed of their construction. One could clearly perceive that their so-called "Punktsubstanz" of Leydig was formed of the lateral twigs of the processes of the unipolar nerve-cells, which twigs could be traced in the

substance in their most delicate ramifications, where they did *not* unite with each other, and on the whole did *not* form a *network* (reticulum), but a *twist-work* (plexus). One could also trace the stem-processes of the nerve-cells even in their various courses through the ganglions towards the periphery (fig. 1).

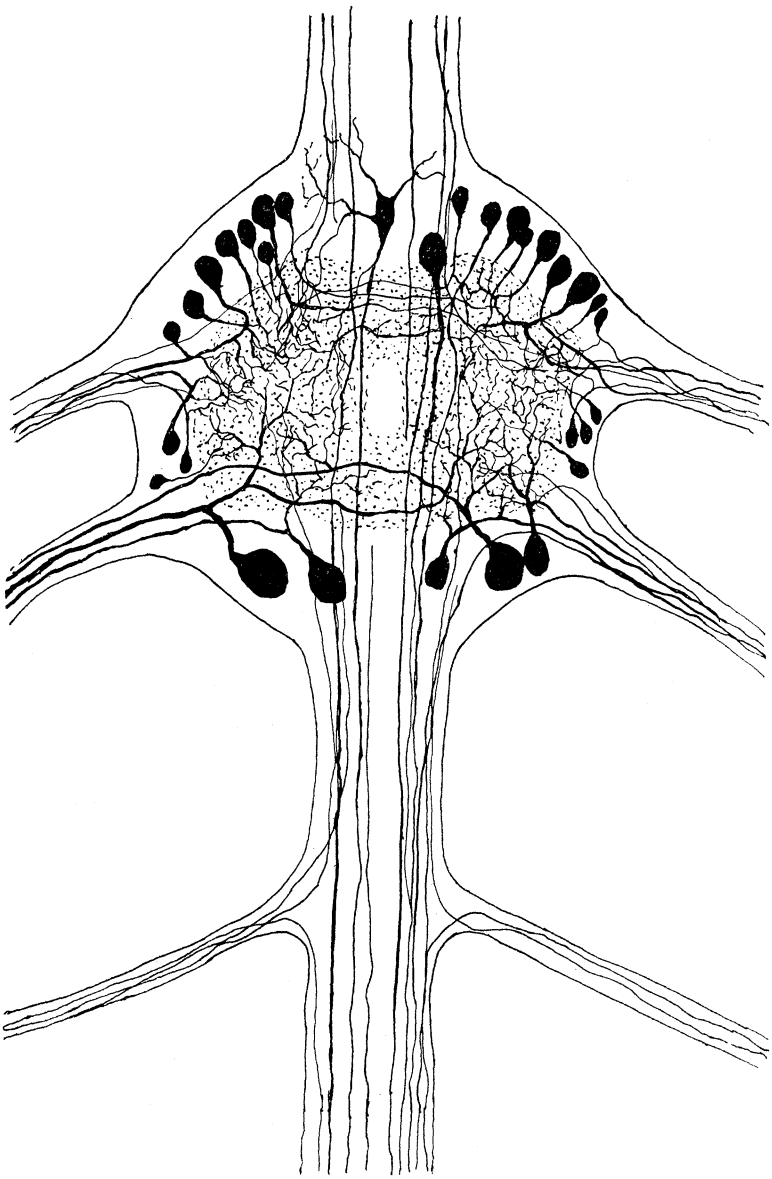

Fig. 1.—A Part of the Ventral Nervous Chain of the common Crawfish (Astacus), showing a ganglion with coloured (black) nerve-cells and their processes.

By similar researches on the spinal cords of Amphioxus and Myxine, I could also trace the condition of their central nerve-cells and the several paths of the cell processes. Still more beautiful and instructive pictures gave the nervous system of the Hirudines (fig. 2), where also Biedermann had studied them with success, and especially in that of a polychæt annelid (*Nereis diversicolor*).

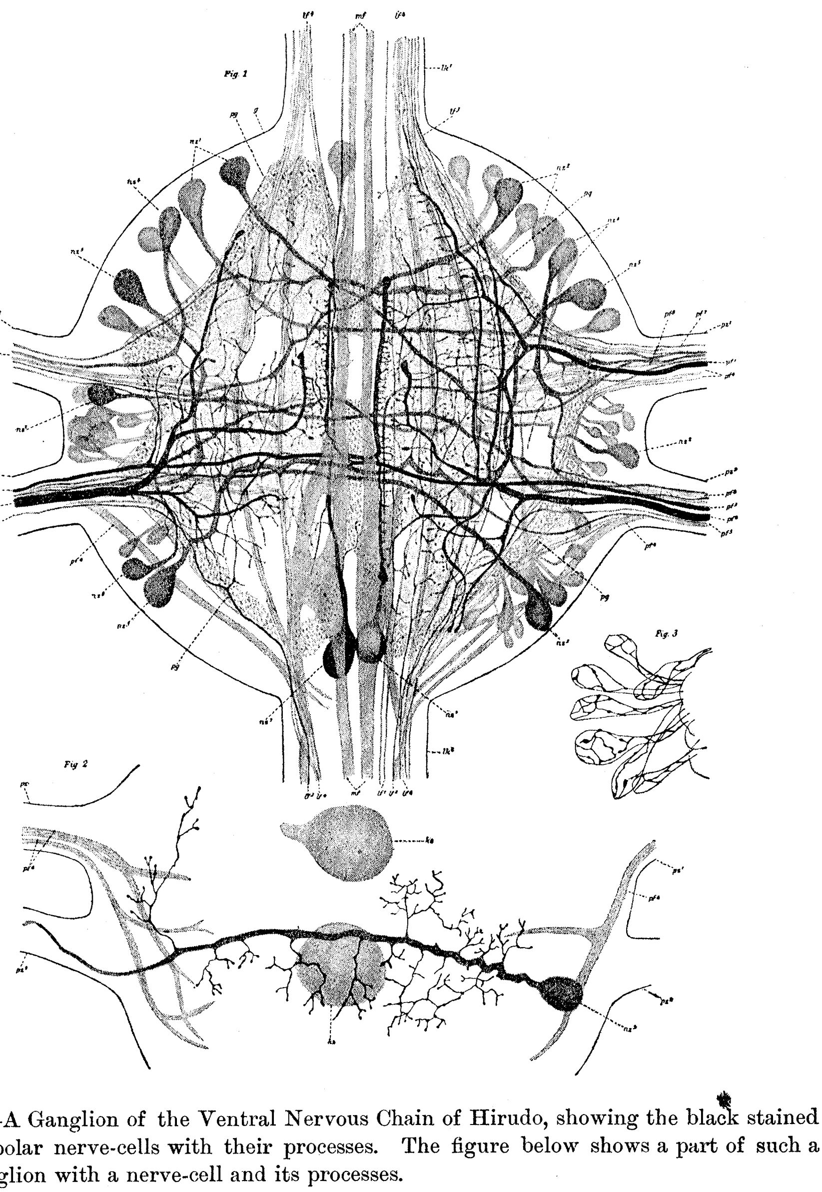

FIG. 2.—A Ganglion of the Ventral Nervous Chain of Hirudo, showing the black stained unipolar nerve-cells with their processes. The figure below shows a part of such a ganglion with a nerve-cell and its processes.

Now, in the years 1891 and 1892, the renowned Hungarian histologist Michael von Lenhossék, applying successfully the Golgi method in the common earth-worm, Lumbricus, discovered that the epithelium cells in the epidermis send fine fibres to the ganglions of the central nervous system, where they divide and terminate with free endings. These cells showed themselves very clearly to be a kind of sensory peripheral nerve-cells, which are in contact with the elements of the nervous central organ, and are capable of conveying to them impressions from the periphery of the body. This discovery of von Lenhossék was shortly after confirmed by myself and developed in conjunction with a closer investigation of the structure of the ganglions (figs. 3 and 4). I showed, by means of the methylene and chrome-silver methods, that similar cells exist in the epidermis of polychæts and molluscs, and also in the crustacea, though the cell body in these animals lies lower down under the epidermis (figs. 5 and 6).

Besides these sensory cells there exist also in the epidermis and the other epithelial tissues ramifications of free endings of tactile nerves, whose cells are to be found deeper.

I have mentioned these investigations in connection, particularly as they have for the most part been carried out by the methylene method. Now, however, a new era had commenced for Golgi's chrome-silver method, as applied to the central nervous system of the higher animals.

In and after 1888 Ramón Cajal, the great Spanish neurologist, published a series of works on the minute structure of the brain and spinal cord of vertebrate animals. By means of Golgi's method, which he improved and used in a masterly manner, Cajal succeeded in investigating the forms and the distribution of the nerve-cells and their processes in the different parts of the central nervous organ. We may date from this time almost a new epoch in our knowledge of the minute structure of the nervous system.

Cajal's first discoveries had an electrifying effect upon those who were working in the same field. For my part I shall never forget the overwhelming impression that the demonstration by Cajal, at the Berlin Anatomical Congress of 1889, of a large series of his preparations produced upon those of us who were specially interested in the subject. Albert von Kölliker and I were enchanted by the sight of the preparations which Cajal placed before us. Both he and I were converted, and we started home to begin working afresh with Golgi's method, which was not in great repute among other anatomists of that day. Kölliker, as well as von Lenhossék, working then in Kölliker's laboratory as his prosector, succeeded in applying Golgi's method, and published several excellent new researches. At the same time I, in Stockholm, and Van Gehuchten, in Louvain, were applying the same method, while

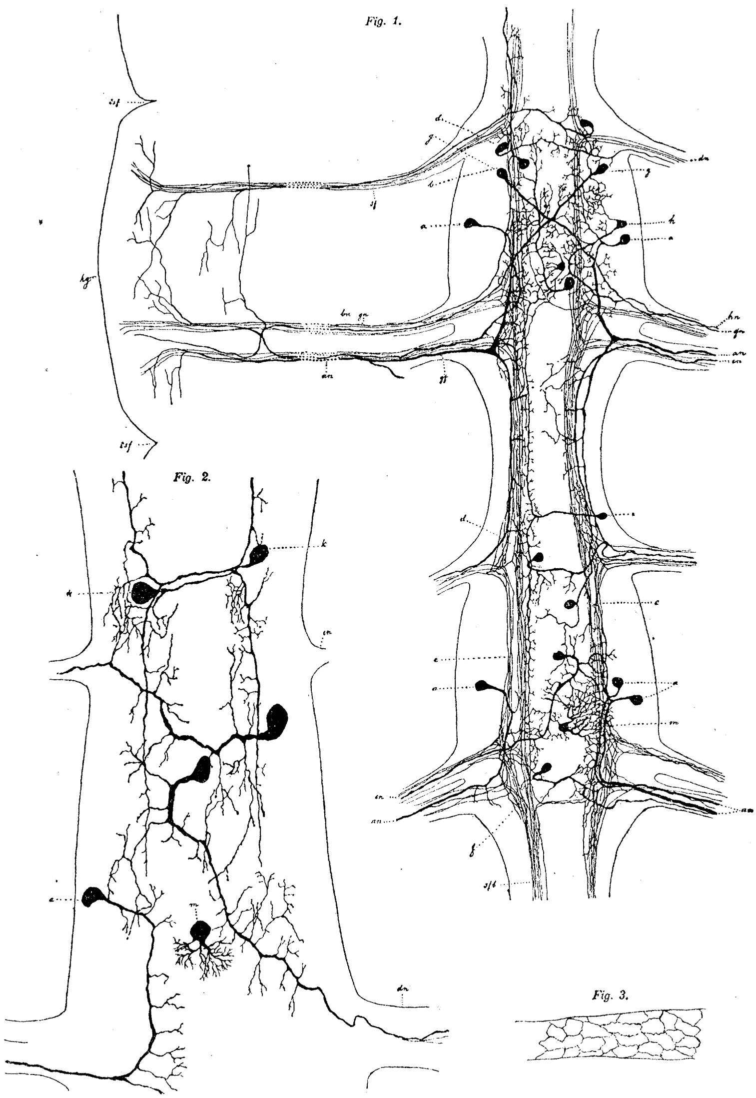

FIG. 3.—The Nervous System of Lumbricus. Parts of the ventral nervous chain of ganglions, with nerve-cells and their processes (nerve-fibres) stained black. 1. Two ganglia; at the upper the sensory nerve-bundles from the cells of Lenhossék are seen coming from the periphery and entering the ganglion, there dividing and terminating in free endings.

Cajal himself went on with one investigation after another, and Golgi and a couple of his pupils continued pursuing their various researches.

It may be said, nevertheless, that Cajal during this whole period was the most leading spirit in this research, so far as the central organ of the

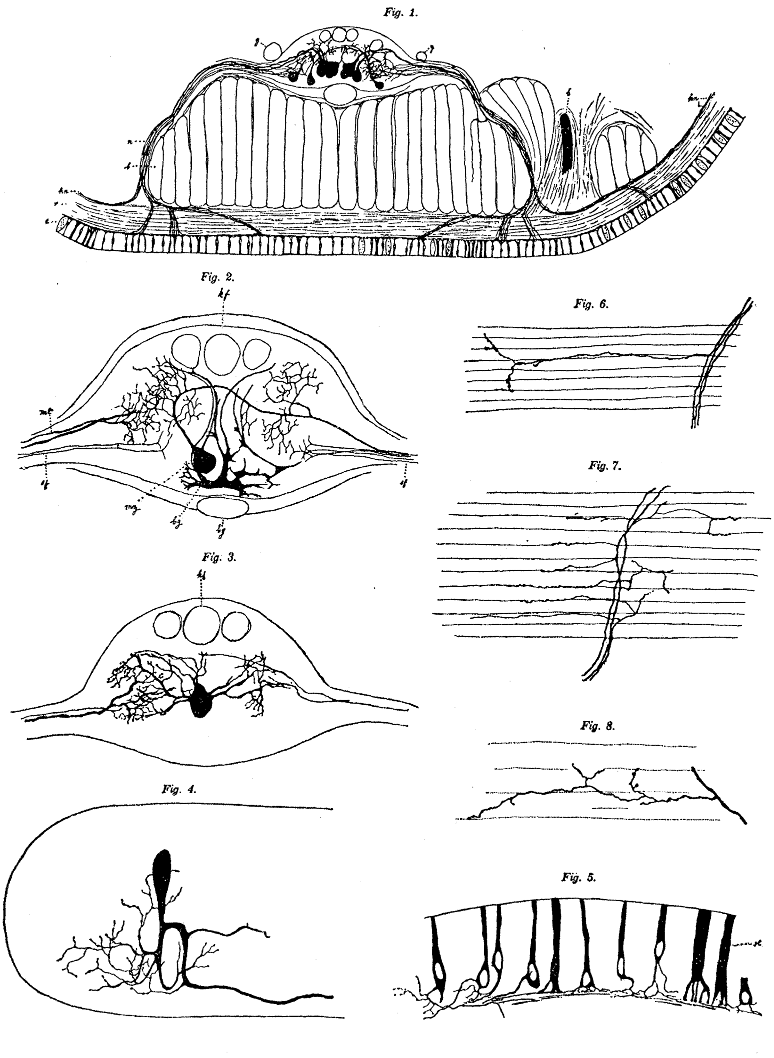

Fig. 4.—Nerves of Lumbricus, stained with the aid of the Golgi method. 1. A portion of a transverse section, with the skin and the cells of Lenhossék, with their central processes running to a ganglion. 2, 3, and 4. Transverse sections of ganglia, with nerve-cells and their processes, and also with some central fibres of the cells of Lenhossék. 5. A little portion of the skin, with the cells of Lenhossék. 6, 7, and 8. Endings of nerve-fibres on muscles.

vertebrate animals was concerned. Of Cajal's works there may here be cited in the first place those dealing with the spinal cord, the cortex of cerebrum and cerebellum, and several of the interior cerebral ganglia, the retina, the olfactory organ, and the peripheral ganglia (the sympathetic and spinal ganglia). In all these organs Cajal not only made important discoveries of

Fig. 5.—Portions of Antennæ, Parapodium, and Skin of *Nereis diversicolor*, with stained bipolar sensory cells and their processes.

new cell types and ramifications of cell processes, he also established the relations of the cells to one another in many respects. It would take too long to give a detailed account here of these researches, and the investigator himself in his Croonian Lecture to this distinguished Society, in 1894, described several of his most important discoveries in this branch of science.

Wilhelm His, of Leipzig, the eminent anatomist and histologist, had formed the conviction as long ago as in 1883, from his studies of the nervous system of the embryo, that the nerve-cells develop from the very first as organs

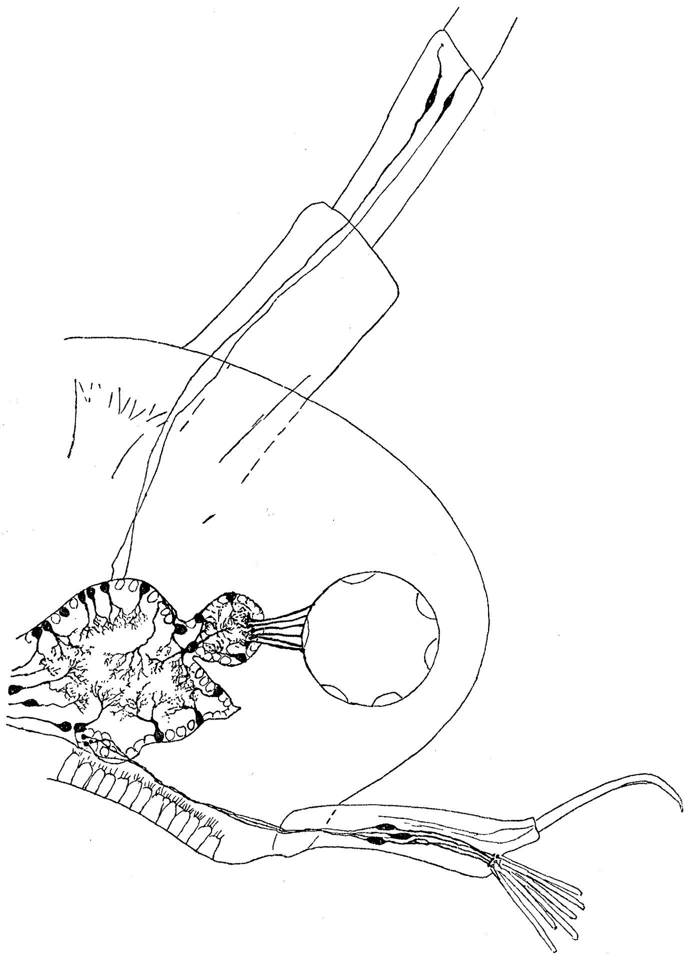

Fig. 6.—Head of small Crustacean (Daphnia, male), from the right side, showing several nerve elements coloured (black). On the left is the brain ganglion, with nerve-cells, and on the right side of it the smaller optic ganglion, in which the optic nerve-fibres, coming from the eye, end. Below, there is seen in the figure the bipolar sensory cells in the first antenna, constituting the so-called organ of smell, with central fibres going to the basis of the brain-ganglion. In the second antenna two tactile cells, with long central fibres are seen.

independent of one another, and do not enter into connection one with another. In agreement with the statement of v. Kupffer, in 1857, His observed the nerve-fibres of the embryo growing as axis-cylinder-processes of the nerve-cells; v. Kupffer and His considered, moreover, every nerve-fibre in the body, both in the nervous central organ and in the peripheral parts of the body, to be processes of that kind more or less lengthened.

This view was now also accepted by Cajal, on the basis of his own researches; by the Golgian method he showed how the axis-cylinder process grows out of the cell body in the embryo, and how at its peripheral end it has as a rule a small thickening, the so-called bud of increscence (*cono de crecimiento*), which gropes its way, as it were, to make a path for the fibre.

Shortly afterwards, v. Lenhossék, v. Kölliker, Van Gehuchten, and myself all arrived at the same opinion as a result of our own individual investigations (fig. 7). We all of us also accepted, more or less definitely, the idea propounded

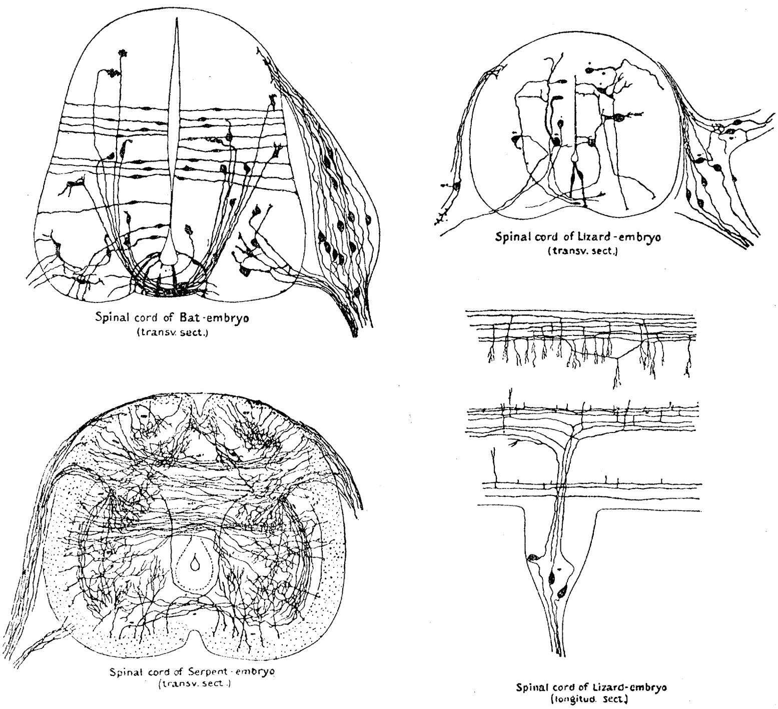

Fig. 7.—Three transverse Sections and one longitudinal Section of the Spinal Cord with Nerve-cells and Nerve-fibres stained by means of the Golgi method.

by His regarding the morphological independence of the nerve-cells in their first inception. Cajal led the way here, too, and the rest of us embraced the same theory on the basis of the results which we had obtained by the Golgian method. We did not discern, as Gerlach claimed, a network in the grey substance of the spinal cord and the brain by a union of the dendrites of the nerve-cells; nor did we find, as Golgi assumed, and still seems to assume, any network which has arisen from a union of the collateral branches of the axons of the nerve-cells.

As above stated, I also did *not* find by the methylene method *any network*

in the grey substance (Punktsubstanz) of the invertebrata, *but only a twist-work,* a plexus, of delicate branches of nerve-cell processes, intricately intertwined.

So we were all prepared, in accord with Cajal's definite pronouncement, to regard the connection between the various nerve-cells and their processes as effected, *not by continuity but by contact.*

In his excellent and concise review of the investigations in this department during the previous years, Waldeyer, in 1891, called this conception of a nerve-cell as an independent unit a *neurone,* a term which has since been generally adopted to imply the independence of the nerve-cells.

This doctrine, *the neurone theory,* as enunciated by Waldeyer, appeared to gain more and more ground in neurology. His', Cajal's, v. Kölliker's, v. Lenhossék's, Van Gehuchten's, and my own investigations had given the basis to and had confirmed this theory in many directions.

As for the *retina,* Dogiel described the nerve-cells as anastomosing, but Cajal's investigations by the Golgian method gave, as to this point, quite different results from Dogiel's. And as regards the peripheral nerve-ends I may say that, though I have carried out extensive researches upon them, I have never been really able clearly to see any formation of network, either among the terminal ramifications of the different neurones or in those of one and the same neurone. Thus, I have never been able to observe a reticulum between the terminal ramifications of a motor nerve-fibre on a muscle, nor in those of a sensitive nerve-fibre, nor on a nerve-fibre of one of the sensory organs. Supposing such a connection were really to occur, as it is described by some histologists, I must regard a reticulum of that kind as rather abnormal, due to some sort of secondary coalescence. I have considered myself bound to specially notify these facts, as they are of importance for the neurone theory as a whole.

The question of the relation and connection of the peripheral sensory cells to the nerve-fibres is also of fundamental importance. Scientists have long assumed, and in some cases asserted that they had observed, that in the higher animals each of those cells was directly connected with a nerve-fibre. That was held to be the case with the organs of *smell* and *taste,* and also with regard to the organ of *hearing.*

Now, how was this fact to be explained by the principles of the neurone theory? This question came forward: Can a nerve-fibre be directly connected with both a central and a peripheral cell, or be actually a process of both of them?

This important question, thanks to the researches of the last two decades, found a perfectly natural explanation and one that fits in with the neurone

theory. The different sensory organs are *differently* constituted, are constructed on different plans (fig. 8).

First, as regards *the organ of taste:* A. Key, who was working at the beginning of the sixties under Max Schultze, stated that he had seen in the

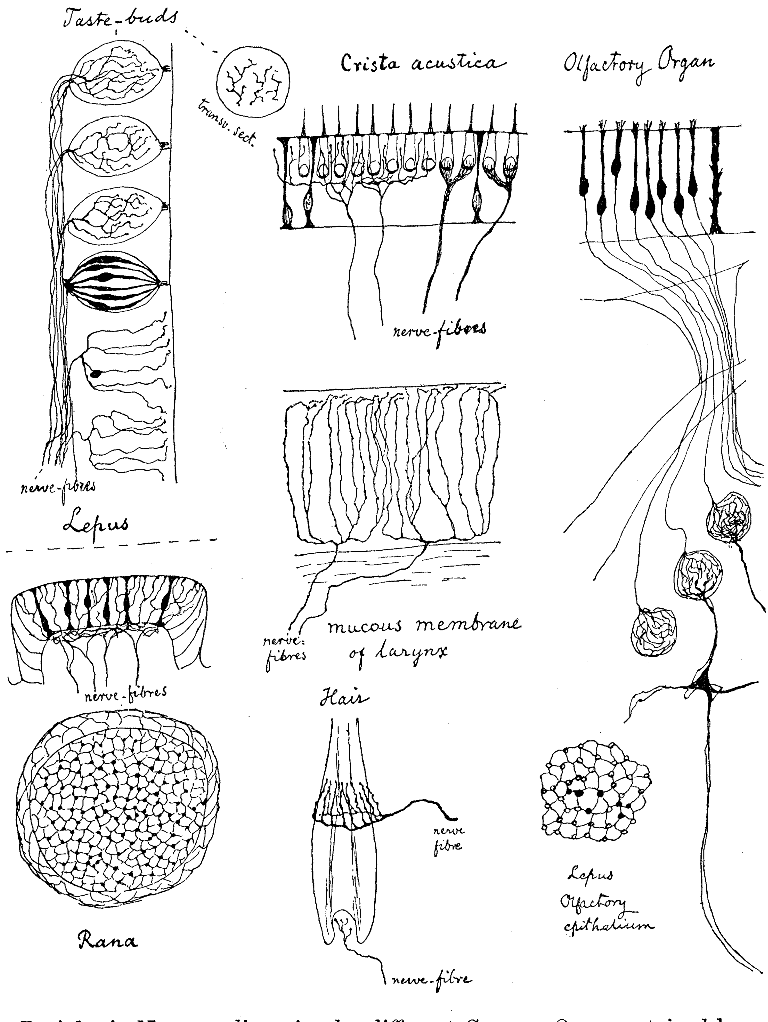

FIG. 8.—Peripheric Nerve-endings in the different Sensory Organs, stained by means of the Golgi method.

frog a direct connection between the ends of the nerve-fibres and certain sensory cells situated on the surface of the so-called taste-papillæ; and in the higher animals, the mammals, the same mode of termination was taken almost for granted. I was enabled by the aid of the methylene method and, later, also by the Golgian method, to demonstrate conclusively, in 1888

and 1892, that no mode of termination of that kind exists, that the nerve terminations find their way into the taste-buds, and copiously ramify there among the taste-cells without coming into direct connection with them.

As regards the *olfactory* organ, it could be shown clearly and distinctly by the Golgian method that the olfactory cells of the mucous membrane send out a central process which makes its way into the glomeruli of the olfactory bulbs, and there copiously ramifies among the ramifications of one or more other axons proceeding from the central nerve-cells, forming with them the glomeruli. That has been shown already by Golgi, and was confirmed by Cajal, Van Gehuchten, myself, and Kölliker; the four last named did not discover any direct connection between the nerve-fibres that proceed from the centre and those from the periphery, though that there is none is often difficult to prove for certain by reason of the exceedingly complicated convolutions of the fibres.

The sensory cells of the olfactory organ are to be regarded as a species of *peripheral nerve-cells.* They must also be regarded as corresponding fundamentally to those bipolar cells in the skin of the invertebrata already mentioned above.

In 1881 to 1884 I had shown that in the maculæ and cristæ acusticæ of *the auditory organs* the nerve-fibres enclose the lower ends of the hair cells by means of calyx-shaped extensions, and even send out fine fibrils that proceed in an upward direction on the surface of these cells. Here the matter proved more complicated, for by the Golgian method I succeeded in 1892 in proving definitely that the terminations of the auditory nerve come to an end with free ramifications among the hair cells, and, to some extent, find their way up to the surface of the epithelium. More recently Cajal has shown by his new silver method that both modes of termination, calyx formation and free ramification, exist side by side in cristæ acusticæ.

It is in any case plain that sensory cells of the auditory organ (the hair cells) may in principle be compared with those of the gustatory organ. Their development makes manifest, too, that they do not send out any fibres which proceed towards the centre, but that the bipolar nerve-cells situated in the ganglion acusticum dispatch their peripheral processes to the sensory cells in the epithelium.

By reason of these circumstances, constituting as they do an essential difference, I here distinguish sensory cells such as those of the olfactory organ, which I call *primary,* from sensory cells such as those of the gustatory and auditory organs, which I call *secondary.* The former are, of course, a species of peripheral nerve-cells, the latter are not.

I do not propose here to enter upon a discussion of the complicated

structure of the organ of sight, the *retina*, which is the less requisite as Cajal described it in his Croonian lecture.

As regards the termination of the *sensitive* and tactile nerves in the epidermis, the epithelia, and the specific sense organ, the Pacinian corpuscles, the Krause end-bulbs, etc., one may formulate a general rule as follows:—They terminate everywhere with free endings and ramifications, though differing in arrangement in different cases, and sometimes among cells (Merkel's terminal discs, Grandry's corpuscles, etc.), which may, to a certain extent, be compared to secondary sensory cells.

To give a survey of these different types of terminations I have drawn up a few diagrams of the various kinds of sensory cells (fig. 9).

The *olfactory* cells and those *sensory* cells of the invertebrata that are here under discussion are consequently to be regarded as a kind of peripheral neurones, the *gustatory* and *auditory* cells on the other hand may not, strictly speaking, be so considered; the real neurones of the latter, as also of the terminal branches of the tactile nerves, are constituted by the nerve-cells situated in the cerebro-spinal ganglion system.

The neurone theory had consequently from a morphological point of view shown itself to be correct, both as regards the facts connected with the central organ and the peripheral one, and the Golgian method had yielded results agreeing in all essentials with those of the methylene staining one. The difference between our knowledge then and that we possessed, for instance, in 1880, was prodigious. Yet, in reality, it was a mere handful of investigators, dwelling far apart from one another, who had accomplished this work. In some quarters, even among eminent anatomists, physiologists, and especially neurologists, the work and results of those investigators were long regarded with a certain suspicion; now and then that suspicion found expression in a rather startling form. I might, for instance, read to you letters which I received from celebrated histologists abroad, who were otherwise favourably disposed towards me and my work, conjuring me in the most serious and moving terms not to go on experimenting with that wretched Golgian method which only resulted in art effects, impure chrome-silver precipitations within the tissues, and were misleading and dangerous for real scientific inquiry. Pretty much the same verdict was pronounced, too, from a specially authoritative source upon the methylene method as we applied it. From the point of view of the history of science it may be of a certain interest to note that our labours by no means met with encouragement and recognition in all quarters.

The new school of investigators found little difficulty in dealing with these antagonists.

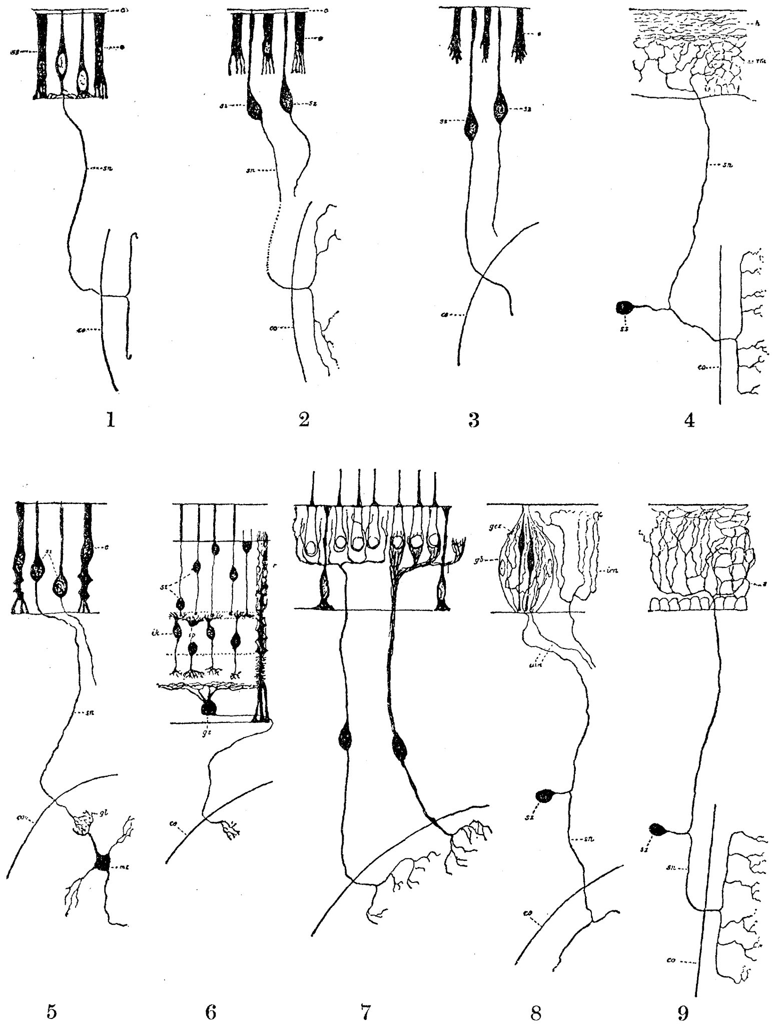

FIG. 9.—Schemes of the various Sensory Organs, with their different Sensory Cells and Nerve-endings. 1. The sensory nervous system of an oligochæte worm (Lumbricus). 2. The sensory nervous system of a polychæte worm (Nereis). 3. The sensory nervous system of a mollusc (Limax). 4. The sensory nervous system of a mammal (the skin). 5. The organ of smell in the Vertebrata. 6. The organ of sight in the Vertebrata. 7. The auditory organ in the Vertebrata. 8. The organ of taste in the Mammals. 9. The tactile organ in the Vertebrata.

But other opponents now came forward who had devised new methods and arrived at other conclusions regarding the minute structure of the nervous system. First came the Hungarian zoologist Stephan Apáthy, of Kolosvar, who after some smaller communications published a larger book

illustrated by elucidating figures, entitled: "Das leitende Element des Nervensystems und seine topographischen Beziehungen zu den Zellen" (1897). By the help of a new gold-staining method he had succeeded in showing in the ganglion cells of certain worms, and especially finely in the unipolar cells of the Hirudines (fig. 10), an intracellular reticulum of fibrils which form a continuous network round the nucleus and also near the cell surface; from that network there proceeds through the single process an unbranched fibril which extends into the Punktsubstanz. In the vertebrata, too, Apáthy had found fibril network in the ganglion cells; this he described, but did not illustrate by figures.

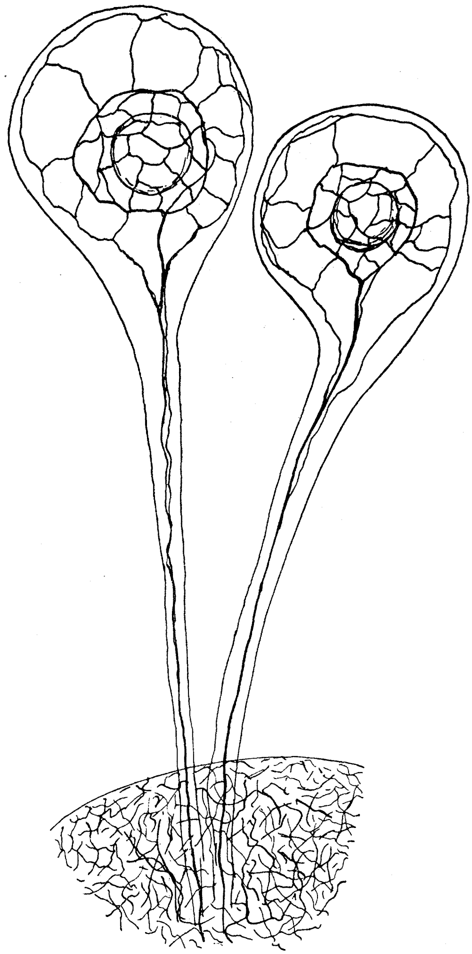

FIG. 10.—Two Unipolar Nerve-cells from a Ganglion of the Ventral Nervous Chain of Hirudo. In the cells is seen the fibrillar network of Apáthy, running down through the cell process into the Punktsubstanz, which consists of fine twisted fibres.

In conjunction with this discovery of the neurofibrils, excellent in itself, Apáthy built up a whole hypothetical theory regarding the minute structure of the nervous system. Of that theory it is not easy to give a brief summary, but these are the chief points in it:—The neurofibrils discovered by him form the specific constituent of the nervous system, the nervous portion proper, the *conducting* element; they are independent structural parts; in the nerve-fibres they preserve their individuality; in three places, however, they form reticula, viz., in the ganglion cells, in the terminal organ (the sensory cells, etc.), and in Leydig's Punktsubstanz, in which they subdivide into an exceedingly intricate reticulum, Apáthy's "Elementargitter," in which the sensory nerve-fibres in particular dissolve and lose their individuality.

In connection with this conception Apáthy constructed his hypothetic theory regarding the minute structure of the nervous system. He maintains that there are two kinds of nervous cells, nerve-cells and ganglion cells. The nerve-cells produce the conducting substance, the neurofibrils, which grow both towards the centre into the ganglion cells and towards the periphery into the sensory cells, the muscle cells, etc. The neurofibrils constitute consequently an element foreign to the ganglion cells which has grown into them from without; they are further capable of independently emerging from the ganglion cells and their processes, the nerve-fibres; they do not accordingly need to remain in them and their paths. They form, moreover, large continuous reticula in the organs of the body and above all in the central grey substance. It is not to be wondered at if the specialists were somewhat astonished at this new system of Apáthy's, which appeared to them to rest on very uncertain foundations. Apáthy's own preparations of Hirudo ganglions were exhibited at zoological and anatomical congresses. The existence of the intracellular fibril network in the ganglion cells of certain worms was clearly apparent in these preparations, but his "Elementargitter" in the Punktsubstanz, on the other hand, was not confirmed; there did not appear a reticulum, but a plexus of non-anastomosing delicate fibres.

However, Apáthy was now to obtain an ardent supporter in a German physiologist, A. Bethe, who declared himself a believer in his theories. This scientist, who had been experimenting especially with the methylene staining method and had invented a good fixative for the preparations resulting from it, devoted himself to the question of the occurrence of fibrils in the ganglion cells of the higher animals, a question which Max Schultze had previously done a good deal to elucidate. Bethe invented a new method of staining these fibrils, which he represents as non-anastomosing among themselves as a rule. Bethe very vigorously championed the main article in Apáthy's theory, both in lectures and essays, and also in a large book on the subject; he was a particularly strong upholder of the idea that the nerve-fibrils are the true conducting element in the nerve-tissue and of their independence. Bethe became one of the chief opponents of the neurone theory and, generally speaking, of the school of ideas of which Cajal was the leading force. Bethe exercised for a time a not inconsiderable influence upon many of the Neurologists' party. Some of the results he obtained by his experiments were especially effective in strengthening his position as a supporter of Apáthy's theory. Bethe had removed certain groups of ganglion cells from some live crabs (*Carcinus mœnas*), but could nevertheless observe reflex activity in the processes of the nerve-cells

belonging to them. Thus, he alleged he had hereby clearly shown the small importance the ganglion cells have as regards the activity of the nerves.

I have myself tried to carry out these experiments of Bethe's on my own account, but have come to the conclusion that it is practically impossible to operate with such precision on the semi-transparent and soft ganglions of the living animal (*Carcinus mœnas*) that a removal of some particular groups of cells will be certain to result. Under such conditions I consequently regard it as exceedingly unsafe to draw the conclusions Bethe has done. The question is fundamentally of such moment that the utmost caution is necessary in arriving at any conclusions at all. I, at any rate, after the experience I have derived from my experiments, must call in question the certainty and accuracy of what he has stated as his conclusions.

Now, however, a new epoch of neurological investigation was to be inaugurated, for Cajal and Bielschowsky almost simultaneously invented methods very similar to one another for staining the fibrils in the nerve-cells and their processes by means of a silver solution. That not only confirmed the existence of the neurofibrils seen by Apáthy, but added very materially to our knowledge, especially of the nervous system of the higher animals, the vertebrata. Thanks to these methods, it was shown by the inventors themselves and by other investigators, who had taken up the study of these problems, that everywhere in the nerve-cells and their processes there exist fibrils which belong to the cell substance and are very early developed in it. Cajal proved, too, that these fibrils form reticula in the cells, and that they increase or decrease in thickness according to the state in which the animal is, different in health and sickness (*e.g.*, rabies), etc.; he also pointed out that in the cell processes these fibrils always remain within their substance, and are not, as Apáthy asserts, capable of emerging from it. Cajal asserted also that the fibrils do not anastomose outside the neurones, and specially not in the central substance and in the Punktsubstanz. This important point, which entirely agrees with the results I obtained before by the methylene method, was confirmed by the new researches I carried out with Cajal's new fibril staining method which gives a very full and distinct colouring to even the most delicate ramifications of the nerve-fibres (fig. 11). Now these form everywhere, even in the most successfully stained parts, in the Punktsubstanz of the invertebrata as well as in the grey substance of the vertebrata, *not* anastomosing *reticula, but only twistwork* (*plexus*); divisions in the fibres occur, but *no network* is visible.

I call attention to this fact once more, since the question has an important

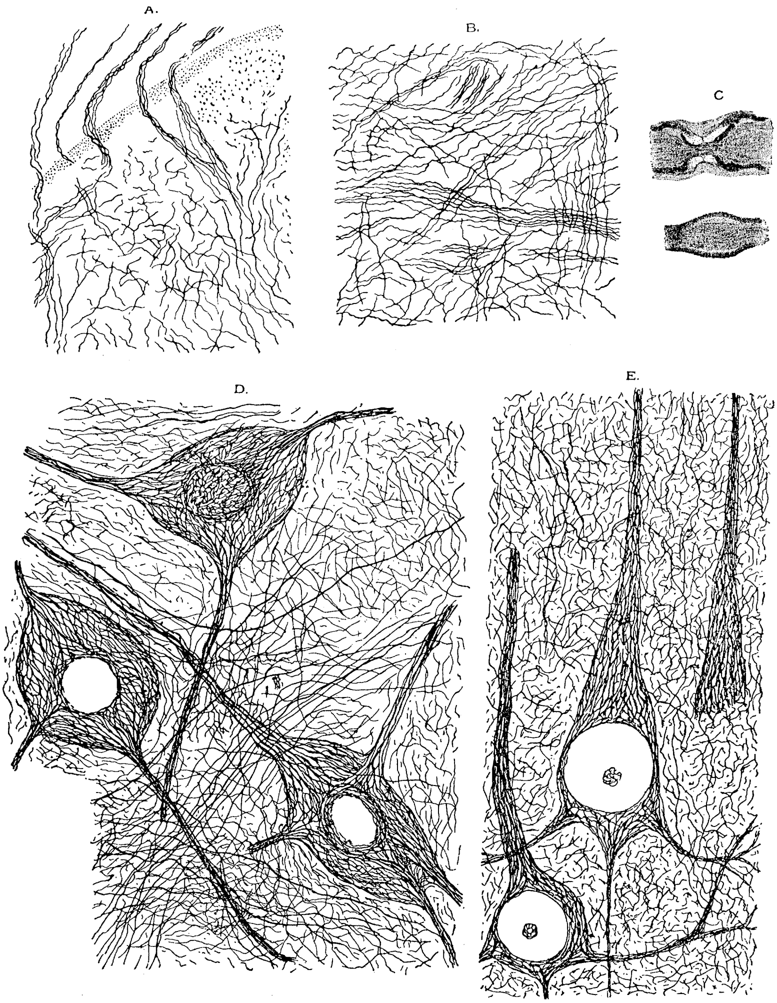

Fig. 11.—The Intracellular Network and the Intercellular Twistwork in the Grey Substance of the Central Nervous Organs. A and B, the Punktsubstanz in the ganglions of Hirudo (twistwork); D and E, nerve-cells in the spinal cord and the cortex of the brain of a rabbit. In the cells is seen the intracellular network of fibrils, and between the cells is shown the twistwork of intercellular fibrils.

bearing on the neurone theory and on our ideas regarding the construction and function of the nervous system as a whole. Those groups of scientists who have proclaimed the presence of reticulum cannot in this particular find support in the results even of their own methods. I have myself seen thousands of excellent preparations produced by the Golgian method, but have never seen real reticula in the grey substance of either the higher or the lower animals. I have carefully studied a series of preparations

produced by both Apáthy's and Cajal's methods—even the preparations made by Apáthy himself—but have never succeeded in discovering the reticula which they maintain as being present.

Apáthy, however, and his followers state that this is simply due to the staining not having been perfect. In that case all the stainings that have been submitted to our examination have been imperfect, *including even Apáthy's own.*

A scientific investigator is in duty bound to confine himself to describing what he really sees; he has no right to formulate *theories* on the basis of what he does not see, but only imagines and assumes that he may see. It is, of course, true that our power of sight is limited, and that even within the range of our vision there may be much of which we have no knowledge. We may form hypotheses and conceive probabilities concerning those regions which are invisible to us, but we must be very careful not to confuse those fancies with the exact results of science. Consequently, it will not be possible for scientific investigators to accept the existence of anastomosing reticula in the grey substance as a fact, and to build up scientific theories on that basis until reliable methods have proved it to be so.

The sum of what has hitherto been shown by the investigations in this field is, according to my opinion, this only: That neurone fibrils are to be found in the nerve-cells and their processes, that they form *in the cells* abundant reticula, which are even plainly to be seen in some of the peripheral terminal organs, and that they do not anastomose *outside* the particular domains of the cell unit or neurones, *i.e.* that they *do not outside these form reticula but plexus.* The several neurones are connected one with another *per contiguitatem,* not *per continuitatem.** Finally, there does not exist any certain proof that the fibrils constitute the sole conducting element.

I know very well that there are instances described where there are observed anastomosing of nerve-cells, but these cases are really very few, and may be, if they are certain, considered as abnormal, and, at all events, very rare. The question as to the independence of the neurones one of another, or

* During the preparation of this lecture for print I have received from the author, Dr. Em. Mencl, in Prag, a memoir on the "Punktsubstanz of the Hirudinees." His researches have led him to the same conclusions about its structure. "Ich habe," he says at the end of the memoir, "das Verhalten der Neurofibrillen und der Zellausläufer wiederholt einer eingehenden Untersuchung unterworfen, natürlich, wie erwähnt, an nach Apáthy und Cajal behandeltem Material, hauptsächlich aber an den Cajal'schen Präparaten, wo die Reaction vollkommen gelungen war—und trotzdem habe ich nie irgendwelche Netze, ausser den intracellulären Körbchen, gesehen, weder in den Verlauf der Ausläufer eingeschaltet, noch in der centralen Masse. In dieser Hinsicht kann ich direkt mit Retzius sagen: 'Auch bei den stärksten anwendbaren Vergrösserungen sah ich in der Punktsubstanz nie ein Netz, nur ein Geflecht, keine Anastomosen der Äste.'"

their continuous connection one with another by means of fibrilliferous anastomoses, either from cell body to cell body or from process to process, has once more come to the front during the last few years and divided investigators into two different camps. As above mentioned, it was shown by His that the nerve-cells of the central organ do not anastomose with each other during the first stage of their development, but are independent cell entities. This has been confirmed by most of the specialists (Cajal, v. Kölliker, v. Lenhossék, myself, Van Gehuchten, etc.), who have made an intimate study of the development of these organs in the embryo.*

There has long existed a theory diametrically opposed to that of His, respecting the origin of the peripheral nerve-fibres; it was first brought forward by the great embryologist Balfour, and has been since vigorously upheld by a number of other investigators. Their theory is that the nerve-fibres owe their formation to special cell chains which are to be found in the various parts of the body from the beginning, or, at any rate, very early.

Among the supporters of this cell-chain theory, however, one, the renowned embryologist Dohrn, has lately announced, that on the strength of his most recent investigations, he has been obliged to give up his earlier opinion entirely, though he had been convinced before of its correctness. Dohrn must therefore not be counted any longer as an exponent of the chain theory. Oscar Schultze is at present the foremost upholder of this theory. The results of several investigators, however, are at direct variance with his. The last researches of v. Kölliker, completed just before and published shortly after the death of the great anatomist, prove with convincing clearness that the nerve-fibres grow out of the central organ towards the periphery. Cajal's numerous researches tell the same story.

But still more conclusive, if possible, is the work of R. G. Harrison, the

* Among the adherents of the neurone theory, the Russian neurohistologist Dogiel, who, especially with the methylene blue method, has made brilliant discoveries in the field of the peripheral nervous system, has pronounced (1904) a theory which is somewhat different from that of the other neuronists. Dogiel thinks that in the central organs certain colonies of nerve-cells form units by means of their dendrite processes: here "verbinden sich somit die Nervenzellen einer Art vermittelst ihrer Dendriten zu Zellkolonien; die in den Bestand aller Zellen einer Kolonie eingehenden Neurofibrillen bilden Reihen von geschlossenen und eng miteinander verbundenen Netzen, welche mit dem Neurofibrillensystem anderer Kolonien, mit welcher die erstere funktionell verbunden ist, organisch nicht zusammenhängen."

In the central organs of the higher animals, I do not know of any proved instances of such colonies of nerve-cells, and in the lower animals I have never found them. This year Dr. Deineka, working in the laboratory of Professor Dogiel, in his researches on the nervous system of Ascaris, has come to the conclusion that the motor and sensory systems do not unite with each other *per continuitatem*, but by contact; the sensory cells, however form organic continuities with each other.

American histologist, who has shown by a series of clever and successful experiments on frog larvæ that the nerve-fibres grow out of the central organ. Harrison was, in fact, able to trace this process under the microscope in the living tissue and could even determine how much the fibres grow in a minute (about half a micron in the minute). By experimental methods he was actually able to check or delay the migration from the central organ of these cells which form the so-called Schwann's sheaths round the peripheral nerve-fibres. It is these Schwann's sheath-cells which are regarded by supporters of the chain-theory as the mother cells of the nerve-fibres; but Harrison was able to show that nerve-fibres will grow even in cases where no sheath-cells exist. Oscar Schultze has tried in his last treatise to minimise the value of these results of Harrison's, which we others consider almost conclusive, by stating that they are due to the attack of the experimental method, and do not therefore represent normal conditions. If that line of argument is to be allowed, then the results obtained by experimental interference with natural processes in general must be rejected, which would mean that a considerable part of the science of physiology would have to be rejected as unreliable, as being essentially based upon experimental interference of that kind. It is in this direction that so many excellent scientific discoveries have recently been made and upon which are centred the greatest hopes of progress for the future.

To this group of phenomena and the results yielded by them we must assign the correct conception, arrived at by study, regarding *the regeneration of the nerves* after having been traumatically injured. It would carry me too far, if I were to attempt to give a detailed account of the numerous and extensive experimental researches upon this highly remarkable and involved process. After having been, with great success, made the object of research for a long time past by a group of distinguished physiologists, Waller, Vulpian, Langley, Sherrington, Vanlair, to only mention some of the more prominent ones, the question was also taken up by the modern histologists some years ago and has since been investigated by their methods; Cajal and Perroncito, experimenting quite independently of each other, arrived at very nearly coincident results.

It has long been known that, if a nerve be severed, the central and the peripheral portions will reunite and the nerve be restored to use; the same regeneration will take place even if a piece be cut out. It had been generally assumed after the date of Waller's renowned investigations that nerve-fibres which are wholly or in large measure separated from the cell body with which they have been in direct communication, will degenerate if they do not speedily regain their connection with it. The German physiologist Bethe, however, maintained some years ago that he had succeeded in showing, by

experiments upon living animals, that a peripheral nerve portion, when separated from its cells, is capable of regenerating of its own accord, the sheath-cells of the fibres being what really effect the regeneration.

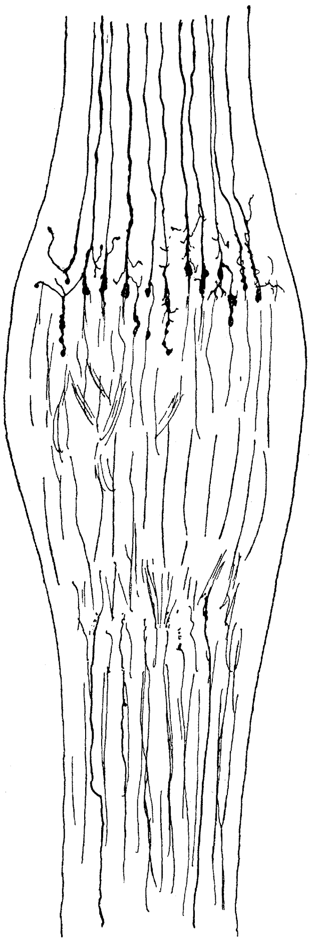

Fig. 12.—Scheme of the Regeneration of a Peripheric Nerve. The upper part is the central portion, the lower part is the peripheric portion; in the midst is the damaged portion.

This discovery aroused a great deal of attention, and was regarded in many quarters as dealing a decisive blow at the neurone theory. The researches, which several other scientists (Braus, Van Gehuchten, etc.) carried out, seemed to confirm Bethe's results. On the other hand, fresh researches made by Cajal and Perroncito, most carefully and accurately, soon proved that Bethe had not exercised due care in the researches he undertook, and that the conclusions which he drew were hasty and incorrect. It was plainly shown by Cajal's and Perroncito's numerous experiments that regeneration proceeds solely from the central nerve-portion, the fibres of which still remain in direct connection with its central nerve-cells, and that the nerve-fibres of the peripheral nerve-portion degenerate; that these however, after a time, are replaced and regenerated by the fibres of the central nerve-portion, which grow towards the peripheral nerve-portion, and replace its degenerated fibres (fig. 12). A regeneration of this kind, issuing from the central nerve-portion, may be effected at surprisingly long distances, and in spite of great obstacles, even through the length of muscles that lie in the way. It is as if a chemotactic law governed the outward growth from the central nerve-portion to the periphery, as indeed was before shown by the experiments of the Swedish pathologist Forssman, in Lund, and still earlier by the experiments conducted by the French histologist Ranvier, upon the nerves of Cornea, which quickly regenerated after destruction, so that Ranvier considered himself justified in establishing a law of the growth of the nerves towards the periphery.

Owing to results thus obtained by experiments with nerve regeneration, the just mentioned objections raised to the neurone theory as a result of the more or less dubious experiments of Bethe and others, and their incorrect interpretation, which for some time were listened to by the scientific world, have thus been refuted.

As far as I can see, the neurone theory, in its main features, has issued victorious from the strife between its supporters and opponents. One may still acknowledge that the latter have rendered good negative service, on the whole, by their opposition, for they have continually prompted others to new researches which have led to the problem being more and more thoroughly cleared up.

The pictures to be obtained by a study of regeneration, as evinced by the central nerve-portion, are, besides, very remarkable. The severed axons send forth finer or coarser branches, which grope their way onwards along the strangest paths and in varying forms. It may be said, in a certain sense, that the description by Cajal and Perroncito forcibly reminds us of the purely normal growth in the embryo of the axons of the central nerve-cells and their buds of increscence, etc. But they also remind us of the pictures presented by a large number of the so-called sensitive terminal organs in their normal occurrence in the adult individual. The Swedish anatomist Ramström, of Upsala, who has been subjecting these organs, Meissner's and Ruffini's, and the Pacinian corpuscles, Krause's end-bulbs, etc., to a close and critical scrutiny, in order to establish their significance, both morphological and physiological, has already arrived at very remarkable results, which may throw light upon the real nature of these bodies and upon their origin and functions.

There remains, however, to be mentioned another opponent to the His-Cajal-Waldeyer neurone theory, in its original form: Held, the German histologist, now the real leader of its antagonists. He had tried previously to show the occurrence of fine terminal ramifications and end-bud formations, by which the ends of some nerves embrace certain nerve-cells, and are described as being in direct connection with their substance.

By a study of the first occurrence of the inner fibril reticulum of the nerve-cells, Held formed an opinion as to the first formation of nerve-fibres in the embryo, which essentially resembles the one pronounced by the German physiologist Hensen, many years ago. Hensen's doctrine was that the nerve-fibres do not grow towards the periphery, but are connected from the very beginning both with their central nerve-cells and with the terminal organ in the periphery.

Held has now conceived the idea that the only thing that grows towards

the periphery is the intracellulur fibril network itself. He has shown that it is formed very early in a special part of the nerve-cells (neuroblasts), subsequently growing towards the periphery (and towards the centre) along the previously formed paths. He maintains also that there are a large number of anastomoses between the special nerve-cells, and even between their processes; these he calls *neurodesms*, and says that the fibrils in them are able to grow from one neurone to another; in that way a large anastomosing fibril network might arise in the organism, somewhat similar to the one Apáthy has proclaimed.

In a criticism of this theory of Held's, which Cajal published recently, he showed forcibly its inadmissibility. For my own part I must join Cajal in his estimate of this attempt of Held's to alter the neurone theory. However, I have no opportunity now of entering into a further discussion of the matter, and so must only refer to Cajal's critique.

In addition to the researches, the progress and present results of which I have here endeavoured to give a brief sketch, there are a few other branches of this extensive field of work that are of great importance for the science of Neurology, which, however, the time at my disposal does not permit me more than briefly touching upon.

One of these lines of investigation is directed towards finding out accurately the finer structure of the cortex substance and the nuclei of the inner ganglia of the brain, with special attention to the exact discovery of the characteristic structure of each several part of it. In this inquiry the aim has been first and foremost to find the distinguishing marks of the different centres in the brain cortex, in accordance with what Physiology teaches us. There came first some few scattered observations of a tentative nature, then, above all, Meynert's subdivision of the brain cortex into five strata on the basis of the differing constitution of the nerve-cells, Betz's discovery of the large pyramid cells, and Bevan Lewis's analysis of their occurrence, which also embraces investigations of Gyrus hippocampi and its special construction. In 1893 the Swedish neurologist Carl Hammarberg, whose early death was a real loss to science, published the results of his systematically conducted studies upon the cortex substance of the human brain, and thereby paved the way for a more exact special investigation into this important department. Golgi, Kaes, and others carried the inquiry still further, but it was reserved for Cajal to effect a real enrichment of our knowledge in this direction as a result of his subtle and accurate researches. The work done by Cajal has also brought to light many important points regarding structure in respect to the ganglia of the brain, as has that of v. Kölliker, of Van Gehuchten, and of several other scientists, but in those

departments there still remains a great deal to be done before the anatomical structure of the parts in question can yield a sure basis for a true conception of their several functions. In the first place, the investigations have been concerned with discovering the special structure of the sensory centres physiologically best known, viz., the optic, olfactory, and auditory centres, and here remarkable discoveries have been made.

The other important line of investigation has been directed towards finding out the course taken by the bundles of nerve-fibres through the substance of the brain and the spinal cord. This problem, so exceedingly important, indeed fundamental, for Physiology and Pathology, has long been one of those which anatomists were most of all desirous of solving, first by macroscopical dissection of brain substance specially hardened for the purpose, and then by an examination of coloured serial sections. In this work the colouring method invented by Weigert has played an important part, as has that of Marchi, but by no means less momentous have been the researches, so ingeniously and energetically pursued, first of all, by Flechsig, into the myelinisation (*i.e.*, the formation of the myelin sheaths) of the different bundles of nerve-fibres which takes place at varying times. The exceedingly important results at which Flechsig arrived on the basis of these investigations have led up, as far as the construction of the cerebral cortex is concerned, to his well-known subdivision into different association-centres.

Time would not allow of my endeavouring to give even a brief survey of these association-centres or of the nerve-fibre paths that lead to and from them; I must also pass by, in silence, numbers of researches carried out by various investigators, some by anatomical, some by experimental, methods, and others, again, by a study of cases of disease, though they have yielded a large quantity of excellent and, to some extent, brilliant results.

Among other fields of inquiry in the large domain of modern neurology there are deserving of mention here: the remarkable transplantation experiments made by Braus, Harrison, Nageotte, and others, which are evidently in affinity with the nerve generation experiments. Furthermore, there should be mentioned the researches that have been instituted by Edinger and his school of investigators into the phylogenetic development of the construction of the brain in the lower vertebrata from Amphioxus upwards in the chain of animals, researches which have already yielded several excellent results and which promise to illuminate many of the hitherto dark points in reference to the organisation of the central nervous system.

However much may be said to have been accomplished by the assiduous investigations pursued during recent decades to elucidate the minute

structure and composition of the central nervous system, there remains, nevertheless, an almost infinite amount to be done in this domain. Almost every year that passes witnesses the rise of new opinions and the discovery of new and unsuspected details of structure. For instance, who would have been able to foretell some years ago that in the spinal ganglions, which to all appearance are so comparatively simple in their structure, such complicated ramifications and connections would be found to exist in the ganglion as those which have recently been made manifest by Cajal and by Dogiel? There still remain without any doubt innumerable discoveries for coming generations in all those domains.

The limited time for this lecture does not permit me to enter any further upon these fields.

When it is remembered, however, what difficulties present themselves to the investigator, it is surely a matter for astonishment that our knowledge has been advanced in so splendid a way during the recent decades, more especially in the last two. This fact warrants us in cherishing the confident hope, that by means of sedulously pursued, thoroughgoing labour on the part of scientists in all civilised countries, the secrets of the nervous system may be brought nearer to light. Still we must not imagine that the truths which we believe to be established are absolutely and unalterably certain. In science, the famous words of Duclaux, the French scientist, will always remain true:

"La science s'avance parce qu'elle n'est sûr de rien."

These words have a wide and profound significance. New methods, new researches, often teach us to see things in a new and to some extent different light, and may even disclose errors in results which have been long accepted and approved.

I am not myself willing to go so far as Carl Ludwig, the renowned German physiologist, when he said: "Die Methode ist Alles," though I admit that there is a good deal of truth in his words. New and good methods carry our knowledge forward, but moreover the investigator requires that perseverance, that devotion and that critical acumen in observation, which, provided he is not a prey to preconceived ideas, make it possible for him to distinguish between appearances and reality. Hypotheses may be excellent as lodestars though they may on occasion lead one astray. Theories can only hold their ground and lay claim to consideration as long as they agree with the facts which have been brought to light and constitute a comprehensive summary of their results; if that is no longer the case they must inevitably fall and yield place to others, in the light of the criticism brought to bear upon them and in obedience to the new observations which science has made.

It seems that these theses do contain such general truths that all may agree about them. But the history of our science shows that there are many digressions from them. We must therefore all be prepared to give up our theories when these are shown to be incorrect. With regard to the *neurone* theory, I also am willing to do this as soon as it is really proved that it does not agree with the certified facts. But that is certainly not yet the case.

The researches of which I have had the honour to give an account to this illustrious audience have in view the study of the construction of the organ of psychic activity, *the nervous system* and above all *the brain.* The goal they seek to arrive at is one of the utmost difficulty, if not, indeed, in the whole of its compass, impossible of attainment. Science cannot stand still. Ultimately the object of the investigation is *ourselves,* the *human brain,* the organ of our own mental being.

Here, above all, the words of the great English poet, Pope, are applicable—words subsequently reiterated by Göthe:

"The proper study of mankind is man."

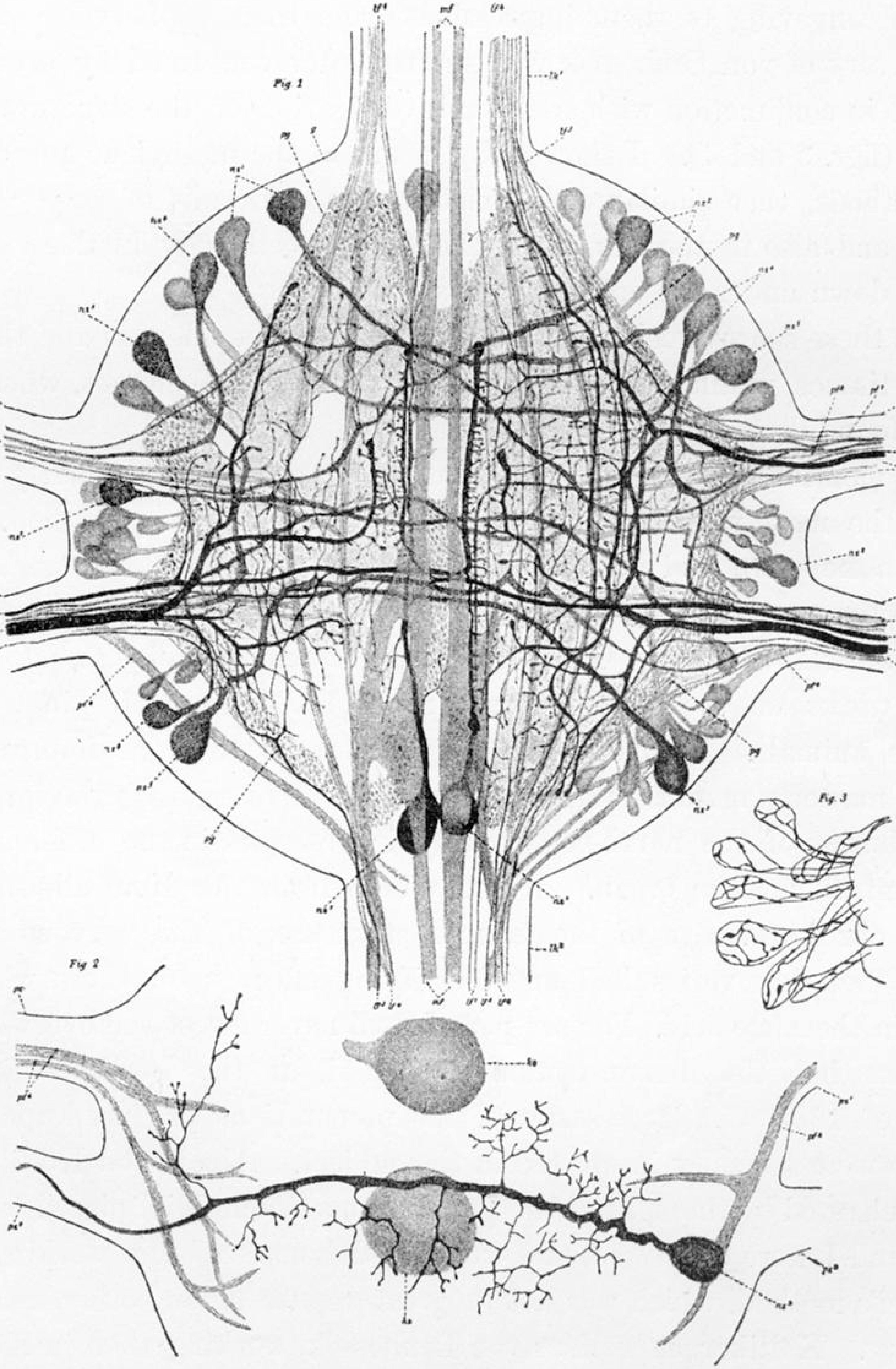

Fig. 2.—A Ganglion of the Ventral Nervous Chain of Hirudo, showing the black stained unipolar nerve-cells with their processes. The figure below shows a part of such a ganglion with a nerve-cell and its processes.

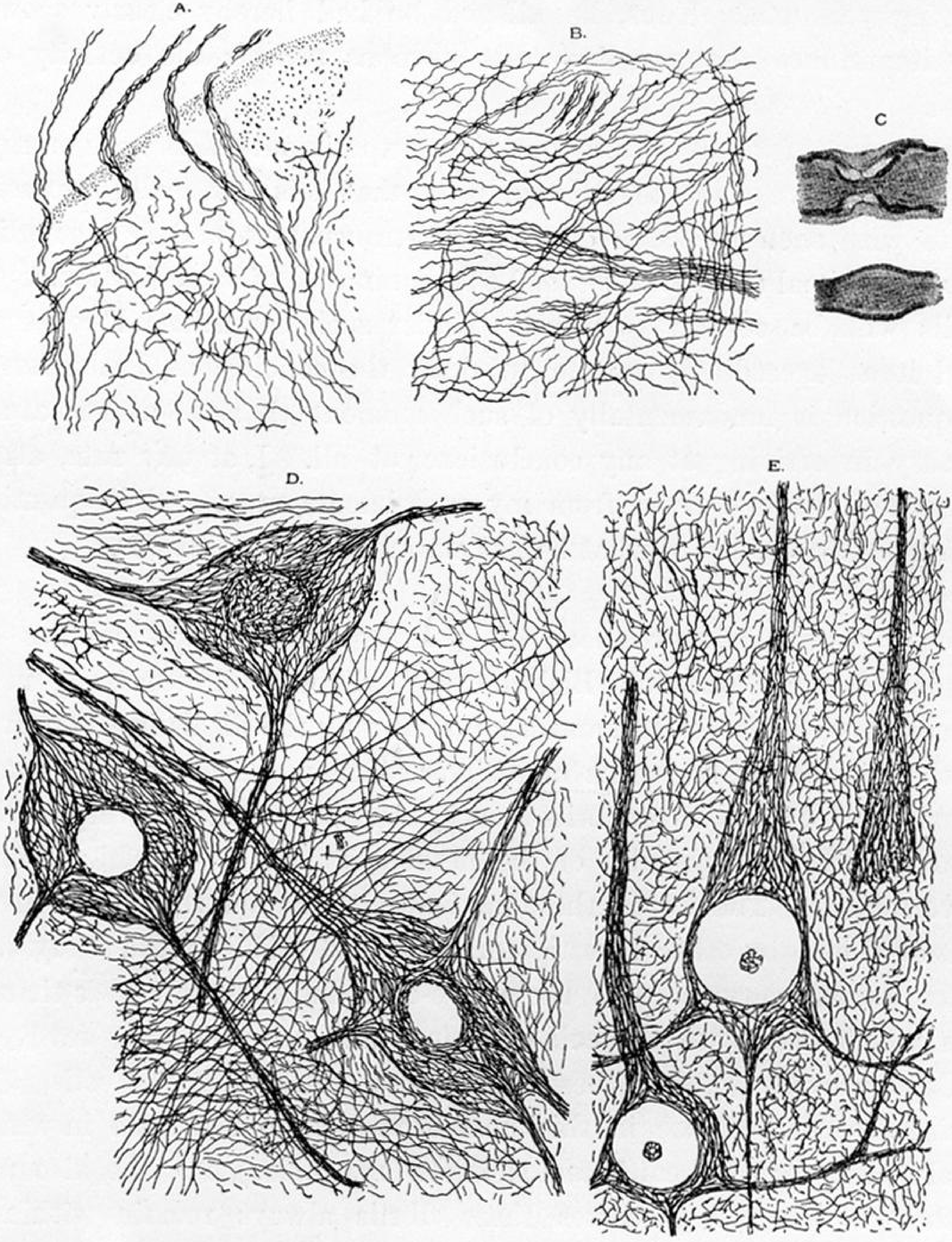

FIG. 11.—The Intracellular Network and the Intercellular Twistwork in the Grey Substance of the Central Nervous Organs. A and B, the Punktsubstanz in the ganglions of Hirudo (twistwork); D and E, nerve-cells in the spinal cord and the cortex of the brain of a rabbit. In the cells is seen the intracellular network of fibrils, and between the cells is shown the twistwork of intercellular fibrils.