

## CONSIDERATIONS OPPOSED TO THE "NEURON THEORY."

BY ALEX HILL, M.A., M.D.

*Master of Downing College, Cambridge.*

THE literature of the neuron has been so frequently summed up during the last three years that it would be a waste of space for me to repeat here what is familiar to all neurologists. Dr. Barker's excellent treatise on the nervous system published at the beginning of this year, brings the history of the neuron controversy up to date.

It should be remembered, however, that the "Neuron Hypothesis," "Neuron Theory," or "Neuron Concept" is not, properly speaking, a theory at all. It explains nothing. It is a statement, supposed to be true, that every nerve-cell, with all the parts that belong thereto (axon, collaterals, terminal arborisations, dendrites) is anatomically distinct from every other nerve-cell. The conclusions with regard to physiological autonomy and the restriction of pathological processes which are often regarded as deductions from the "Neuron Theory," are really deductions from the Cell Theory of Schwann, and would equally hold good if all the neurons of the body were continuous one with another. When Hooke, in 1696, examining a slice of bottle cork, observed that it is divided into chambers like the "cells" of honeycomb, he supposed that the partition walls of these chambers were impervious. When, in 1839, Schwann applied the "cell theory" to animals, he imagined all plants and animals to be colonies of separate and distinct "cells." The discovery by Sachs, Gardiner and Russow that a plant is not, as Schwann supposed it to be, a colony of

separate cells, but a single protoplasmic unit imperfectly divided into cells by perforate cellulose septa, does not in any degree invalidate the cell theory. The discovery that the substance of any given cell is united by myriads of protoplasmic threads with the substance of the cells by which it is surrounded does not affect our conviction, based on innumerable observations, that every cell grows, lives and dies as an individual. The trophic individuality of the nerve-cell or "neuron" is a matter of observation. We have no reason to think that if every neuron were continuous with other neurons at a multitude of points the trophic control of one neuron would extend to any parts of its neighbours. Nerve-cells are uninuclear. Each nucleus is therefore the capital of a cell territory. Whether or not the economic processes carried out within the territory are in any way controlled from the capital, it is quite certain that each territory is self-governing. It may be easier to grasp, in the case of discrete cells, the fact that the metabolism of the territory stops at its boundary, than it is to realise that it stops at the histogenetic boundary of confluent cells; but we are acquainted with many tissues in which the cells are in various ways and in varying degrees united together, yet in none of these is there reason to think that confluence of structure indicates co-operation in nutritive processes. Each individual cell grows, carries on the business of its life, and dies, as a unit.

The belief that the neurons are discrete is based upon the appearances presented by chrome-silver and methylene-blue preparations. As to the distinctness of the coloured elements there can, as a rule, be no manner of doubt; but even here the rule is not absolute. I have found instances of the union by coarse bridges of two or even three cells in all classes of nerve-cells. Dogiel, Masius and others also maintain that, in certain cases, the dendrites anastomose. But such a union of homologous elements is of little interest. It merely points to their origin by cell-division. The neuron-statement is based upon the supposition that heterologous elements are never directly united together. Chrome-silver and methylene-blue preparations appear to

demonstrate the structural isolation of heterologous elements. Histologists have accepted their evidence as conclusive on this point. In a series of papers published since 1885, and especially in my presidential address to the Neurological Society of London, in 1896,<sup>1</sup> I have urged that the credibility of these witnesses should be further tested before their evidence is accepted as conclusive. At one time neurologists held, universally it may be said, a contrary opinion. Since the publication of Apáthy's paper in 1897 it has been recognised that, for invertebrates at any rate, the neuron-statement is untrue.

The union of homologous elements by means of their dendrites not being to the point, there are only two ways in which neurons can be mutually connected. (1) The axon of a central cell A may divide to pass without arborisation into several smaller (distributive) cells B ; or, in other words, the apparent axons of several small cells B may be the subdivisions of the axon of a larger cell A : (2) The terminal arborisations of the axon of A may be continued into the dendrites of B. I shall endeavour to prove that unions of both kinds occur.

In recent years histologists have shown an ever increasing tendency to lay stress upon the direct connection of basket-like arborisations with the bodies of nerve-cells. Some histologists appear, indeed, to look upon the various forms of "basket," "pericellular network," and "pericellular tangle" as the chief means by which neurons are linked together. The subject is one of the greatest difficulty. But it appears to me on general grounds highly improbable that the basket is the most important terminal apparatus through which one neuron influences another. Phylogenetically it cannot be so : for it is through the neuropil that the branchings of associated neurons are first connected. Again, it is not a universal method of association, since no baskets are described as surrounding some of the most important cells, those of the spinal cord, for example. Looking at the matter from the opposite point of view the widely

<sup>1</sup> Hill. "The Chrome-silver Method," *BRAIN*, 1896, p. 1.

branching dendrites of such cells as the pyramids of the cortex or cells of Purkinje must have a significance, as collecting apparatus, which far surpasses that of any system of direct cell-body endings. The growth of a Purkinje cell is most instructive in this respect. When it is first recognisable as a distinct element (fig. 27) it is an oval cell from which an axon is already beginning to grow out. Soon its cell-body seems, if the chrome-silver method is to be trusted, to receive afferent filaments (fig. 28); at any rate it is always shaggy at this stage. Then with great rapidity its copious branching system of dendrites extends towards the surface—coarse and woolly as if connected with multitudes of fibrils—while the cell-body becomes clean and free from filaments (fig. 29). It seems to me incredible that any direct ending of nerve-branches in or around the body of a Purkinje cell, if there be such endings, can compare in importance, as a mechanism of association, with the elaborate dendrites of the cell.

Amongst descriptions of arborisation-endings within cells those of Held<sup>1</sup> are the most precise. Using iron hæmatoxylin staining Held exhibits certain minute rod-like particles or “neurosomes,” which are closely aggregated in the axon and its terminal ramifications, and more widely scattered in the neuropilasm of the cell-bodies. By their aid he is able, as he believes, to follow the nerve-terminals given off by the fibre-baskets, which surround the cells of the nucleus trapezoides and other nuclei, into the substance of the cells and their dendrites. He shows these filaments entering the cell-bodies and penetrating even as far as their nuclei. But he believes that, having entered the cell-body, these filaments end abruptly, and do not pass out of it through its axis-cylinder. Held is therefore an upholder of the neuron theory, *i.e.*, of the theory of the discontinuity of the neurons, with this modification: that the end-branches of one neuron may actually penetrate into the body substance of others.

Had Held used a precipitable stain only, we should have discounted his results by the considerations—(1) that his

<sup>1</sup> Held. “Beiträge zur Structur der Nervenzellen und ihrer Fortsätze,” *Arch. f. Anat. u. Physiol., Anat. Abth.*, 1897, p. 204.

fixing agents—alcohol, chloroform, acetic acid, and picrosulphuric acid—cause the formation of coagulation products, which may have no existence in life, and yet be coloured after death—this is an objection to which Held himself calls attention; and (2) that iron hæmatoxylin gives a solid deposit in the cell substance. There is no problem in minute anatomy more puzzling than that of the weight to be assigned to precipitates within tissue elements as indicative of structural differentiation. For example: I have endeavoured to check Held's results by using Weigert's hæmatoxylin method after carmine-alum, and then overbleaching the sections in ferrid-cyanide of potassium. Cells so treated are seen to be full of black granules, but the granules are not rod-shaped like the "neurosomes," nor can I detect any indications of a differential arrangement. Indeed, the size of the granules, which are always round or oval, and their condition of aggregation appear to depend upon the exact treatment to which they have been exposed.

Held's results have not been left unchallenged, as may be seen in a paper by Veratti,<sup>1</sup> which is illustrated with very striking figures of the author's own results. Turner and Hunter<sup>2</sup> also, using methylene blue, *intra vitam*, conclude that the filaments of the pericellular network do not enter the cell-bodies but lie upon them, and are continued on to their protoplasmic processes. The whole subject is one upon which it is permissible at present to retain an open mind. Especially is it legitimate to consider that the nature of these pericellular baskets is not yet definitely settled, when one reflects that neither Held's method nor the methylene blue exhibit the conducting fibrils of the nerves, but only the neuroplasm in which they lie. For my own part, I am inclined to believe that Turner and Hunter are right in supposing the fine nerve-filaments to lie upon the body substance of the cells which they invest. It appears to me that when nerve-fibres are split into their constituent

<sup>1</sup> Veratti. *Sul alcuni particolarità di struttura dei centri acustici nei mammiferi*, Pavia, 1900, pp. 81, 7 plates.

<sup>2</sup> Turner and Hunter. "On a Form of Nerve Termination in the Central Nervous System demonstrated by Methylene Blue," *BRAIN*, 1899, p. 123.

fibrils, or fine bunches of fibrils, the nutrition and insulation of these fine fibrils, which doubtless consist of conducting elements invested in neuroplasm, is in some way provided for by bringing them into juxtaposition with the cells near which they are passing, and the large dendrites of these cells. The neuroplasm of these cells is in some way favourable to the vitality of the fine fibres. It provides for the insulation and nutrition of the fibrils throughout the distance through which they lie upon it. To this subject I shall recur when speaking of granules.

With these preliminary observations I pass to the consideration of the question which I propose to discuss in this paper, namely: *Are the neurons genetically and structurally discrete; or do the distributing processes of one neuron form true anastomoses with the collecting processes of other neurons?*

As evidence of union of neurons I propose to consider:

(1) The relation of the terminal arborisation of axons to so-called "granules."

(2) The neurons of the sympathetic system.

(3) The evidence that "thorns" are portions of conducting fibrils surrounded by the neuroplasm of the collecting processes of nerve-cells.

#### (1) GRANULES.

When the chrome-silver method first came into use the extraordinarily distinct pictures of large nerve-cells which it presented in the cortex cerebri et cerebelli, the spinal cord, the olfactory bulb and elsewhere, attracted universal attention. They were so sharply defined and apparently so complete that they distracted attention from the other elements of which nerve-tissue is composed. Even now we frequently meet with an attempted counting of the "nerve-cells" in the cortex or in the central nervous system as a whole, in which no account is taken of the granules and other small cells! Yet the granules are far more numerous than the pyramids or cells of Purkinje, and each granule is equally complete, and equally entitled to the designation of

"nerve-cell" or "neuron." When Pedro Ramón showed the axons of the granules of the cerebellum, and his brother, S. Ramón y Cajal, the axons of the granules of the retina, they demonstrated that each of these granules is a perfect nerve-cell, with dendrites and axon and all other features of a neuron. They differ from the great cells which give off efferent fibres in no respects other than size. I have shown that the granules of the olfactory bulb (which other histologists set aside as "amacrine" cells or even as glial cells), have axis-cylinder processes and thorny protoplasmic processes, and are therefore also complete nerve-cells; <sup>1</sup> a fact of some importance, apart from its particular application, because it leaves it open to us to conclude that when, in the future, we see a cell which has all the ordinary characters of a nerve-cell, and especially when it bears branching *thorny* dendrites, it cannot be a glial cell, however difficult we may find it to demonstrate the axis-cylinder. As further evidence of the nervous nature of the granules of the olfactory bulb Blanes <sup>2</sup> has pointed out that they readily take the vital methylene-blue stain, whereas the glial elements remain uncoloured; and further that they are to be found with their characteristic form in vertebrates which do not possess in this situation any typical glial cells. It is clear that no plan of the structure of nerve-tissue is complete which does not include the granules, or which, in any situation in which they occur, sets them aside as non-nervous elements. Indeed they are just as important elements or units as the largest nerve-cells.

When a nerve-fibre reaches a muscle-fibre, or the modified muscle-fibre of an electric organ, its terminal arborisation, or the sarcogleia in which it is embedded, contains nuclei. In the end-plates of the frog these nuclei, which rest immediately upon the nerve-twigs, were termed by Henle the "nuclei of the branches of the axis-cylinder,"

<sup>1</sup> Hill. "Notes on Granules," BRAIN, 1897, p. 125. It was only after making thousands of preparations that I was able to demonstrate the axis-cylinders; and so curiously capricious is the chrome-silver colouration in this matter that, although I am always glad to show the sections in which axons are visible, I am afraid to part with them, since I have but two or three!

<sup>2</sup> Blanes. "Sobre Algunos puntos dudosos de la estructura del bulbo olfatorio," *Riv. trimestr. microgr.* 3, 1898.

and distinguished by him from the nuclei of the sheath of epilemma. No one, I think, will deny that there are, in the end-plate, nuclei which are different in appearance to those of the muscle substance. There are two, if not three, forms of nucleus on the fine nerve-twigs, which are distributed to the electric organ of the skate; but I do not find it possible, after allowing for the nuclei of the sheaths of the nerves (after they have lost their myelin), to distinguish with certainty any nuclei which clearly belong to the nerve-twigs. It seems to me quite possible, however, that Henle's nuclei of the branches of the axis-cylinder are nuclei of nervous elements through which the conducting fibrils of motor nerves are distributed to muscle-substance. If this conjecture be justifiable the conception of a motor neuron is incomplete unless the minute cells (daughter cells of the large cell in the anterior horn of the spinal cord?) are included in the neuron. This is equivalent to saying that the theory of the individuality of the neuron breaks down. I lay no stress upon this hypothesis of the mode of ending of motor nerves, however, but use it merely as an illustration of the mode of ending of ascending (sensory) fibres which I am about to describe.

The crucial test of the neuron theory lies, as it seems to me, in the proof that fibres which ascend from cells in the cerebro-spinal axis end freely in the cortical fields. If the ascending fibres pass without breach of continuity from cells in the spinal ganglia or in the nuclei of Goll and Burdach into cells in the cortical field—if, that is to say, they start in one large cell (or, accepting Apáthy's findings, if they originate with a "fibre-cell," pass through a "ganglion-cell") and join several small cells—the neuron theory falls to the ground. It is true that various qualifications are introduced by recent writers into the expression of the theory; "relative individuality of the neurons" is often substituted for the definite expression of absolute independence; but if as a mechanism each nerve-cell with its collecting and distributing processes is not an anatomical integer but a part of a chain of cells, the theory loses all significance.

It is generally assumed, in the case of the cortex cere-



belli at any rate, that afferent fibres come into relation with "granules" and that the axons of the granules transmit the impulses, which the afferent fibres bring, to the more superficial elements of the cortex. Ramón y Cajal represents the branching afferent fibres (mossy fibres) as being in relation with the clawed dendrites of the granules, and the bifurcating axons of the granules as in relation with the dendrites of the Purkinje cells. Neglecting all other elements and reducing the scheme of connections to a diagram, the conducting arc of the cortex cerebelli consists of a mossy fibre—its end-branches, granules; their axons, dendrites of a Purkinje cell—its axon. The granules are, according to this scheme, secondary or tertiary neurons of the chain leading from sensory cells to the cortex cerebelli, and each granule is supposed to be as independent, as self-contained, as the larger neurons between which they are intermediaries.

In my preparations I find a few instances of granules which (figs. 1, 2 and 3) are distinctly connected with fibres of the arbor vitæ on the one side and with divaricating axons, passing between the cells of Purkinje to the molecular layer, on the other side. I find a very large number of granules which are connected with fibres from the arbor vitæ. In some cases the axon of the granule passes with a much twisted course towards the arbor vitæ (figs. 4, 5). In the two specimens figured (4, 5) the connection of the granule and the nerve-fibre occurs at a point which will afterwards become the clawed end of one of the arms of the granule.<sup>1</sup> Fig. 6 shows a granule the axon of which joins, apparently, a branch of a fibre from the arbor vitæ which ends by ramifying in the molecular layer. Figs. 7 and 8 illustrate a not uncommon disposition of the axon of a granule in which, before it reaches the sheet of Purkinje cells it bifurcates, giving one branch to the molecular layer and another which runs inwards towards the arbor vitæ. In fig. 9 is seen a granule the axon of which has an extra-

<sup>1</sup> It will be understood by everyone who has worked with the chrome-silver method that when I assert that a fibre is continuous, or that two fibres are in connection, I wish to imply that all attempts to prove discontinuity by careful focussing, by oblique illumination, &c., have failed. When two opaque black objects are superposed or in close juxtaposition, they appear to be in continuity. It is never possible to make sure that this is the case.

ordinarily tortuous course and gives off several branches in the granular layer as well as one or more branches to the molecular layer.

It will be noticed that none of the granules figured have the ordinary form of the cerebellar granule. This, as is well known, is a round cell with four or five dendrites ending in clawed hands and a single axon which divaricates into two long fibres in the molecular layer. But granules of this form do not make their appearance until comparatively late in development; in puppies at about 18 days, kittens at about 14 days, hedgehogs at about 18 days. It is, I fear, impossible to give exact dates owing (1) to the unreliability of the chrome-silver method, and (2) to the fact that the histogenetic development of the cortex cerebelli takes place gradually. Granules having the immature, carrot-like form represented in figs. 1 to 8 are to be found long after the first mature granules have made their appearance. To make this part of the subject clear it will be necessary to give some account of—

### *The Development of Ordinary Granules.*

In a paper published in 1889 Bellonci and Stefani<sup>1</sup> gave an accurate account of the changes in the external nuclear layer, which might have suggested the migration of the granules subsequently discovered by Ramón y Cajal. They described the formation of a molecular layer containing some scattered cells before the overgrowth occurs, from behind forwards, of the nuclei of the ependymal stria of the velum medullare posterius. As the nuclei spread forwards from this stria (the Rautenlippe of His?) their mitotic figures indicate active division. For some time before the appearance of the cells of Purkinje, and still more after these are differentiated, the nuclei are distinguishable into two zones—an external, in which the nuclei are round and rich in caryokinetic figures; and an internal, in which the nuclei are elongated transversely and rarely show caryo-

<sup>1</sup> Bellonci et Stefani. "Contribution à l'histogénèse de l'écorce cérébrale," *Arch. ital. de Biologie*, xi., 21.

kinetic figures. The molecular substance is chiefly made up of transverse fibrils which Bellonci and Stefani presume to be derived from the elongated cells. "The deepest nuclei of this layer appear uncoloured and are consequently seen with difficulty. As the molecular layer grows in thickness they are destroyed in great numbers." Löwe<sup>1</sup> had previously described the molecular substance as formed by the fusion into a mass of the cell bodies of these nuclei, the nuclei becoming vesicular and gradually disappearing.

In the light of Ramón y Cajal's observations, to which reference will be made immediately, it is clear that the disappearance of the nuclei is due, not to their degeneration, but to their migration past the cells of Purkinje into the granular layer.

Simultaneously with Bellonci and Stefani, Lahousse<sup>2</sup> described in very similar terms the appearance and overgrowth of the external nuclei. He named this layer "the layer of Obersteiner," since the Viennese professor was the first to describe it;<sup>3</sup> but he prefers to call the cells of which it is composed "cellules conquérantes" or "cellules de renfort." "The reinforcing cells multiply abundantly and invade, from behind forwards and from within outwards, almost the totality of the external surface of the cerebellum, with the exception of the median line and the posterior part of the inferior vermis, in the neighbourhood of the median line."

It is evident from the descriptions just quoted that the cells of the external granular layer have a secondary origin. They are not formed from the general mantle-layer of the cerebellum. It is curious and probably significant that their site of origin should correspond nearly with that of the spinal ganglia, and that each little cell should be in the mode of its growth—a fusiform cell converted into a round cell with an axis-cylinder in the form of a T—a root-ganglion

<sup>1</sup> Löwe. *Anat. u. Entwicklungsgeschichte d. Nervensystems*, vol. ii., Leipzig, 1883.

<sup>2</sup> Lahousse. "Recherches sur l'ontogénèse du Cervelet," *Arch. de Biologie*, viii. (1888), p. 43.

<sup>3</sup> Obersteiner. "Beiträge z. K. von feineren Bau der Kleinhirnrinde," *Sitz. d. K. Akad. d. Wissensch.*, Vienna, 1860, and again in *Biologisches Centralblatt*, iii. (1883).

cell in miniature, *plus* five or six clawed arms. We owe to a very remarkable piece of histological work carried out by Ramón y Cajal the proof that the granules undergo the transformation just described.

According to Ramón y Cajal, the precursors of the granules are fusiform cells, tapering into a fibre at each end (figs. 18 and 19).

That Ramón y Cajal's description of the transformation of fusiform cells into granules is right is borne out by appearances such as are shown in figs. 18, 20, and 22, as well as by the fact that the fusiform cells are not to be found in adult cerebella. There are, however, some difficulties in explaining how the one kind of cell is transformed into the other.

It is, for example, to be noticed that in the embryonic state of these granules—when they are fusiform or “fibre-cells”—there is an obvious distinction between the thread-like axon on the one side and the thicker process on the other side, which has the appearance of a dendrite (fig. 18), and yet both alike, according to Ramón y Cajal, become horizontal limbs of the T-shaped axon of the granule. Further, certain noteworthy physiological difficulties result from this. In the first place, since the granules cannot be supposed to have any function until they have, by sinking beneath the layer of Purkinje cells, established connections with afferent (mossy) fibres, it is remarkable that their processes should be so long. The length of the tangential fibres, to which the fusiform cells which Ramón y Cajal regards as embryo granules give rise, is very remarkable. I have traced them in a puppy for fully  $1\frac{1}{2}$  mm. A study of the histogeny of the nervous system leads to the conclusion that the growth of conducting strands, if it cannot be described as a response to function, keeps but little, if at all, ahead of function. Yet here we have what, to all appearance, are well-developed nerve-cells and fibres which cannot, so far as we can understand the conditions which obtain in the embryonic cerebellum, take on functional activity for some time. We should have expected to see the lateral extension of the limbs of the T delayed until there was a

possibility of impulses passing into them up the vertical limb. In the second place, if the view universally held as to the function of the granules—that they collect impulses from the afferent (mossy) fibres and distribute them to the dendrites of the Purkinje cells by means of their divaricating axons, a view enunciated by Ramón y Cajal in his Croonian lecture—be correct, the distinction between cellulipetal and cellulifugal conduction, in the case of granules, breaks down. Both the axon and the dendrite of the precursor of the granule conduct (when they become the two limbs of the T-formed axon) outward from the cell. It may be said that a similar difficulty has to be met in the case of the cells of spinal ganglia; but the cases are not quite parallel. It is open to us to consider the distal process of a root-ganglion cell as the dendrite, the proximal process as its axon; since the one conducts cellulipetally, the other cellulifugally. Of course, if Apáthy's theory of "nerve-cells" and "ganglion-cells" be substantiated, this point loses its significance, since the root-ganglion cells must be "nerve-cells," from which fibrils are developed, which grow both outwards to the sensory cells and inwards into the axial cells. If the description given by Ramón y Cajal of the formation of the granule be correct, the cell-body withdraws from the fibre, just as in the case of a root-ganglion cell; but the horizontal limb of the T is not a direct conductor from left to right, but a distributor of impulses to the left and to the right.

Here I ought to mention a difficulty which has met me in tracing the origin of granules from these fusiform cells. In long hardened tissue I find these fusiform cells—which might be termed "fibre-cells"—in the developing molecular layer in very great numbers; but I have never succeeded in demonstrating the first step in their conversion into granules. I find granules with a carrot-like apical process which points towards the granular layer, and a very short T-process which branches right and left in fine nerves (fig. 20), which looks as if it might have been derived from a fibre-cell; but after a most prolonged search, I have failed to see the first step in the pinching together of the two processes of a fibre-cell. Again, in certain animals, especially

the puppy (fig. 18), the fibre-cells appear to be larger and better developed than the first-formed granules. Lastly, these well-developed fibre-cells often show fine branches given off vertically to their lateral continuations, both axonal and dendritic (fig. 19). Such branches appear to have no place in the constitution of the granules.

Athias<sup>1</sup> insists that the bipolar cells are at first connected with the surface by a thick vertical process. Ramón y Cajal figures the same condition. But as soon as the body of the granule has withdrawn from the horizontal fibre it shows a thick process directed towards the granule layer. This reversal is certainly very remarkable, and I have looked carefully for transitional stages, but without success.

Occasionally I find a developing granule with a thick apical process which points towards the surface; but this condition is rare, and I think that Cajal, Popoff, Athias, and others, have confused with developing granules cells of a different kind (figs. 15, 16, 17) which are to be found in the deeper part of Obersteiner's layer, or just below it. Under any circumstances it is very difficult to understand the transitions through which a truly bipolar cell (fig. 18) passes in becoming a granule. At first it has an axon to one side and an apical process to the other. Then, according to the received account, it has an apical process directed towards the surface, and axons to right and left. Next it has a centrally-directed apical process and axons right and left. It appears to me that three different kinds of cell are developed in the molecular layer or superficial to it—A and B, the granules which I have called carrot-granules, and the ordinary granules from Obersteiner's layer—C, the cells of Cajal, either from the deepest part of Obersteiner's layer or from the underlying superficial part of the mantle-layer.

Our information with regard to the histogenesis of the cerebellum is far from complete, but the following points seem to stand out clearly: (1) The nuclei found at birth and for some time subsequently, outside the sheet of cells of Purkinje in the cortex cerebelli, are much more numerous

<sup>1</sup> Athias. "Recherches sur l'histogénèse de l'écorce du cervelet." *J. de l'Anat. et de Physiol.*, XXXIII. (1897), p. 372.

than the nuclei of the molecular layer in the adult. (2) There is no sufficient indication of cell division on the ventricular side of the cells of Purkinje to account for the formation of the granular layer. Hence the granules are migrants from the superficial tissue. (3) From Obersteiner's layer are developed granules, "carrot-granules," Cajal's cells, and the small cortical cells or stellate cells of the molecular layer. (4) In the mantle proper are developed glial cells, Golgi cells, and Purkinje cells.

*The further stages in the growth of the granules* have not been described, but they are of great interest. As soon as the granule has passed through the layer of Purkinje cells its apical carrot-shaped process increases considerably in length and gives off several slender side branches (figs. 1, 3, 23) which divide two or three times into long slender twigs. In this stage it shows none of the clawed arms which are so characteristic of the fully formed granule. These appear later as lateral branches, very short at first (fig. 25). In the meantime the long apical process makes its way towards the arbor vitæ, which it frequently enters, becoming lost among the fibres (fig. 1). Its appearance at this stage is strongly suggestive of its feeling down amongst the fibres for nerve connections.

In puppies until they are about 18 days old, hedgehogs 18 days, kittens 2 weeks, none of the typical round granules with four or five arms ending in claws are to be found. All the granules have the appearance shown in figs. 1, 2, 3, &c. It is at this stage that the granules show a double connection—with the fibres of the arbor vitæ on the one side, and with an axon divaricating in the molecular layer on the other.

It is also to be noticed that the granules, which at first are placed with their long axes horizontal (fibre-cells), are next placed vertically, as they migrate past the cells of Purkinje, and lastly, more or less horizontally again as they approach the arbor vitæ.

The meaning of the "claw" is at present obscure. The claw assumes, in chrome-silver preparations, many different forms. Sometimes it appears as a hand with four or five fingers. Occasionally it is a complete basket, which is often

larger than the granule which it appears to enclose; too large, that is to say, to be in contact with the body substance of the granule which it envelops. Every intermediate condition between these two forms is seen. Every now and again one sees a basket which appears to re-form into a fibre, as if the arm of the granule which had divided into a basketwork were in continuity through this basketwork with a (? mossy) fibre.

In my paper on the Chrome-silver Method I called attention to the fact that the baskets of Ramón y Cajal which invest the cells of Purkinje are frequently seen to reunite beneath the cells into bunches of fibres, which enter the granular layer. In other words, the tassel of fibrils depends beyond the base of the Purkinje cell. Instead of the tassel of fibres being closely applied to the surface of a Purkinje cell it is loose and large, and its twigs surround the axon of the cell. This observation is confirmed by Dr. John Turner, staining with methylene blue.<sup>1</sup> On the other hand, fibres which branch in the granular layer break up into baskets which approach the cell from below. Fibres are frequently seen in the granular layer which have just the same relation to the Purkinje cells as the branches from the axons of Cajal's cells, except that whereas the latter approach them from below, the former approach them from above. It is quite possible that the two kinds of basket are continuous, or, to speak more correctly, that there is only one kind of basket into which the fibre from the one side breaks up, and from which the fibre on the other side is re-formed; the chrome-silver method revealing sometimes the one half of the basket, and at other times the other. It is very difficult to account for such an arrangement as a basket-work which envelops the body of a cell without establishing any connections with it; and I hesitate to suggest a hypothesis, but it seems to me not impossible that where connection is to be established between two kinds of nerve-fibres the fibres break up into their constituent fibrils, which rest upon the body of a neutral cell. If this be possible, the

<sup>1</sup> Turner. "A Note on the Staining of Brain in a Mixture of Methylene Blue and Peroxide of Hydrogen." *BRAIN*, 1900, p. 524.



cell of Purkinje in some way provides for the insulation and nutrition of the isolated fibrils. In the same way the baskets into which the arms of the granules appear to end may be bunches of elementary fibrils separated out at the spot where the arm of a granule joins some other kind of fibre. I shall amplify this hypothesis later on.

*Carrot-Granules with Centripetal Axis-Cylinders.*

In 1896<sup>1</sup> I described and figured granules whose axis-cylinder processes join the fibres of the arbor vitæ. They are distinguished by their carrot-like form, and are only found in tissue which has been hardened in bichromate (with or without osmic acid or formalin) for a long time.<sup>2</sup> Subse-

<sup>1</sup> BRAIN, 1896, p. 35, fig. 14.

<sup>2</sup> *Method.*—All the sections figured in this paper were prepared from tissue which had been immersed in bichromate of potassium and osmic acid or formalin for a long time. When endeavouring to ascertain the nature of the chrome-silver reaction I varied the length of time during which the tissue was immersed in the respective fluids within very wide limits. This research was undertaken without any thought of discovering new elements of nerve-tissue, but merely with a view to ascertaining the nature and the limitations of the method. Unlike Lenhossék, Ramón y Cajal, and others, I find that nothing is lost by a long immersion in the chromate. I know of no structural feature which is exhibited in tissue hardened in bichromate of potassium and osmic acid for a few days, which is not also to be found in tissue which has been hardened in this mixture for two or three years before being transferred to silver nitrate. On the other hand, I have never found "carrot-granules" or the most delicately-branched fibres of the granular layer in tissue which has not been hardened for at least a month; and I am disposed to think that they are best seen in tissue which has been hardened for at least three months.

After a year the tissue becomes very brittle and difficult to handle, and since nothing more is to be gained by such a prolonged hardening, I regard the best length of time for immersion in the chromate as from three to six months. This method is especially successful with young animals—cats, dogs, &c., of not more than a month old. Among my specimens from adult brains which have lain in bichromate of potassium and osmic acid for more than a year the greater number are complete failures. Some, on the other hand, are admirably coloured. Evidently, therefore, other conditions beside the long hardening help to determine the success or failure of the impregnation. How admirably it may succeed is well shown in fig. 12, of a Golgi cell from the cerebellum of a cat twenty-seven days old, hardened for five months. This cell lies at the apex of a convolution, and it is curious to note that its branched axis-cylinder is continued by a very delicate fibre to the extreme base of the convolution, a distance of at least 2 mm. Whether or not this revelation is due to the method it is impossible to say, but I have never seen such a connection in a specimen hardened as directed by Golgi or by Ramón y Cajal. Nor is it in accordance with any description of these cells of Golgi's type II., the specific character of which is supposed to lie in the complete arborisation of their axons within the cortex.

It is to be noticed that the dendrites of the Golgi cells are destitute of thorns. In this respect they contrast in a very marked way with the extremely thorny dendrites of the Purkinje cells, fragments of which are to be seen on the right and left of the figure.

quently (BRAIN, 1897, pp. 125 and 466) I described and photographed granules of extremely similar form, which I had found in the molecular layer. After Ramón y Cajal's description of the origin of the granules from bipolar cells, I am satisfied that those which I described are embryonic granules, strangely unlike to adult granules though they are. Carrot-granules with centripetal axis-cylinders are, however, cells which cannot be confused with developing clawed granules. They are most numerous at the apices of the folia, when they appear (as shown in fig. 13) as cells of considerable length. They always take a brown colouration, the nucleus remaining clear. Their apical processes divide two or three times as they extend outwards towards the cells of Purkinje. Their axis-cylinders may be undivided, or they may give off branches which return towards the surface. In the developing cortex cerebelli, at an early stage, cells are to be seen which cannot be embryonic granules of the ordinary form (figs. 15, 16, and 17). They are placed vertically to the surface. Their apical processes reach at first to the pia mater, where they usually end in a knob, which rests against this membrane. Their axons take a centripetal course. Subsequently the apical process withdraws from the pia mater, and the cells sink more deeply in the molecular layer. Their axons frequently give slender lateral branches. It is possible that these cells will grow into Golgi cells or even into cells of Purkinje; but considering the very early date at which cells of both these classes assume a well-developed appearance, I am disposed to think that the fusiform cells just described are not destined to undergo this transformation, but are developing carrot-granules. The cells represented in fig. 17 in the molecular layer certainly appear to be the same as those which are represented in fig. 13 in the granular layer.

I have found carrot-granules in very large numbers in rats (up to 12 days), kittens (to 14 days), puppies (to 21 days), hedgehogs (to about 18 days). I have never found them, with certainty, in adult cerebella. It is true that I have found a few doubtful specimens in adult sheep, but they were not sufficiently distinct for me to lay any stress

upon them as proving that the granule with centripetal axis-cylinder is a permanent structure. On the other hand it should be noted that these granules make their appearance only after long hardening, and I have but very little adult tissue which has been so treated. One is afraid to lay down any rule for the chrome-silver reaction, the next set of sections prepared may prove it fallacious; but in several specimens of tissue which were tested by the nitrate of silver at intervals during the hardening process, the granules with centripetal axons were not found until after long hardening, the earliest case being after immersion for five months in bichromate and osmic acid.

Are the carrot-granules with centripetal axons, like the carrot-granules with centrifugal axons, embryonic cells? A very large number of observations have failed to reveal any transitional forms, and it is difficult to conceive, if they be embryonic, into what adult elements they grow. It might be supposed that they grow into Golgi cells; but the Golgi cells are remarkably mature in appearance in sections which abound in carrot-granules; indeed, they are amongst the earliest of the cerebellar elements to take on an adult form. Again, the Golgi cells are always supposed to belong to "Golgi's type II.," that is to say they are cells with short axis-cylinders. (A curious instance of an axis-cylinder which does not terminate by arborisation in the vicinity of the cell is shown in fig. 13; but this does not justify us in drawing the conclusion that all Golgi cells have connections with the fibres of the arbor vitæ.) I cannot at the present time see any indication that the carrot-granules are young Golgi cells. The only alternative left open is, therefore, that either they are cells found in the young animal which disappear in the adult, or that they are cells which the chrome-silver method reveals in the young animal (owing to its peculiar suitability for embryonic tissue) and does not reveal in the adult.

If these cells belong to a distinct and hitherto unrecognised class it is most important that they should receive a distinctive name. The application to tissue elements of the names of their discoverers is to be deprecated except in very

special cases. That Purkinje, Golgi and Cajal should have written their names on the cerebellum is no more than their due, but even in their case the application of the name should be rigidly limited. The cells most intimately associated with Cajal are the basket cells. Cells of the molecular layer which do not form baskets must bear another name, and probably none is better than "small cortical cells," proposed by Schäfer. Golgi's cells are the remarkable large cells with branching axis-cylinders. Some of them lie amongst the cells of Purkinje and branch in the molecular layer, whereas others are restricted to the granular layer. The application of Golgi's name to other cells, and especially to the granules, is extremely confusing. Probably the time-honoured name "granule" is the least likely to be misunderstood. If the cells which I have described are distinct from the typical round granule, the term "carrot-granule" will probably as well as any other mark this distinction and at the same time convey to the reader's mind the idea that they are so small as to belong to quite a different class of element from the Golgi-cells. Their rarely-branching axis-cylinder continued into the arbor vitæ completely separates them from the "cells with short axis-cylinder of Golgi's type II."

Since the cells of Purkinje are the only recognised cells with descending axons, I have spoken of the carrot-granules as connected with ascending fibres; but this is, of course, a hypothesis in support of which we have not, at present, any evidence.

## (2) SYMPATHETIC SYSTEM.

When evidence derived from the central nervous system led to the formulation of the neuron theory, it was concluded that the cells of the sporadic ganglia must be brought into line with the neurons of the axis. Instead of the sympathetic cells being "distributive," in the sense that each receives one nerve-fibre of a certain thickness and gives origin to a number of thinner fibres—the afferent fibre being usually medullated and the efferent fibre non-medullated—it was assumed that the thicker fibre is the

axon, the thinner fibres dendrites. But the histological evidence upon which this view is based is not by any means satisfactory. I may summarise my doubts as to its justice under the following heads :—

(a) The alleged dendrites do not present the characters by which dendrites are usually distinguished. This is shown in all figures with which I am acquainted, (see, for example, Kölliker's "*Gewebelehre*," vol. ii., figs. 834, 835), and therefore I have not thought it necessary to prepare fresh illustrations. The end branches of the so-called dendrites are exceedingly slender filaments, often of a great length. They are usually varicose—a very characteristic feature of the finest nerve-fibres and a rare feature in dendrites. They are destitute of thorns. For reasons which will appear later I regard thorns as the distinctive markings of true dendrites, but on this point I possibly take too strong a position.

(b) The so-called dendrites may often be followed beyond the limits of the ganglion. Where stained cells lie near the point of exit of a gray ramus the so-called dendrites frequently pass as a bundle of very slender fibres into the ramus.

(c) If it be accepted that the branching processes are dendrites it is very difficult to assign to them any function. Setting aside the doctrine of their purely nutritive function, dendrites are regarded as establishing connections between the cells to which they belong and the end-branches of axons of cells lower or higher in the system. The tissue of which the ganglia are composed is however peculiarly unfavourable for such connections. It is a dense connective tissue packed with large nerve-cells and traversed by innumerable nerve-fibres. There is no "gray matter." There is none of the tissue which, in the cerebro-spinal axis or in the ganglia of invertebrates, seems to be essential for the establishment of such connections.

(d) Failing communications between end-branches and dendrites, the manner in which the neurons of the axis influence the neurons of the ganglia is insufficiently explained. It appears to be limited to the various forms of "basket" which have been described. Ramón y Cajal, Retzius, Kölliker and others, have described certain of the "dendritic

branches" as forming baskets, upon which Kölliker very properly remarks: "Welchem Verhalten ich jedoch bei genauer Ueberlegung keinerlei physiologische Bedeutung zuschreiben kann und dasselbe nur für etwas zufälliges erklären muss" (*loc. cit.*, p. 853). The whole question of baskets, pericellular plexuses, and pericellular tangles is most obscure. Their primary purpose does not seem to me to be to establish a connection between end-branches and the cell-body which they invest; to this question I have already referred, suggesting a hypothesis, when treating of the granules of the cerebellum.

(e) It is beyond question that the præganglionic nerves (white rami, &c.) contain fewer fibres, and these larger (medullated) than the postganglionic nerve. As Gaskell's<sup>1</sup> careful analysis of the sympathetic system showed, the ganglia may be looked upon as stations in which medullated fibres are replaced by bundles of non-medullated fibres. If the old view that the cells of the sympathetic ganglia receive each a large fibre and give off a number of fine fibres be discarded, the enormous multiplication of fibres which occurs in the ganglia must be effected by the subdivision of the axons of their cells. Such a subdivision is assumed; but in cases in which that process of a cell which is, beyond doubt, its axon can be followed for some distance, it is, so far as my own observations go, conspicuous for the absence of collaterals or side branches of any kind.

(f) If the neuron theory be applicable to the sympathetic system, which is, so far as we know, entirely an efferent system, the præganglionic fibres must end by arborisation, the axons of the cells must constitute postganglionic fibres. I have made various preparations with a view to ascertaining if this is the case. Owing to technical difficulties these preparations are not quite satisfactory, but they leave me in little doubt but that the axons of the cells of the sympathetic ganglia are directed towards the præganglionic fibres, *i.e.*, towards the cerebro-spinal axis. In the superior cervical ganglion, for example, the axons leave the ganglion at its

<sup>1</sup> Gaskell. "Nerves which Innervate the Visceral and Vascular Systems." *Journal of Physiology*, vii., 1.

cervical end. This is a question upon which I hope to give a further report in a short time.

(g) The mode of origin of the sympathetic ganglia is suggestive of a permanent connection between their cells and cells in the cerebro-spinal axis. The sympathetic neuroblasts are cells which at a very early stage have migrated from the neuro-epithelium which forms the cerebro-spinal axis and the spinal ganglia. It may well be that they retain, during their migration outwards, a connection with the cells with which they are genetically associated. They may each "pay out" a strand—the subsequent axis-cylinder which keeps them in union with their mother cell. This is, of course, a mere speculation. If the sympathetic rudiments are separated off from the rudiments of the spinal ganglia as His teaches, the genetic connection would be difficult to explain, since the fibres of the white rami communicantes travel chiefly in anterior roots. At any rate the fact of migration makes the retention of connecting fibres between mother cells and daughter cells possible, whereas, if the ganglia had completely independent rudiments, it would be impossible.

The strongest argument for discontinuity of neurons in the sympathetic ganglia is to be derived from the well-known observations of Langley and Anderson, that nicotin paralyses the ganglia, preventing the passage of impulses *via* the ganglion-cells, while it does not paralyse the fibres which pass without interruption through the ganglia. It would seem natural to suppose that the nicotin prevents the end-branches of the higher neuron from acting upon the cell-body of the lower neuron. But, on the other hand, against this interpretation is the fact that nicotin does not thus stop the passage of impulses in the ganglia of Auerbach and Meissner in the intestine.

Langley, on this account, doubts whether these are ganglion cells in the proper sense of the term. They have, however, exactly the same histological characters as the cells of the ganglia. This is shown in figs. 841, 842, 843, 844, 845, of Kölliker's handbook. A study of these intestinal plexuses reveals their amazing richness in nerve-cells. If these cells are stations for breaking up nerve-fibres

afferent to the plexus into bunches of efferent nerve-fibres for the supply of the musculature of the intestinal wall, it is not impossible that they provide a separate fibril for every muscle-cell.

If the neuron theory is true it is applicable to the sympathetic system. The evidence that this is the case is not, as yet, complete or convincing. There are, on the contrary, reasons for supposing that fibres which start from cells in the cerebro-spinal axis end in cells in the sympathetic ganglia, and that fibres from cells in these ganglia end in cells of the intestinal plexuses. If such a direct connection obtains between cell and cell, the neuron theory of the separateness and isolation of all nerve-cells breaks down.

### (3) THORNS.

In papers already referred to I have called attention to the following facts:—(a) By varying the method of preparation, although using absolutely fresh and healthy tissue, specimens of cortical pyramids and other large cells may be obtained which in some cases are absolutely thornless, whereas in other preparations they bear thorns. (b) Thorns present a great variety of form. Usually they are short rods ending in knobs; occasionally they appear as filaments without knobs, two or three times as long as the knobbed rods. (c) In certain specimens no thorns are seen, but their place is taken by one or more minute black dots. When there are several of these dots they are always arranged in a straight line.

From these facts I draw the conclusion that the substance which has the power of fixing the chrome-salt, and, therefore, on the entrance into the tissue of silver-nitrate, of forming a silver-chrome salt which is subsequently reduced,<sup>1</sup> is a semi-fluid substance which surrounds and in-

<sup>1</sup> The nature of the reaction which occurs in the Golgi method of colouration does not seem to be generally understood. The reaction appears to be as follows:—When nerve-tissue is placed in a chromate, certain cells and fibres fix the chrome-salt. When the block is dropped into nitrate of silver, the loose chrome-salt quickly diffuses out into the silver-nitrate, which it precipitates as silver-chromate. The silver-nitrate enters the block more slowly, and wherever it finds a tissue-element which has retained the chrome-salt it combines with the chrome-salt to form an unstable subchromate of silver. Osmic acid and formalin favour the fixation of the tissue, without in any way taking part in, or interfering with, the reaction.



vests unstaining fibrils. The usual appearance of a rod and knob is due to the fact that at the time of fixation the semi-fluid cytoplasm of the dendrites is extruded outwards along the unstained filament which every thorn contains. Beyond a certain distance from the dendrite the film, which presumably becomes thinner and thinner the farther it is from the dendrite, collects, under the force of cohesion, into a droplet. The thorn, therefore, appears as a rod ending in a knob, because this is the form which the stainable cytoplasm assumes; but there is no ground for supposing that the supporting unstained fibril ends at the knob. If a thin wire be plunged into syrup, the viscid liquid which forms a film around the wire at the moment when it is withdrawn, runs the next moment into drops. When a thorn is replaced by a row of black dots, it seems clear that the droplets are supported upon a something which resembles the wire which supports the drops of syrup.

Thorns, therefore, are not artifacts in any proper sense of the word. They are the unstained (conducting?) fibrils surrounded for a longer or shorter distance with the cytoplasm of the dendrites, the cytoplasm alone being coloured.

This hypothesis is justified by a study of the development of thorns. In young cells, in which the cytoplasm is, relatively to the nerve-fibrils, apparently more abundant than it is in adult cells, the thorns are larger and coarser. This is conspicuously the case on the woolly-looking dendrites of the cells of Purkinje at a very early stage. It may also be noticed, as was pointed out by Athias, that when the cells of Purkinje are first recognisable, filaments appear to join their cell-bodies; whereas, *pari passu* with the growth of the dendrites, the cell-body becomes clean and free from filaments, as if the dendrites carried the connecting filaments away from the body of the cell. Figs. 27, 28, and 29 represent three very typical stages in the development of a Purkinje cell.

If this evidence be admitted, gray matter contains a scaffolding formed of an infinite number of fibrils, which place the arborisations of axons and of collaterals in connection with dendrites. Owing to the extreme tenuity of

these fibrils in higher animals, no method of staining them outside the cell, in such a way that they are amenable to examination by the microscope, has yet been devised; although, as will be presently explained, Bethe seems to have stained either certain of the larger fibrils or groups of fibrils. Yet the delicate fibrils of vertebrate nerve-tissue are probably the phylogenetic successors of the coarser fibrils, which Apáthy, using chloride of gold, demonstrates in invertebrates. For the protection, nourishment, and insulation of such fibrils some "intercellular substance"—in the sense in which Nissl<sup>1</sup> uses the term—seems to be needed. Within the cell the fibrils are supported by cytoplasm.

If it be urged that the chrome-silver staining ought to reveal the presence of this labyrinth of primitive fibrils, it may be answered that it very frequently does so; but all preparations in which there is evidence of the existence of an infinity of fibrils are set aside as mis-stainings. Everyone who uses the Golgi method is familiar with the blotches of black deposit, looking like a burr on a wild rose-bush, which are seen here and there in most preparations. They are set aside as "deposits" because no details of structure can be seen within them; but the fibrils which appear around the edge of the blotch are no doubt actual structures about which the deposit has occurred.

Further, it must be remembered that intracellular fibrils have been described by many observers. It can hardly be doubted that such primitive fibrils exist; and if—as there seems every reason for thinking—they are the conducting elements of the nervous system, it is much more likely that they come to the cell from outside than that they originate within the cell and its dendrites.

Since Max Schultze, in "Stricker's Handbook of Histology" (1871), described the fibrillation of the cell-body, fibrillæ have been described by H. Schultze, Flemming, Benda, Dogiel, Kronthal, Apáthy, Nissl, Held, Bethe, *et al.* No two of these descriptions exactly agree, so far as regards the size and disposition of the fibrils within the cell, and it

<sup>1</sup> Nissl. "Nervenzellen und graue Substanz," *Münch. med. Wochenschrift*, 1898, pp. 988, 1023, 1060.

must be admitted that it is impossible at the present moment to form a clear idea as to their nature. Bethe's<sup>1</sup> descriptions are the most definite. He stains the primitive fibrils with toluidin blue after solution of Nissl's bodies in ammonia. The fibrils are so closely set in the axons that it is difficult to distinguish them individually, although the fibrils destined for collaterals are recognisable owing to their greater distinctness and dark colouring. But by no means all the fibrils which join dendrites are destined for the axon. Some traverse the cell body on their road from one dendrite to another. Others again, enter by one branch of a dendrite and leave by another. Bethe's description differs from Apáthy's in one very important respect. He sees the primitive fibrils as distinct and separate fibrils, traversing the cell-body without anastomosis, whereas Apáthy finds that in the majority of cases the entering fibrils form a plexus in the periphery of the cell from which radial branches pass to the neighbourhood of the nucleus where they form a second plexus, out of which arises the, usually single, neuro-fibril of the axon. Neither Apáthy's nor Bethe's description fits in with the description of Golgi<sup>2</sup> of a comparatively coarse plexus in the periphery of the cell. This latter is not perhaps a very important point. From many preparations of Golgi's intracellular network which I have made, I am inclined to regard it, since it is sometimes coarser, sometimes finer, as not the demonstration of definite structural elements but a somewhat irregular deposition of silver in the "unstainable" substance of Nissl. It seems to me that the protoplasm in which the tigroids are embedded fixes the chrome-salt, and this subsequently combines with the silver, without regard to any primitive fibrils which may pass through it, except in so far as the arrangement of the fibrils determines the arrangement of the silver-reducing substance of the cells.

With Apáthy's and Bethe's definite results before us, as well as the less certain observations of many previous

<sup>1</sup> Bethe. "Ueber die Primitivfibrillen in den Ganglienzellen vom Menschen, &c." *Schwalbe's morphologische Arbeiten*, viii., 1898, p. 95.

<sup>2</sup> Golgi. "Sur la structure des cellules nerveuses." *Archives ital. de biol.*, xxx., 1898, p. 60.

observers, it is impossible to doubt that the non-staining substance of Nissl is traversed by fibrils, although we still have much to learn with regard to their thickness, course and disposition. Especially must we regard it as uncertain at present (1) whether the fibrils form a plexus within the cell or cross one another in a feltwork, and (2) whether each fibril is a distinct unit which always retains its individuality, or whether it may fuse with other fibrils. Bethe regards every fibril as an independent conducting strand, presumably incapable of fusion with other fibrils. Apáthy sees the fibrils unite to form thicker fibrils and subdivide into finer fibrils.

Accepting Bethe's description of fibrils, it is to be noted that he observes them entering and leaving the dendrites by their *branches* only. Here I venture to think that Bethe's observations are incomplete. It appears to me that no account of the minute anatomy of the nerve-cell is satisfactory which ignores the "thorns." Thorns as shown by chrome-silver colouration are most definite structures of obvious physiological importance. From Bethe's figures and description I gather that his staining method does not reveal their presence, and this being the case, I take it that his stain fills in a part of the picture only. The arguments already used lead me to the conclusion that *every thorn is a fibril near its junction with a cell*. Apáthy's and Bethe's "primitive fibrils" may be bundles of fibrils, or they may be fibrils formed by the fusion of a number of truly primitive fibrils—"elementary fibrils," as Apáthy terms them—but the combined fibrils are not properly entitled to be styled primitive. Every thorn is the cell-end of a primitive fibril. Probably the true primitive fibrils fuse to form the fibrils which Apáthy recognises, when stained with chloride of gold, in the same way as Apáthy's elementary fibrils unite into his "primitive fibrils," and then fuse again to form "neuro-fibrils."

In one of the papers already referred to I have hazarded the conjecture that nerve-conduction depends upon the establishment of a certain relation between the conducting fibrils and the cell-protoplasm by which they are invested.

I have endeavoured to show that if this be the case, all the phenomena of attention, inhibition, sleep, which have been supposed to have their physical basis in the condition of extension, to a greater or less extent, of pseudopodial processes of the dendrites, might be just as well explained as the result of the extension along the conducting fibrils, to a greater or less extent, of the cytoplasm. My hypothesis, indeed, removes a fundamental difficulty in the conduction-by-contact theory. Upholders of this theory speak of the extension of processes from one neuron to another as a natural physiological precursor of conduction. They talk of "conduction by contact" as if it presented no physical difficulties. They forget that at the time when an impulse has traversed the neuron A on its way to the neuron B, the approximation of the conducting processes of the two neurons can be effected by no means other than the *passage across the gap* which separates them of the impulse which is about to be conducted along a physiologically continuous strand. *Conductio in distans* must precede conduction by contact. In other words, the contact theory does not in any way explain the antecedent adjustment by which contact is brought about. Now, my hypothesis of continuity of the conducting filaments, with variability of their effectiveness as conductors, gives a more intelligible explanation of "attention" and "inhibition." The conducting fibrils never lose a low degree of conductivity. The first impulse which struggles through from nerve-cell A to nerve-cell B brings about an overflow of cytoplasm from the one to the other which, *ipso facto*, creates an open road along which subsequent impulses—all impulses are, of course, vibratory—pass with ease. At the same time other paths, not in the circuit, are blocked by withdrawal of cytoplasm; producing the well-known phenomenon of inhibition for all competing reflexes.

This hypothesis also disposes of what has been termed the "physiological evidence in favour of the neuron theory." Physiologists have resisted the doctrine of the continuity of conducting fibrils, on the ground that such continuity leaves the nerve-cells nothing to do—gives no opportunity for the

explanation of the tiring of nerve-cells, the delay of impulses, &c. But if effectiveness of conduction depends upon a certain relation between the conductor and the cytoplasm in which it is embedded, it is free to the physiologists to restore to the nerve-cells any prerogatives which they may consider that their status in the system requires.

We can imagine that some day the quality of all nerve phenomena, from a knee-jerk to a thought, will be explained as due to the distribution of sensory impressions through the labyrinth of fibrils, the conductivity of which is automatically regulated by the impulses themselves, within the limits imposed by the hereditary tendency of the individual's cytoplasm to overflow in certain directions, and with certain urgency, and the functional condition of the cytoplasm at the time ; but until my hypothesis has some basis on histological observations it is futile to consider the more detailed applications which may be made of it.

Lastly, not all kinds of cells bear thorns. In the case of the cerebellum, for example, it is remarkable that whereas the superficial molecular cells, Cajal's cells, and Purkinje's cells are conspicuous for their thorniness, the cells of Golgi have thornless dendrites. As the cells of Golgi are indubitably nervous, the absence of thorns cannot be without significance ; and one naturally notes that these cells are remarkable for the extreme richness of the branching of their axis-cylinders. Their elaborate arborisation provides a complicated system of intercommunication with other nerve-cells or fibres, without any need for the dendrite system to be called into play, to the same extent as in the cells of Purkinje for example. We may suppose that, in the case of Golgi's cells, the collection of fibrils from afferent nerves does not, as in the case of other cerebellar cells, occur chiefly through the dendrites. Hence the dendrites are not studded with the ends of entering fibrils, *i.e.*, there are no thorns.

#### THE CONNECTION OF DENDRITES WITH CONNECTIVE TISSUE ELEMENTS.

As is well-known the continuity of dendrites with pia mater and with blood-vessels was described by Golgi and

Rámon y Cajal. If the chrome-silver method is to be trusted such a connection is beyond dispute. The apical processes of developing granules are seen to end in knobs beneath the pia mater, and the connection of dendrites with connective tissue elements is in certain cases unmistakable. The dismissal of such connections as occasional does nothing to clear the ground. If it ever obtains, and it is difficult to suppose that the definite silver colouration occurs in the absence of any underlying substance, it is a matter of profound significance, for it compels the conclusion that the dendrites are not solely composed of conducting substance. They must consist of a non-conducting cell-substance which fuses with, or at any rate reaches to, the connective tissue elements, and of conducting substance, presumably fibrils, which does not extend to the tips of the dendrites. We must figure the cytoplasm as forming dendrites through which conducting fibrils pass. Provided the fibrils are isolated from the connective tissue it matters little whether the rest of the cell substance is connected with it or no. Rohde<sup>1</sup> described the continuity of the spongionoplasm of nerve-cells with the spongionoplasm of connective tissue cells in the electric lobe of Torpedo, whereas the hyaloplasm of the nerve-cell is distinct. He had not observed primitive fibrils.

#### SUMMARY.

The neuron theory, or statement, alleges the anatomical independence of nerve-cells.

This statement is based upon appearances obtained by methods which colour the cytoplasm and leave the conducting elements uncoloured.

(1) Even in chrome-silver preparations evidence is forthcoming that fibres which start as the axons of certain larger cells end, after subdivision, by uniting directly with smaller cells. Such a connection of cell with cell is to be seen or inferred in the case of (A) the granules of the cerebellum and in (B) of the cells of the sympathetic system.

(A) If the granules of the cerebellum are observed in

<sup>1</sup> Rohde. *Arch. f. mikros. Anat.*, 1895, p. 408.

PLATE II.

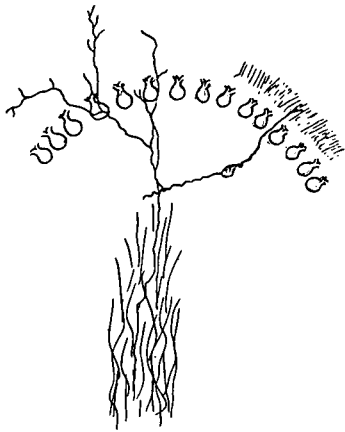


FIG. 6.

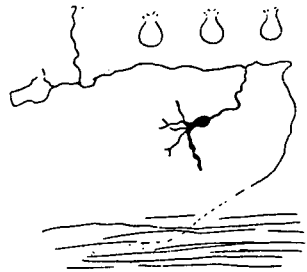


FIG. 7.

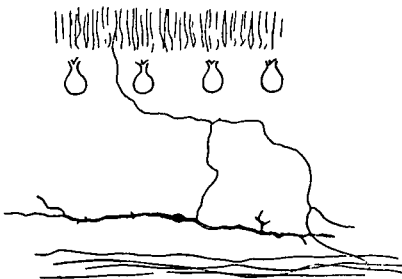


FIG. 8.

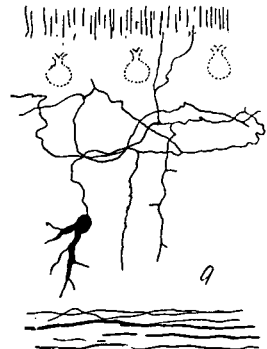


FIG. 9.

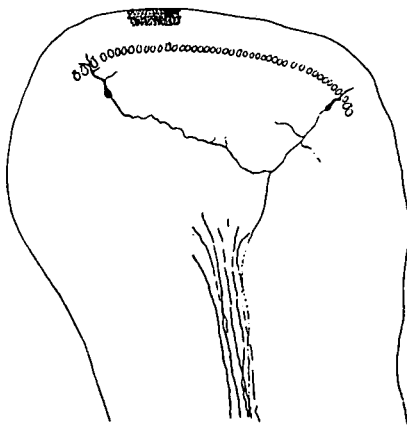


FIG. 10.



PLATE III.



FIG. 11.



FIG. 12.

PLATE IV.

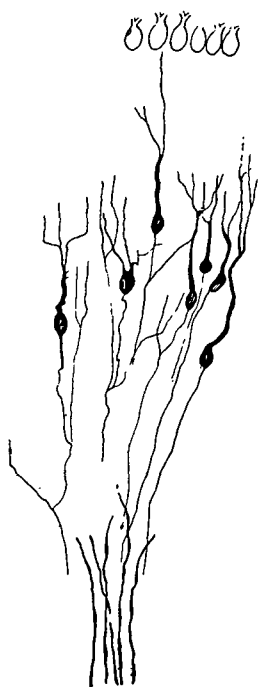


FIG. 13.

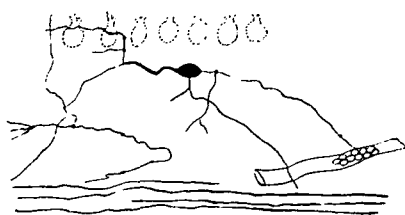


FIG. 14.

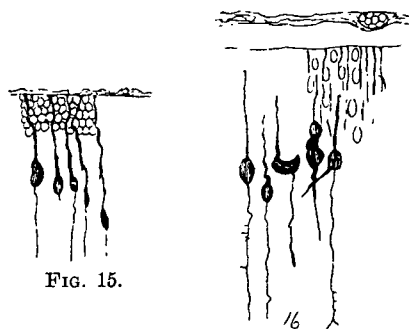


FIG. 15.

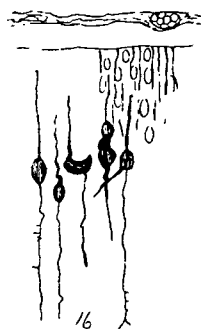


FIG. 16.



FIG. 17.

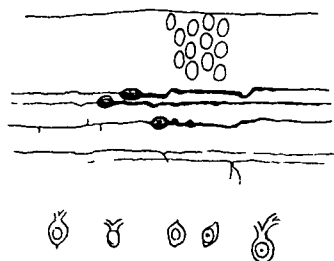


FIG. 18.

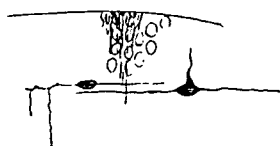


FIG. 19.

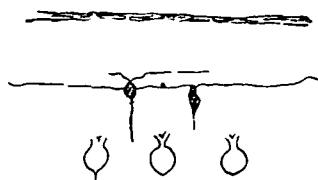


FIG. 20.

# PLATE V.

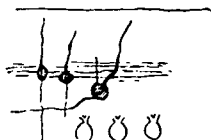


FIG. 21.

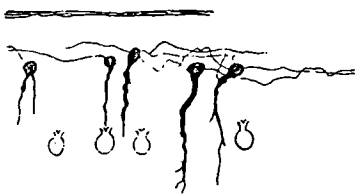


FIG. 22.

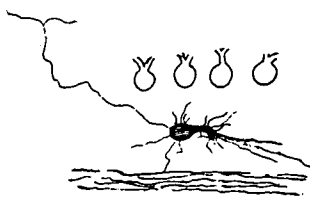


FIG. 23.

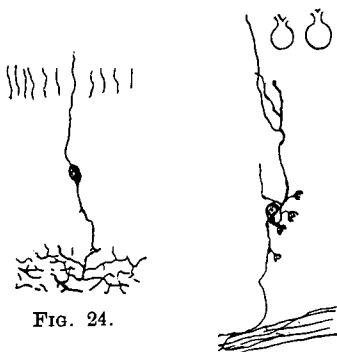


FIG. 24.



FIG. 25.

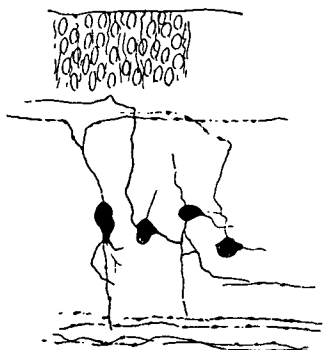


FIG. 26.

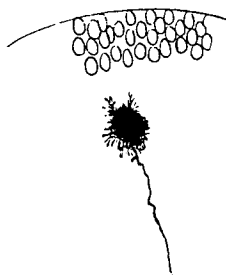


FIG. 27.



FIG. 28.



FIG. 29.



## PLATE 2.

FIG. 6.—Same preparation as fig. 2. A granule which shows a curiously thick process passing between the cells of Purkinje into the molecular layer, and a centripetal axon which appears to join a fibre which branches in the molecular layer.

FIG. 7.—Same preparation as fig. 2. The axon of the granule divides into one branch which passes backwards to the arbor vitæ and another branch which again gives off a branch before it enters the molecular layer.

FIG. 8.—Rat, 12 days old. Cerebellum hardened in bichromate of potassium and osmic acid for twelve months. The granule, which lies near to and parallel with the fibres of the arbor vitæ, gives off an axon which divaricates before it has passed the layer of cells of Purkinje, one of the two branches entering the molecular layer and the other returning towards the arbor vitæ.

FIG. 9.—Kitten, 10 days old. Hardened six months. A granule, the axon of which has a very complicated and tortuous course before it gives a branch which bifurcates on its way to the molecular layer.

FIG. 10.—Kitten, 4 days old. Two carrot-granules at opposite sides of the folium are provided with axons which unite into a single fibre which can be followed for a considerable distance in the arbor vitæ. The nuclei of Obersteiner's layer are shown at one place beneath the pia mater.

## PLATE 3.

FIG. 11.—Kitten, 7 days old. Hardened for two months. Two granules with united axons.

FIG. 12.—A single Golgi-cell is seen lying between two fragments of the thorny dendritic systems of Purkinje-cells at the apex of a folium. The dendrites of the Golgi-cell are thornless. The axon of the cell, after giving rise to a copious arborescence, is continued to the very base of the folium, a distance of at least 2 mm.

## PLATE 4.

FIG. 13.—Kitten, 1½ days old. Hardened nine months. The section, which cuts the folium transversely, passes obliquely through the granular layer, from the cells of Purkinje to the arbor vitæ. It shows a very typical group of carrot-granules. The axons of some of the granules are unbranched, others give off collaterals.

FIG. 14.—Kitten, 7 days old. Hardened in bichromate of potassium and osmic acid for nearly two years. The cell, which is rather larger than an ordinary granule, gives off three processes, each of which has the character of an axon.

FIGS. 15, 16, 17.—Kitten, 4 days old. Three groups of cells placed vertically to the pia mater, which appear to be developing carrot-granules. FIGS. 15 and 17 with obj.  $\frac{1}{8}$  in., oc. 4; fig. 16, obj.  $\frac{1}{8}$  in., oc. 8.

FIG. 18.—Kitten, 17 days old. Section parallel to long axis of folium; oblique to surface. In the molecular layer just below Obersteiner's layer (superficial granular layer) are three cells lying parallel to the surface. The distinction between the apical process and the axon is marked with unusual clearness; but every intermediate form is to be observed between such cells as these and cells which appear to give off a long axis-cylinder process on either side. The axon of the deepest of the three cells gives short lateral branches. The divaricating fibres into which the axons of granules divide are seen beneath the three "fibre-cells."

FIG. 19.—Kitten, 17 days old. Two tangential cells in the molecular layer, immediately beneath Obersteiner's layer. The cell to the right shows an apical process directed towards the surface.

FIG. 20.—Kitten, 17 days old. Two granules in an early stage of development. They lie in the molecular layer just beneath Obersteiner's nuclei. According to Ramón y Cajal's account they have been formed by the pinching together of the processes of tangential cells similar to those shown in figs. 18 and 19.

#### PLATE 5.

FIG. 21.—Kitten, 4 days old. Cells in molecular layer just beneath tangential cells of an ambiguous character—apparently developing carrot-granules.

FIG. 22.—Kitten, 1½ days old. Developing granules the apical processes of which reach as far as, or beyond, the cells of Purkinje.

FIG. 23.—Puppy, 6 days old. A granule in a more advanced condition. The apical process is carrot-shaped with large numbers of slender branches. It lies almost parallel to the fibres of the arbor vitæ. Its axon bifurcates in the molecular layer.

FIG. 24.—Hedgehog, 2 weeks old. The apical process appears to join one of the branches of a "mossy" fibre. This is typical of a large number of preparations in which a direct union between a mossy fibre and the apical process of a developing granule can be traced.

FIG. 25.—Hedgehog, 2 weeks old. A granule which still shows an apical process extending into the arbor vitæ as well as an axon which enters the molecular layer; but it also exhibits commencing arms with claws. Figs. 20, 22, 23, 24, 25 represent successive stages in the development of granules, intermediate between the tangential "fibre-cell" and the adult round granule with five or six clawed arms.

FIG. 26.—Kitten, 2 days old. Four granules which lie in the granular layer. Each gives a characteristic axon to the molecular layer, and, in addition, several slender processes towards the arbor vitæ. The processes of the two middle granules appear to unite together.

FIG. 27.—Kitten, 1½ days old. A young Purkinje-cell which has not yet developed a dendritic system. A multitude of fibrils appear to enter the body of the cell.

FIG. 28.—Hedgehog, between 2 and 3 weeks old. A young Purkinje-cell, the dendritic system of which has begun to develop. The body of the cell has fewer fibrils connected with it than in fig. 27.

FIG. 29.—Puppy, 6 days old. The dendritic system is more developed than in fig. 28. The body of the cell is almost free from fibrils. A somewhat more advanced Purkinje-cell. The thorns in the last two specimens are much larger and coarser than they are in the adult.