[Dedicated to the memory of my friend MRS. SUSANNA PHELPS GAGE]

FURTHER CONTRIBUTIONS ON NEUROBIOTAXIS

IX. AN ATTEMPT TO COMPARE THE PHENOMENA OF NEUROBIOTAXIS WITH OTHER PHENOMENA OF TAXIS AND TROPISM. THE DYNAMIC POLARIZATION OF THE NEURONE

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NEUROBIOTAXIS AND ITS SELECTIVE CHARACTER

In various articles,¹ first in 1907, I have published observations concerning the shifting of nerve cells in the central nervous system, which could be shown by the different places that

¹ The principal points are mentioned in:

Die phylogenetische Verlagerungen der motorischen Oblongata-Kerne, ihre Ursache und ihre Bedeutung. Neurologisches Centralblatt, 1907, and Rapport du Congrès international de Psychiatrie et de Neurologie, Amsterdam, 1907.

Weitere Mitteilungen über die Verlagerungen der motorischen Oblongata-Kerne: der Bau des autonomen Systems. Folia Neurobiologica, Bd. 1, 1908.

Specially in: Weitere Mitteilungen über Neurobiotaxis. Die Selektivität der

the motor nuclei of the oblongata exhibit in the series of vertebrates.

Ontogenetically the same phenomenon could be stated. Since it was most evident that the shifting of these central groups took place in the direction of the point whence the majority of stimuli proceeded to their cells, we apparently had to do with a phenomenon of taxis or tropism, which I called Neurobiotaxis, because it occurs in the nervous system during life (in its phylogenetic and ontogenetic development) and I did not know where

Zellen-Wanderung. Die Bedeutung synchronischer Reizverwandtschaft, etc. *Folia Neurobiologica*, Bd. 1, 1908.

Über die Bildung von Faserverbindungen auf Grund von simultanen und sukzessiven Reizen. Bericht des III. Kongresses für experimentelle Psychologie in Frankfurt am Main, 1908.

Further anatomical details are found in:

Weitere Mitteilungen über Neurobiotaxis, II. Die phylogenetische Entwicklung des horizontalen Schenkels des Facialiswurzelknie. *Folia Neurobiologica*, Bd. 2, 1908.

Weitere Mitteilungen über Neurobiotaxis, III. Über den Einfluss der Neurone der Geschmackskerne auf den motorischen Facialis und Glossopharyngeuskern und ihr Verhalten zur Radix descendens Nervi quinti. *Folia Neurobiologica*, Bd. 3, 1909.

Weitere Mitteilungen über Neurobiotaxis, IV. The migrations of the abducens nucleus and the concomitating changes of its root-fibers. *Psychiatrische en Neurologische Bladen*, Amsterdam, 1910.

The migrations of the motor cells of the bulbar Trigemini, Abducens and Facialis in the series of vertebrates and the differences in the course of their root-fibers (counted as Mitteilung V.). *Verhandelingen der Kon. Akad. v. Wetenschappen*, Amsterdam. Tweede Sectie, Deel 16, Nr. 4, 1910.

Weitere Mitteilungen über Neurobiotaxis, VI. The migrations of the motor root-cells of the vagus group and the phylogenetic differentiation of the hypoglossus nucleus from the spino-occipital system. *Psychiatrische en Neurologische Bladen*, Amsterdam, 1911.

Weitere Mitteilungen über Neurobiotaxis, VII. Die phylogenetische Entwicklung der motorischen Wurzelkerne in Oblongata und Mittelhirn. *Folia Neurobiologica*, Bd. 6, Sommergänzungsheft, 1912.

Weitere Mitteilungen über Neurobiotaxis, VIII. Über den motorischen Facialis und Glossopharyngeus Wurzel bei niederen Vertebraten. *Folia Neurobiologica*, Bd. 9, 1912.

The structure of the autonomic nervous system compared with its functional activity. *Journal of Physiology (England)*, vol. 37, 1908, p. 139.

Phenomena of neurobiotaxis in the central nervous system. Section Anatomy and Embryology, of the XVIIth International Congress of Medicine, London, 1913.

to classify it under the phenomena of galvanotaxis, chemotaxis or other processes of taxis or tropism known at that time.

This phenomenon of shifting is clearly shown by figures 1 and 2, where the dorsal position of the abducens nucleus in the shark with its huge fasciculus longitudinalis posterior (*f.l.p.*, fig. 1) strongly contrasts with the ventral position of the same nucleus in a bony fish (fig. 2), where the fasciculus longitudinalis

Fig. 1 *Acanthias vulgaris*, showing the dorsal position of the abducens nucleus. *f.l.p.*, fasciculus longitudinalis posterior; *Nuc.VI*, abducens nucleus; *N.VI*, abducens nerve; *r.VII.m.*, motor facialis root. After Van der Horst.

posterior is much smaller, but where the ventral set of central afferent tracts which influences this cell group is much more strongly developed (*tr. tecto-bulbares ventrales*, *tr.t.b.v.*, fig. 2).

The first way in which I formulated this law was thus: When from different places stimuli proceed to a cell, its chief dendrite grows out and its cell-body shifts in the direction whence the

majority of stimuli proceed.² The truth of this was soon confirmed also in other parts of the cerebrum, by Tretjakoff,³ Herrick,⁴ Bartelmez,⁵ Obenchain,⁶ Bok, Van der Horst⁷ and others.

I observed, however, on an increase of afferent stimuli in a given center, that not all the neighboring cells approach this center, but that only certain cells proceed to that center which apparently had a certain relation to it, while other cells (even lying nearer by) did not migrate into the direction of the increased sensory field, because evidently they had nothing to do with it and did not stand in relation to it.

Further researches convinced me that the functional relation which appeared to be the condition for the approach was shown to be a correlation depending on simultaneity of function—of stimulation.

So the abducens nucleus shifts from one center of visual co-ordination fibers (the *f.l.p.*) to another set of visual co-ordination fibers (the tr. tecto-bulbaris) if the latter increase; but an increase of the taste fibers for instance, does not have any effect upon it.

² Later I found that a similar observation had been already made by Strasser ('92) and by Cajal ('99). Compare: Strasser, *Alte und neue Probleme der Entwicklungsgeschichtlichen Forschung auf dem Gebiete des Nervensystems. Ergebnisse der Anatomie und Entwicklungsgeschichte*, Bd. 1, 1892, p. 721. Cajal, *Textura del sistema nerviosa del hombre y de los vertebrados*, vol. I, 1899, p. 560. See also Cajal, *Algunas observaciones favorables a la teoria neurotropica. Trabajos*, vol. 7, 1908, p. 63. Both, however, failed to see the correlative character in this process, and Cajal ascribes a great influence to the spongioblasts (ependyma and glia) in the secretion of attracting chemicals for the axones, in which I do not at all agree with him.

³ Tretjakoff. *Das Nervensystem von Ammocoetes*, II. *Das Gehirn*. *Archiv f. mikrosk. Anat.*, Bd. 75, 1909.

⁴ Herrick. *The morphology of the forebrain in Amphibia and Reptilia. Jour. Comp. Neur.*, vol. 20, 1910.

⁵ Bartelmez. *Mauthner's cell and the nucleus motorius tegmenti. Jour. Comp. Neur.* vol. 25, 1915.

⁶ Obenchain (with Herrick). *Notes on the anatomy of a cyclostome brain, Ichthyomyzon concolor. Jour. Comp. Neur.* vol. 23, 1913.

⁷ Van der Horst. *De motorische kernen en banen in de hersenen der visschen, hare taxonomische waarde en neurobiotactische beteekenis. See also: Tijdschrift der Ned. Dierk. Vereen.* 1917.

Then I found—though not starting my work with a psychological scope—that the anatomical relations of the dendrites and the cells in the nervous system were regulated in accordance with the law which, in psychology, is known as the law of association, in which law (in all the different forms⁸ in which it may appear) the simultaneity of stimulations or residua of stimulations is the essential part.

Fig. 2 Tetrodon, showing the ventral position of the abducens nucleus. *f.l.p.*, fasciculus longitudinalis posterior; *Nuc.VI*, abducens nucleus; *N.VI*, abducens nerve; *r.VII,m.*, motor facialis root; *tr.t.b.v.*, tractus tecto-bulbaris ventralis. After Van der Horst.

This anatomical observation, first made on motor cells, led me to study more carefully the courses of several axon-tracts, sensory tracts, as well as the so-called "central motor tracts," such as the pyramids, and it soon appeared to me that a criti-

⁸ Those forms are simultaneity, successivity, similarity and contrast. In the three first named forms the presence of one stimulus, or remains of a stimulus, while the other is added, is obvious. The association by contrast is also due in the first place to simultaneity of impression since the simultaneous or successive contrast makes us discriminate things: black and white, father and mother, etc.

cal study of their relation showed most clearly that the same law of neurobiotaxis, the simultaneous relationship in their stimulative function, had been the cause of their final arrangement.⁹ So I was able to formulate the phenomena of neurobiotaxis in the following words:

I. If in the nervous system several stimulation-charges occur, the growth of the chief dendrite, and eventually the displace-

Fig. 3 Showing that, while the axis-cylinder runs with the direction of the nervous current, the dendritic outgrowth and the final shifting of the cell body occur against the nervous current. *A*, giant dendrites grown out towards the center of stimulation. *B*, the cell body (perikaryon) has shifted toward the center of stimulation; the axis-cylinder is consequently elongated.

ment of the cell-body itself, takes place in the direction, whence the majority of stimuli proceed to the cell.

II. Only between correlated centers does this outgrowth or shifting take place.

III. The growth of the axis-cylinder (i.e., its final connection) is not primarily regulated by motor centers,¹⁰ but also here synchronic or successive stimulation (correlation) acts a part.¹¹

⁹ *Folia Neurobiologica*, Bd. 1, 1908.

¹⁰ Not by some undefined transcendental willing (teleologically).

¹¹ That is, it is defined by correlation.

While, however, it was evident that the approach of the dendrites and nerve cells to a territory (fig. 3) took place towards the center of the stimulation (as a stimulopetal or centripetal tropism), that is, against the nervous current of stimulation proceeding from this center, the problem became much more difficult to explain how the connection between correlated centers was effected by the axis-cylinder, since it was obvious that the axis-cylinder does not grow towards the stimulation (stimulopetal) to meet it, but moves in the same direction as the stimulus-irradiation (stimulo-fugal or centri-fugal).

BOK'S RESEARCHES: THE STIMULOGENOUS FORMATION OF THE
AXON

That the axis-cylinder really grows with the current and that the irradiation of this current plays an important part in its growth has been proved and very carefully examined in this Institute by S. T. Bok, who got highly important results.

Bok¹² found that when an axis-cylinder or a bundle of myelinated nerve-fibers grows out and passes nerve cells on its way, these nerve cells can be activated to send out an axis-cylinder of themselves in a region perpendicular to the activating axon or bundle (fig. 4).

This fact was found with the fasciculus longitudinalis posterior in such a form as left no doubt, since it appeared that the motor nuclei which undergo the influence of this bundle were only activated according to the degree in which the fasciculus longitudinalis posterior had grown out. So the axons of the trigeminal¹³ cells first grow out, then follow the axons of the facialis cells, then those of the glossopharyngeus and vagus.

The same was seen in the activation of the oculomotorius, abducens and hypoglossus nuclei which are activated by another influence of the same character.

¹² Bok. Die Entwicklung der Hirnnerven und ihrer Zentralen Bahnen. *Dei Stimulogene Fibrillation. Folia Neurobiologica.* Bd. 9, 1915. See also Bok, *Stimulogeneous Fibrillation. The cause of the structure in the nervous system.* *Psych. en Neurologische Bladen*, Amsterdam, 1915.

¹³ Concerning the Trochlearis. See the first-named original.

Bok, considering the fact that the formation of the axis-cylinders in those cells took place under the influence of the current irradiating from the primary activating axis-cylinder, called this stimulogenous fibrillation, following the direction of that current in contrast to the outgrowth of the dendrites and

Fig. 4 The activation of adjacent neuroblasts by an amyelinated (growing) fascicle. The vertical arrow indicates the direction of growth of the activating bundle and the direction of its nerve current, which starts at A. The horizontal arrow indicates the course of the irradiating influence (current) perpendicularly to the activating bundle. Notice that the proximal cells are sooner activated (and have moved further) than the more distant ones. After Bok.

the shifting of the cell body,¹⁴ both of which also only occur later and which move towards the center, i.e., against the current of the stimulus that proceeds to them.

This observation and Bok's interpretation of it are very important, and no doubt correct. It is evident, however, that the final end-point of the growing axis-cylinder can not be determined by this process alone, as was also realised by Bok, who came to the conclusion that the final connection was determined by the principal law of neurobiotaxis, viz., by the stimulative (simultaneous) correlation of the growing axis-cylinder and its end-point, i.e., the cell or dendrites with which it is going to be connected.

Bok thought that this could be effected by the fact that if two centers are in simultaneous stimulation the ideal line between the two is the path where the plasmodesms undergo the greatest influence of this relation. He called this the principle of the 'doppelte Bahnung,' and thought that Einstein's (physical) law of attraction between synchronic energies also had some influence on it.

It seems to me, however, that the principle of 'doppelte Bahnung,' as laid down in this theory, can not explain from which of two simultaneously stimulated cells the axis-cylinders grow out, and that even the adaptation of the protoplasm to the formation of the axis-cylinder, eventually a fibrillation of the neurodesms, then might begin in the middle between two cells which, as we know, it never does. Moreover, the expression "adaptation of protoplasm to its biological function" is too general an expression to explain anything.

It has appeared to me that the literature of recent years concerning the microchemistry of the neurones and the phenomena of tropism and taxis known and experimentally examined in other organisms, together with Bok's discovery, concerning the

¹⁴ If the normal *stimulation* of the cell body is of little importance or eventually absent, the cell may also shift in the same direction in which the axon grows out. (See my paper on the autonomic nervous system. *Journal of Physiology*, 1908, vol. 37, p. 139.)

stimulogenous outgrowth of the axis-cylinders from the activated cell by and with the irradiating current from a primary or activating axis-cylinder in its neighborhood, gives us a key of exceptional importance to comprehend the phenomena of neurobiotaxes in general, and the contrasting behavior in outgrowth direction between dendrites and axons and allows us to consider, perhaps to explain, *how it is possible that a unit such as the neurone is may exhibit two opposite directions of growth.*

EXPERIMENTS CONCERNING PHENOMENA OF TROPISM AND TAXIS
IN PLANTS AND ANIMALS. KATAPHORETIC PHENOMENA

It is evident that, in any attempt to explain the neurobiotactic phenomena, these must be compared with other phenomena which are better adapted to experimental investigation. As such we may mention the galvano-tropic phenomena in the growth of plant-roots and the orientation of animals in the constant current, about which we have obtained many data during the last decennia.

As is known, the phenomenon of galvanotropy in plant-roots was discovered in Hermann's laboratory by Müller-Hettlingen,¹⁵ who found that, if the sprouting seed of the bean (*Vicia faba*) be exposed to a constant current, the tips of the root turn and grow towards the negative pole (kathode).

An analogy¹⁶ of this galvano-tropic phenomenon is found in the galvano-tactic phenomenon described by Bancroft,¹⁷ viz., that the tentacles and the manubrium of a medusa, *Polyorchis*, during the transmission of a constant current turn towards the kathode.

In the experiments with the latter this peculiar phenomenon was observed, viz., that with a long-continued current the side turned to the anode extended, becoming thinner and weaker; this last phenomenon being a symptom of decay, according to this author (*vide infra*).

¹⁵ Müller-Hettlingen. Ueber galvanische Erscheinungen an Keimenden Samen. Pflüger's Archiv, Bd. 31, 1883, p. 192.

¹⁶ Not a homology, probably.

¹⁷ Jour. Exp. Zool., vol. 1, 1904, p. 289.

As third example of galvano-taxis the phenomenon discovered by Verworn¹⁸ in one-celled creatures must be mentioned here, viz., that these (ameba, for instance) on the transmission of a constant current through the surrounding medium, send out enlargements and finally shift in the direction of the kathode.

Verworn at first held the opinion that there were also Protozoa which shift under normal circumstances to the anode, and he therefore made a distinction between kathodic and anodic galvano-taxis. Later investigations revealed that the anodic galvano-taxis must be considered as being something different from the kathodic, and that the direction and shifting of the bodies observable in Protozoa under normal circumstances is invariably a *kathodic galvano-taxis*.

Also Boruttau (personal communication) holds the opinion that every real galvano-tropism is a kathodic stimulation phenomenon. This usual kathodic galvano-tropism can be brought into correlation with Pflüger's law, as has been pointed out by Loeb and Maxwell.¹⁹

As far as the anodic tropism is concerned, Loeb and Budgett²⁰ and after then Coehn and Barratt²¹ found that when a protozoan, *Paramecium*, in pure water or in a weak solution of common

¹⁸ Verworn. Die polare Erregung durch den galvanischen Strom. Pflüger's Archiv, Bd. 45, 1889. Verworn. Die polare Erregung der Protisten durch den galvanischen Strom (Fortsetzung). Pflüger's Archiv, Bd. 46, 1890. Verworn. Untersuchungen über die polare Erregung der lebendigen Substanz. 3te Mitteilung. Pflüger's Archiv, Bd. 62, 1896, S. 415. Verworn. Die polare Erregung der lebendigen Substanz durch den Constanten Strom. 4te Mitteilung. Pflüger's Archiv, Bd. 65, 1897.

¹⁹ J. Loeb und S. S. Maxwell. Zur Theorie des Galvano-tropismus. Pflüger's Archiv, Bd. 63, 1896.

See also J. Loeb und Walter Gerry. Zur Theorie des Galvano-tropismus, II. Versuche an Wirbelthieren. Pflüger's Archiv, Bd. 65, 1897, S. 41. J. Loeb. Zur Theorie des Galvano-tropismus, III. Ueber die polare Erregung der Hartdrüsen von *Amblystoma* durch den Constanten Strom. Pflüger's Archiv, Bd. 65, 1897, S. 308.

²⁰ Loeb und Budgett. Zur Theorie des Galvano-tropismus. IV. Mitteilung über die Ausscheidung electropositiver Ionen an der äusseren Anodenfläche protoplasmatischer Gebilde als Ursache der Abweichungen vom Pflüger'schen Erregungsgesetz. Pflüger's Archiv, Bd. 65, 1897, S. 532.

²¹ Coehn und Barratt. Ueber Galvano-taxis von Standpunkt der physiologischen Chemie. Zeitsch. f. allgemeine Physiologie, Bd. 5, 7, 1905.

salt, was influenced by a constant current, the movement was in the direction of the kathode, but that this direction of galvano-taxis may be reversed by placing the animal in a stronger (even physiological) solution of salt. If in the latter case the constant current was transmitted through it, a movement towards the anode was observable. This phenomenon of reversal, first observed in a galvano-tactic process, was confirmed shortly after in a galvano-tropic process, in the case of the root-tips of pease.

Gassner²² found that an increase of salt in the medium influences the effect of the constant current in those objects also. When he increased the quantity of salt of the water in which pea-roots sprouted, the constant current could no longer cause a kathodic tropism. He was inclined to ascribe this to a diminution in the quantity of electricity running through the tip of the root, since the greater conductivity of the water (salt solution) caused a greater quantity of electricity running through the solution itself.

Schellenberg²³ obtained the same result, but went even farther, and on increasing still more the percentage of salt was able to obtain a reversed tropism, the root then growing to the *anode*.

If the percentage of KCl in the water was only 0.074 per cent the root-tip continued to grow kathodic galvano-tropic; if, however, the percentage was raised to 1 per cent, a distinct anodic direction in the growth appeared, and with a fair degree of exactness such a concentration of KCl could be found in which, after the transmission of the constant current, no tropism was evinced.²⁴

²² Gassner. Der galvano-tropismus der Wurzeln. Botanische Zeitung, 1906, Parts 9-11.

²³ Schellenberg. Untersuchungen über den Einfluss der Salze auf die Wachstumsrichtung der Wurzeln, zunächst an der Erbsen Wurzel. Flora, vol. 96, 1906, p. 474.

²⁴ It may be mentioned that the current strength which caused this tropism was but slight, and varied from 1/10 to 1/1000 milliampere, with a density of current of 0.0025 to 0.000025 milliampere per sq. cm.

That Elving's curves (which are also anodic) could be formed under these circumstances is out of the question, since Brunchorst found the current density necessary in this case to be about 0.2 milliampere.

Like Gassner, Schellenberg also seems to be inclined to ascribe the anodic tropism to the greater amount of electricity running through the water, or rather to the weakness of the current that runs through the root-tip and which should be too weak to cause a kathodic tropism, a supposition that seems to be accepted by Rothert,²⁵ though he admits that it has not been proved. If only a weaker current were sufficient to cause the anodo-tropic phenomenon, a smaller amount of electricity would have to do the same! These authors, moreover, do not explain biochemically why a weak current should cause an anodic tropism and a stronger current a kathodic one.

Coehn and Barratt (loc. cit.) tried to explain biochemically this *phenomenon of reversal of the galvano-tropism* in the following way. They assumed that on the boundary between the object used for the experiment and the surrounding medium (the water) a semipermeable membrane is present that possesses a different permeability for positive and negative ions. This assumption is quite legitimate, since the occurrence of such semipermeable membranes is a very common phenomenon in nature.

If we now assume that the permeability for negative²⁶ ions is greater in this membrane than that for positive ions, of the ionized NaCl or KCl (provided the concentration thereof in the surrounding fluid be greater than in the protoplasm) a larger quantity of negative ions will be transferred into the cell than of positive ions, and the cell will then be overcharged with negative ions and pass to the positive pole on the transmission of the constant current.

On the other hand, if the concentration of KCl or NaCl in the medium be less than in the cells, a larger quantity of negative ions than positive will leave the cell, and the cell-bodies, charged

²⁵ Rothert. Die neuen Untersuchungen über den Galvano-tropismus der Pflanzenwurzeln. Zeitschrift für allgemeine Physiologie, Bd. 7, 1907, p. 192.

²⁶ Such a special permeability for negative ions (anions) has been proved to exist in the case of blood corpuscles by Hamburger (Zeits. f. Biologie, Bd. 28, p. 405, 1891). Compare also Hamburger und Van Lier, Durchlässigkeit der rothen Blutkörperchen für die Anionen von Natriumsalzen. Arch. f. Anat. u. Physiol., Physiol. Abt., 1902, p. 492.

with a surplus of positive ions, will on the transmission of the constant current pass to the kathode.

If we accept this theory as correct, we shall have to assume that in ordinary circumstances—under which the kathodic tropism or taxis predominates—also a greater charge of positive ions is present in the cell-body of the ameba, or in the protoplasm of the tentacles or root-tips, than in the surrounding extra-protoplasmatic medium. This explanation is not generally accepted, but that the condition of the extra-protoplasmic medium is of great importance has also been emphasized by Loeb and Budgett, who are equally inclined to ascribe the exceptions to Pflüger's law (the anodic migrations) to alterations in the extra-protoplasmic medium. They refer to a phenomenon which may be exhibited by that side of an ameba or paramecium that is turned to the anode, viz., the extension of the protoplasm on that side, eventually followed by liquefaction. This anodic extension, first observed by Verworn (*loc. cit.*), is the first thing that appears when Protozoa are exposed to the constant current and precedes the real kathodic galvano-tropism.

Loeb and Budgett (*loc. cit.*) have submitted it to a more detailed examination and also came to the conclusion that this process is a result of the extra-protoplasmatic medium. Their explanation of this anodic phenomenon differs from the one given by Coehn and Barratt. They are, however, equally inclined to consider this phenomenon as due primarily to changes in the extra-protoplasmatic medium²⁷ in contrast to the phenomena of common tropism following Pflüger's laws of irritation. It may be mentioned still that the most favorable strength of current in those experiments with ameba was only 0.4 milliampere.

Besides these galvano-tactic and galvano-tropic phenomena of living protoplasm, we know of polar phenomena in dead organic substances rendered evident by the direction in which albumen shifts when subjected to a constant current: viz., the phenome-

²⁷ Perhaps this mode of explanation may be also applicable to the above-mentioned reversal of the galvano-tropism of root tips and to the anodal phenomenon observed by Bancroft (*vide supra*).

non of kataphoresis. I refer here to the investigations of Hardy,²⁸ which showed that as long as an albuminous solution is alkaline the particles suspended in it shift towards the anode on the transmission of a constant current, whereas they shift towards the kathode when the solution is made slightly acid.

One is apt to look for an explanation of this also in the fact that on the boundary between a colloid particle and the surrounding fluid, a double layer in the sense of the theory of Helmholtz-Quinke is present.

If now the solution is alkaline, a transmission of ions will take place, in consequence of which the albuminous particle itself becomes negative and thus shifts to the anode on the transmission of a constant current, while in the case of an acid reaction of the surrounding fluid the contrary takes place. From the reversibility of the kataphoretic phenomenon (Hamburger)²⁹ the curious fact thus follows, viz., that also proteid particles have the peculiarity that their electric character is determined by the reaction of the surrounding medium.

That here too, just as in the above tropism of the root-tips, an iso-electric condition occurs is clear.

APPLICATION OF THESE EXPERIMENTS TO THE GROWTH OF THE NEUROBLAST. THE FORMATION OF THE AXON

If, with these facts before us, we consider the phenomena which appear during the formation of an axis-cylinder³⁰ in an activated cell (which precedes the formation of dendrites—see

²⁸ Hardy. On the coagulation of proteid by electricity. *Jour. of Physiol.*, vol. 24, p. 2881, 1899. *Proc. Roy. Soc.*, vol. 68, p. 110, 1900.

²⁹ Hamburger. *Osmotischer Druck und Ionenlehre*. Wiesbaden, Bergmann, 1904, vol. 3, p. 68.

³⁰ It is hardly necessary to say that the fact that isolated ganglion cells, as in Harrison's experiments, may also send out axis-cylinders proves nothing against the following text. Harrison (*loc. cit.*, p. 833) remarks that this is a process of self-differentiation entirely independent of external conditions. This is true to a certain extent, but we must assume that before it becomes a self-differentiation its differentiation has been induced to the neuroblast in former generations by external circumstances and that its doing this by itself is based on hereditary engrammatic qualities. It is better to see a problem in things than to explain them by a word which implies a still greater problem.

fig. 4), we shall first have to mention the fact that the stimulation center with respect to the surrounding tissue is negative, forming a kathode with reference to the non-stimulated surroundings, as physiological experiments abundantly prove.

Moreover the strength of the electrolytic potential differences occurring in the nervous system in consequence of stimulation appears to be of the same category as those that are applied in artificial phenomena of galvano-taxis (see above) since it may vary from 3 millivolt to 0.8 millivolt and lower, so that the forces developed here are certainly strong enough to influence processes of formative tropism and functional taxis.

Now, it may be the same whether this stimulated center is the body surface in or under which nerve cells lie or whether we start our deductions with a primary growing axis-cylinder which on its way passes neuroblasts. This negative potential not only runs along the primary axis-cylinder (fig. 4) but also, we may assume, as long as the axis-cylinder is not provided with an insulating medullary sheath, that this negative potential stands perpendicular to the length of the activating axis-cylinder (or body surface), irradiating from it.³¹

In accordance with this perpendicular irradiation of the electrolytic influence, or current, we see that the neuroblasts near the primary activating bundle send out axis-cylinders perpendicular to the activating bundle, and that similarly perpendicular collaterals may grow out from the original (activating) axis-cylinders themselves.

In both cases, in the formation of collaterals as well as in the outgrowth of the axis-cylinder of the secondary (activated) neuroblasts, the axis-cylinder substance proceeds in the direction of the perpendicular irradiation of the stimulated fiber, i.e., to the anodic pole.

³¹ The irradiative stimulus of naked axons is very clearly illustrated by the position of the dendrites of Purkinje's cells perpendicular upon the parallel fibers in the molecular layer of the cerebellum and of the dendrites of the motor cells on the longitudinal (naked) axons in the spinal cord of *Petromyzon*. See my paper, *Ueber das Rindenproblem*, etc., in the *Folia Neurobiologica*, Bd. 8, 1914, pp. 529-530

This first outgrowth which, in the beginning, can be complicated with an anodal kataphoretic shifting of the cell body itself (fig. 4) may be entirely independent of a propagation of the nervous current itself along the newly formed short axis-cylinder. As soon, however, as this axis-cylinder is fit for nervous conduction its rate of outgrowth will be considerably increased, a much stronger negative current running in the direction of its growth to the anodal field.

Why does this anodic growth occur before the kathodic tropism of the dendrites and the cell body? I will consider this question in the light of the above-mentioned experiences.

We know that the neuroblast is embedded in an organic solution, the pericellular lymph, containing a good deal of potassium salts.

Macallum has emphasized that the amount of potassium salt external to the nerve cell is great and that a considerable condensation of this element is present on its exterior surface.

Now Verworn has shown that on the transmission of a constant current the first thing to appear is an anodal expansion of the cell body, thus showing that a change of tension may be localised, by electric influences, on the anodal pole.

We may expect that this extension, being under the influence of a considerable amount of K and Cl, derives certain chemical and tropic characteristics from it.

That this really occurs in nerve cells is proved by the chemical constituents of the axon, compared with those of the dendrites and cell body.

We know from the researches of Macdonald, Macallum, Alcock and Lynch that the axis-cylinder is distinguished from the dendrites and the cell body by a much larger quantity of potassium and chlorides³² (which, according to Macdonald, may also contribute to its conductivity for the nervous current).

³² MacDonal. The injury current of nerves, The key to its physical structure. Report of Thomson-Yates Laboratory, vol. 4, 1902, p. 213.

MacDonal. The structure and function of nerve-fibers. Proceedings of the Royal Society, vol. 76, B. 1905, p. 322.

Macallum. On the distribution of potassium in animal and vegetable cells. Journal of Physiology, vol. 32, 1905.

Macallum. Die Methoden und Ergebnisse der Mikrochemie in der Biologie.

The large quantity of KCl then present around its colloidal substance will favor (according to the experiments of Gassner, Schellenberg, and others) the anodo-tropic character of the axis-cylinder.

The phenomenon of the formation of the axis-cylinder and its collaterals in the direction of the anodic field, may thus be so expressed that we say that the neuroblast embedded in a solution containing a good deal of potassium and of chloride exhibits, in harmony with the experiments of Loeb, Budgett, Coehn and Barratt, a tropism at the anodal side of the neuroblast and that the KCl constituents of the neuroblast gathering on this side thus increase (besides its conductivity) the anodo-tropic character of its colloidal substance. This anodo-tropic character of the colloidal substance of the axis-cylinder is, moreover, in harmony with Hardy's experiments on the kataphoresis of albuminoids.

Considering the fact, that the kataphoresis which genuine albumen and lecithin show is already generally an anodic one (Höber, loc. cit.) it is clear that the additional composition of the neurone and its surroundings still favors this, since the colloid particles of the young axon are embedded in a medium containing a quantity of KCl, that makes its preponderating reaction alkaline. Moreover the greater conductivity which KCl gives it, may cause the greater quantity of electricity to be led through it.

That the constituents of a peripheral nerve are strongly conveyed to the anode is also experimentally shown by Hermann, to whose experiments I return later (see p. 291).

From every standpoint indeed it seems that the conditions for the primary outgrowth of the axon along with the kathodic current to the anodic field have been realized in the nervous system.

chen Forschung. Ergebnisse der Physiologie von Asher und Spiro, Jahrg. VII, 1908.

Alcock and Lynch. On the relation between the physical, chemical and electrical properties of the nerves. Part IV: Potassium, chlorine and potassium chloride. *Journal of Physiology*, vol. 42, 1910.

Macallum. Surface tension and vital phenomena. *University of Toronto Studies*, No. 8, Physiological Series, 1912.

The outgrowth of the axis-cylinder begins in the chick embryo about the second day of incubation (Bok).

Not until much later—according to Cajal when the growth tip of the axis-cylinder has reached, or nearly reached, its end point (about the 6th day of incubation in the chick embryo, Bok)—does an outgrowth of the dendrites begin, which make their way in the direction of the stimulus, that is in the direction of the kathode.

THE FORMATION AND CONTRACTION OF DENDRITES. THE FINAL SHIFTING OF THE PERIKARYON

I believe that there is a principal difference biologically as well as biochemically between the anodic elongation of the axon and the kathodic tropism of the dendrites.

The primary growth of the axon is in the beginning not directed to a certain point, but merely from a certain kathodic center, the outgrowth of dendrites, however, is much more influenced also in the beginning by their final end-points.

Their tropism corresponds with the regular appearance of the law of stimulation of protoplasm and exhibits a kathodic character, probably related with a more advanced nervous function for which a further stage of development is necessary.

This kathodic growth direction, as well as the kathodic taxis, is the usual thing in nature and, as Loeb and Maxwell have shown, is in harmony with Pflüger's law. We only have to prove that there are no factors which might interfere with it and change it into an anodal elongation.

This question is the more important since it may be that in the first phase of outgrowth of dendrites, which is not yet accompanied by a secondary shortening of the dendrite and the shifting of the perikaryon, a kataphoretic process might introduce it or at least be involved in it. Anyhow, the kataphoretic qualities of the dendrites may never be such that they should counteract the kathodo-tropic process which certainly is the chief factor in the shortening (contraction) of the dendrite and the shifting of the cell.

Now we know from the chemical examinations of Grandry³³ and Macallum and Menten³⁴ that KCl is hardly present in the cell and the dendrite, so that for us there is no reason here to expect an anodal kataphoresis.

Looked at from the point of view of Hardy's investigations, which according to Greeley³⁵ we may apply to intra-protoplasmatic colloidal granules, there are perhaps more arguments which favor the shifting of the dendrites, and later of the cell-body, in the direction of the stimulus. For we know that the dendrites and the cell-body differ from the axis-cylinder by the presence of Nissl's substance which during life is probably in a more or less fluid condition (see Cowdry's papers³⁶ on the bio-chemical conditions of nerve cells). This substance is probably a derivative or compound of nucleic acid³⁷ and the presence of acid in it will, according to Hardy's investigations, promote the shifting of the colloids which are suspended in them to the kathode. While, therefore, the absence of a larger quantity of KCl does not prevent the first outgrowth of the dendrite from proceeding in the kathodic direction, the presence of acid nuclein derivatives would even promote it.

³³ Grandry. Recherches sur le structure du cylindre-axe et des cellules nerveuses. Bulletin de l'Academie de Bruxelles, 2 me Series, vol. 28, 1868, p. 304.

Idem. Journal de l'Anatomie et de la Physiologie, vol. 6, 1869, p. 289.

³⁴ Macallum and Menten. Distribution of chlorides in nerve-cells and fibers, Proceedings of the Royal Society, vol. 76B, 1905, p. 217.

Macallum. Die Ergebnisse und Methoden der Microchemie in der biologischen Forschung. Ergebnisse der Physiologie von Asher und Spiro, Jahrg. 7, 1908, p. 697.

³⁵ Greeley. Experiments on the physical structure of protoplasm of Paramecium and its relation to the reactions of the organism to thermal, chemical, and electrical stimuli. Biological Bulletin, vol. 7, 1904.

³⁶ Cowdry. The development of the cytoplasmatic constituents of the nerve-cells in the chick. Mitochondria and neurofibrils. Am. Jour. Anat., vol. 15, 1912.

Cowdry. The relations of mitochondria and other protoplasmatic constituents in spinal ganglion cells of the pigeon. Internationale Monatschrift für Anatomie und Physiologie, Bd. 29, 1913.

Cowdry. The general function and significance of mitochondria. Am. Jour. Anat., vol. 19, 1916.

³⁷ M. A. Van Herwerden. Ueber die Nuclear-wirkung auf tiersche Zellen. Ein Beitrag zur Chromidienfrage. Archiv f. Zellforschung, Bd. 10, 1913.

This substance perhaps also helps to explain the relatively late formation of the dendrites, since the nuclein substance does not appear until late in the cell body in the form of Nissl bodies which, originating from the chromatin of the nucleus (Scott),³⁸ pass through the nuclear membrane in a stage of development when the axis-cylinder has already completed its growth over a certain extent, and has even become fairly considerable.

Cajal³⁹ did not find this substance before the time when the dendrites start to grow out. Consequently when this substance is present in the protoplasm we observe a tendency in the protoplasm to shift in the direction of the stimulated field (the kathode) and to be followed by the contraction of dendrites and finally the shifting of the whole perikaryon in the direction of the stimulation field, i.e., in the direction of the negative electric field.

The difference of time between axis-cylinder outgrowth and dendrite formation thus would be a result of the general anodic kataphoretic character of genuine albumen and lecithin, the alkaline reaction of the pericellular lymph and the quantity of KCl salt present around the young cell and, further, the greater conductivity that this gives to the axis-cylinder on one hand, and on the other hand the late appearance of the nucleic acid derivatives in the protoplasm.

It cannot surprise us in this respect that only small dendrites are found on those cells whose chromatin is still entirely in the nucleus (granular cells), and that the smallest quantity of nuclear chromatin is found in those cells whose dendrites have developed most (motor cells, reticular cells and others).

Only the question would remain why the alkaline reaction of the body lymph, which is the same around the axis-cylinder and the dendrite, does not interfere with a kathodic outgrowth of the latter and this fact seems to prove the truth of the opinion

³⁸ Scott. On the structure, microchemistry, and development of nerve cells with special reference to nuclein compounds. Trans. Canadian Institute, vol. 6, part 142, p. 405, Dec., 1899.

³⁹ Cajal. Textura del sistema nerviosa del hombre y de los vertebrados, tomo 1, p. 528, Madrid, 1904.

of Loeb and Budgett that the kathodic tropism, following the law of irritation, is chiefly dependent on *intra-cellular* protoplasmatic conditions and that the extra-cellular medium does not act such a part here as it does in anodal extensions.

Indeed, it seems more probable that the later outgrowth of the dendrites as well as their secondary contraction, including the shifting of the cell body is a process different in principle from the anodal outgrowth of the axis-cylinder, a process for which a greater functional completeness of the neurone is necessary, and that we may only say that the character of the chemical constitution of the dendrite is not such that it would interfere with it by a disturbing anodal process.

There are still three questions that may be mentioned in this discussion.

MONOAXONISM AND POLYDENDRITISM

The first question is why only one axis-cylinder leaves the cell, one which becomes complicated only by collaterals which proceed perpendicularly from it during its course, while from the cell-body, a large number of dendrites may and generally do grow out to several centers of stimulation (monoaxonism and polydendritism).

To explain the monoaxonism we may first consider what would happen if two kathodic currents traversed the young neuroblast at the same time. In a purely polar tropism, as galvano-tropism preëminently is, it is a familiar feature that the object under the influence of the current places itself so that the influence is equally great on both sides of the object. Only then does the state of equilibrium begin.

J. Loeb⁴⁰ in particular has shown this repeatedly, for example in his 7th Lecture, in which he speaks of radiating energy and heliotropism, and points out that the orientation of a simple object will continue until all its parts lie at the same angle with reference to the influence.

⁴⁰ J. Loeb. Vorlesungen über die Dynamic der Lebenserscheinungen. Leipzig, Joh. Ambr. Barth, 1906, p. 171.

As long as the influence on right and left, or indeed on all sides, be unequal, the object will change its position until the state of equilibrium is arrived at and the influence is the same everywhere.

Let us now apply this to a charged field from which a stimulus irradiates and passes to a cell in the neighborhood.

It will be clear, without anything further, that the outgrowth of the axis-cylinder in the current from the cathodic field to the anode has a state of equilibrium only in the course, that is, lengthways, of the current, i.e., in a collateral growing out perpendicularly or, where the growth stimulus proceeding from the irradiating current activated a cell in its neighborhood, the latter must send out its axis-cylinder also perpendicularly from the source along with the current. This explains the peculiar fact of collaterals of axis-cylinders in the commencement of their course having invariably a strictly perpendicular position with regard to the axis-cylinder.⁴¹

The irradiation current which radiates sideways from an activating axis-cylinder must naturally move in a direction perpendicular to this axis-cylinder. This is a physical fact that is only changed at the growing point of the activating axone.

It will thus be seen that the presence of one axon, as well as the perpendicular position of the collaterals on the axis-cylinder, are but natural consequences of the perfect bipolar character of the current. Now the same holds good if two or more differently running tracts, or differently placed centers, activate one cell simultaneously. We then may also expect only one axis-cylinder in the resultant line of the two current directions (two bio-electric fields), since only in this line the equal influence on both sides of the growing point, the energetic equilibrium, is realized.

What will be the case if two or more activating centers are present not acting simultaneously? One of these activating centers has to be the first and causes the initial outgrowth.

⁴¹ At the time when coloration and impregnation methods were not so advanced as now, the differential diagnosis of collaterals and dendrites was sometimes made on account of the perpendicular position of the latter on the axon.

If, however, an axis-cylinder has started to grow, we may expect that the favorable conditions which it offers for the current, on account of its greater conductivity, are such that the obstacle to the formation of a new axon at some other place is so much greater, that the current will take the present path of enlarged conductivity, the course of which it may influence perhaps without, however, causing a new axon to grow out, the point of application of forces being localized.

The conditions with the dendrites are quite different.

This process is by no means necessarily limited to one part of the surface of the cell since its whole body containing Nissl substance is equally sensitive and any stimulation may cause protoplasmatic shiftings in their direction, whereby the principal dendrite and finally the shifting of the cell-body itself will doubtless take place in the direction of the maximal stimulus.

In other words, if another stimulus than the one which formed the axis-cylinder reaches the cell, it will form no new way out, since this would require more energy than a following of the present path of greatest conductivity, but a new stimulus coming from another center, may produce—or even must produce—a new dendrite. Since the perikaryon is equally sensitive (except the axon hillock) to it everywhere and since already existing dendrites are not in its path, the nearest cellular or dendritic surface will be the point of application for its influence, i.e., for the formation of a new dendritic outgrowth.

THE SELECTIVITY IN THE PROCESS OF NEUROBIOTAXIS IN HARMONY WITH PSYCHOLOGICAL LAWS

I now come to the second and most important point in the tract formation, that which determines the selectivity of the definite connections.

It has escaped the observation of all the earlier investigators that the selectivity of the tract formation depends upon simultaneous, or better, correlative, stimulation. Cajal assumed chemical secretions coinciding with stages of evolution, also ascribing an influence to the glia cells in the secretion of such “substances attractives” and *without pointing out by which factors*

these stages of evolution were defined, which he could not do since his conclusions were chiefly, if not solely, based on ontogenetic, that is engrammatic observations. Held speaks of a "Prinzip der Auswahl," upon the character of which he does not enter, and with regard to his own researches Harrison⁴² justly remarks:

There is nothing in the present work which throws any light upon the process by which the final connection between the nerve and its end-organ is established.

That it must be a sort of specific reaction between each kind of nerve fiber and the particular structure to be innervated seems clear.

That the relationship for the final connection, which holds good in the central nervous system for the dendrites and the cell-shifting as well as for the axis-cylinders exists in the correlative, mostly synchronous stimulation condition of the elements, I first deduced from the selective character of the cell shifting, and this could be further clearly demonstrated by the axonic connections existing in the nervous system. It even explains a series of peculiarities in the course of the fiber tracts which otherwise confronted us as constant but inexplicable facts, especially in the so-called central motor tracts such as the pyramids.

This fundamental law of neurobiotaxis shows us not merely that the fundamental law of association in psychology is at the same time an anatomical law, but also how wonderfully polar the whole character of tract formation is, and how it therefore falls within the range of the galvano-tactic and galvano-tropic phenomena.

In order to explain this phenomenon of selectivity in an electro-chemical way, I must draw attention to the following points.

It is presumed that the presence of potassium salts has the peculiarity that it greatly increases the conductivity of the axis-cylinder for the electrolytic current.

There is even an inclination to ascribe the strong conductivity of the axis-cylinder, as compared with the synapse, to the high percentage of potassium salts in the axon (MacDonald, Macallum).

⁴² Harrison. The outgrowth of the nerve fiber as a mode of protoplasmic movement. Jour. Exp. Zool., vol. 9, 1910, p. 787.

We may assume that a state of stimulation once raised at the beginning of that axis-cylinder will proceed rapidly—it is even supposed under a gradually increasing force (the axis-cylinder increases in caliber centrifugally: Johnston,⁴³ Tretjakoff⁴⁴)—and a current of relatively great negative electric potential reaches the growing point of the axis-cylinder.

If we now assume that in the neighborhood of this growing point two nerve cells lie, one of which is already in a condition of stimulation but the other not, on which of these two cells will this growing point then exercise the greatest influence, and which cell will exercise the greatest influence on the growing point?

As we know, the cell which has just been stimulated will be in a state of greater electrolytic dissociation than the cell which is in rest.

The negative ion current which runs along the axis-cylinder in its neighborhood, will find its natural selection in this strongly dissociated field, and not in a cell which is not stimulated and, being relatively indifferent with respect to this growing axis-cylinder, does not form a place of selectivity amid all the other passive (non-stimulated) cells which, so to speak are *corpora aliena* for it.

Now we know (see above) that the dendrites of a cell begin to grow out about the time when the telodendria of an axis-cylinder reach it or approach very near to it, and this is in striking agreement with the explanation given here of the neurobiotactic processes, because at the moment when the approaching and stimulated axis-cylinder comes into the vicinity of the cell, the influence of the approaching kathodic potential difference will make itself more strongly felt, and a shifting of the protoplasm into its direction, i.e., a tropism towards the telodendria, is induced, which is a kathodic phenomenon of irritation like most tropisms under normal circumstances where no special conditions for a reversal occur.

⁴³ Johnston, J. B. Additional notes on the cranial nerves of *Petromyzon*. Jour. Comp. Neur., vol. 18, 1908.

⁴⁴ Tretjakoff. Das Nervensystem von *Ammocoetes*. I. Das Rückenmark. Archiv f. mikr. Anat. u. Entwickl., Bd. 73, 1909, plate 24, fig. 11.

A closer approach of the two neurones, a contiguity, will be the result. That this will not (or not easily) occur if the growing axis-cylinder reaches a cell in rest, may result from the fact that this passive cell, or neurone, is not in that strongly electrolytically dissociated condition and possesses no considerable electrical potential difference from the surroundings. Or to put it otherwise, the passive, non-stimulated cell has thus no other significance for the growing axis-cylinder in its vicinity but that of a *corpus alienum*, i.e., it is fairly indifferent to it.

As far as concerns the fact that axonic endings never communicate with axonic endings and dendritic endings never with dendritic endings, no further explanation is necessary from the standpoint of polar electrolytic conditions accepted here, which necessarily implies that homonymic outgrowths do not act on each other.

FASCICULATION OF AXONS. IMPROVEMENT OF THE NERVOUS PATH

One might ask in this connection why nerve fibers, if homonymic forces repel each other, tend to group together in fiber-tracts or bundles, as we always see even if they do not end on the same level (as the pyramidal tracts).

This process may, however, be analogous with the mono-axonism, that an axon shall tend to place itself in the way of the current, and if now such a current reaches a pluricellular center it is not strange that the chief resultant line for the outgrowth of one cell is also the state of equilibrium for the outgrowth of the other adjacent cells. The orientation of a number of nerve-fibers (axons) from a cell group into one bundle⁴⁵ may be no more than a repetition of the same process concerning the neurofibrils in one axon, which tend to a state of central equilibrium in the axis of the neurite.

Perhaps also a sort of magnetic field formed by equally running currents may exercise an attraction here. Such a magnetic field is also present around colloidal threads.

⁴⁵ Perhaps also a sort of magnetic field formed by currents running parallel exercises an attraction here.

Just as we saw that with the dendrites of one cell the question is different (see above), we also see that dendritic outgrowths of more cells rarely fasciculate in a bundle. The latter would be only the case if only one stimulation center attracted them all, which rarely happens.

As far as concerns the neurites, I will discuss below still another point in which it seems to be indicated that conditions which hold good for one neurite may also hold good for a collection of neurites, for a bundle.

I will not leave, however, the question of interneuronal connection without emphasizing that the greater conductivity of the axis-cylinder (based on much more K and Cl) in comparison with the dendrites, gives a peculiar character to the shifting of the nerve cell in the direction of the center of stimulation. This shifting causes a shortening of the dendritic path and a lengthening of the axonic path for the nervous current and consequently a diminution of the resistance, or if this expression be less happy, an improvement in the conductivity.

It seems probable that the retardation which the nerve current experiences in the synapse is diminished by this process. Very interesting in this connection is Mauthner's cell in fishes, where the transmission of the afferent current takes place in part on the axon cap itself (Bartelmez⁴⁶), and where probably the least resistant synapse is formed.

Similar facilitation of the transmission of the current may be seen in other structures concerned with equilibrium, e.g., in the basket cells of the cerebellar cortex where, as Oudendal,⁴⁷ among others, has shown, fibrillae of the basket are continuous with the fibrillae in the bodies of Purkinje's cells.

Since the shortening contraction of the dendrites in such cases as the descent of the facialis nucleus in mammals is accompanied by a lengthening (extension) of the axis-cylinder (fig. 5), we may ask whether there is not an analogy of this process

⁴⁶ Bartelmez, G. W. Mauthner's cell and the nucleus motorius tegmenti. *Jour. Comp. Neur.*, vol. 25, pp. 87-128, 1915.

⁴⁷ Oudendal. Ueber den Zusammenhang der Ausläufer der Korbzellen mit den Zellen von Purkinje in der Rinde des Kleinhirns. *Psychiatrische en Neurologische Bladen*, Amsterdam, 1912.

with the process seen in muscles, which at the closure of the current exhibit, besides the contraction at the kathode, also an extension at the anodal pole, the broad analogy between the law of stimulation for muscles and nerves being known.

Fig. 5 Migrations of the motor facialis nucleus in the animal series, which is correlated with a shortening of the dendrites and an elongation of the axis-cylinders.

THE FORMATION OF THE MEDULLARY SHEATH

The third point that might be mentioned in this discussion is the question as to why most axis-cylinders in the central nervous system get a medullary sheath, and why this medullary sheath is not present on the cell body and the dendrites.⁴⁸

If one were content here with a teleological explanation, it would be sufficient to say that the presence of a myelin sheath around the axis-cylinder probably has the function of insulating the current, and that an insulating sheath should not occur in places where this current proceeds from one neuron to another (dendrites, cell body, telodendria). And yet that would not bring us one step nearer to the solution of the question as to the way in which the process of myelin accumulation is effected by the axis-cylinder.

Let us endeavor here also to trace the influence which may lead to the accumulation of myelin around the axon, and why it is not accumulated sheath-like or otherwise in the cell and the dendrite.

That the primitive axis-cylinder itself is able to form myelin is proved most clearly in the central nervous system, where the cells of Ranvier (i.e., of the neurilemma) which may have to do with it in the peripheral nervous system, do not occur, and other adjacent (glia) cells are but seldom found provided with myelin granules.⁴⁹

⁴⁸ I do not refer here to the medullary sheath around the peripheral fiber of a sensory root, which is a dendrite anatomically and ontogenetically (it develops later than the central process). In the millions of neurons in the nervous system this is the only exception, which certainly requires explanation but at present need not disturb our reasoning concerning the central pathways. The peripheral nerve fibers—especially the sensory ones—do not seem to be the most adequate material to elucidate the questions involved here, since they seem to require more explanation instead of helping to elucidate these questions. Moreover the fact that spinal ganglion cells belonging to the sensory system of the skin receive stimuli from other neurones (of the sympathetic system—Dogiel) proves that nervous currents may also run toward their periphery.

⁴⁹ Vignal. *Le développement des éléments du système nerveux cérébro-spinal*. Masson, Paris, 1889. See also, Ariëns Kappers. *Recherches sur le développement des gaines dans le tube nerveux*. Petrus Camper, Amsterdam, vol. 2, part 2, 1902.

We know, from the researches of Ambronn and Held⁵⁰ that myelin formation is greatly affected by the function of the tracts, and consequently strongly influenced by the stimuli passing through it.

I have already referred to the fact that the genuine albuminous substance and also the lecithin which forms the chief component of the myelin sheath generally exhibit, under normal circumstances, an anodic kataphoresis.

Concerning the myelin itself this has been experimentally shown by Hermann, who described its connection to the anode as "eine der gewaltigsten microscopischen Erscheinungen," he ever witnessed.

Putting a part of a peripheral nerve of a frog in a constant current in the line connecting the electrodes (which, however, remained at a distance from its ends), he saw a vigorous outflow of the nerve content—especially the myelin—at the anodal pole of the nerve, where it collected in a mass.

Reversing the current, this myelin could again be absorbed by the nerve and the myelin flowed out at the other (then, anodic) end.

The tendency of the peripheral nerve constituents—chiefly its myelin—to move in the direction of the anode is clearly proved by this experiment.⁵¹

If now we apply this phenomenon to the structure of the axon in the central nervous system we may expect that the nerve current which has—as pointed out above—an anodal direction, will convey the lipoid substance, even that which is produced by the cell itself, chiefly in the axis-cylinder; but, since from this axis-cylinder an irradiation current of the same character flows out, the myelin is necessarily conveyed to the periphery of the nerve fiber.

The difficulty consequently is not why only axis-cylinders have myelin and why this myelin is conveyed from the center

⁵⁰ Ambronn und Held. Ueber Entwicklung und Bedeutung des Nervenmarks. Sitzungsberichte der Kön. Sächsischen Gesellschaft der Wissenschaften, 1895.

⁵¹ I am much indebted to Prof. Höber (Kiel) for calling my attention to Hermann's paper, which was unknown to me when I started to write this article. It is found in Pfüger's Archiv, Bd. 67, 1897, p. 240.

to the periphery and there gathering sheath-like round it; but the greater difficulty is why it remains there, and why is it not conveyed further away from the sheath. Perhaps in the beginning of sheath formation this really occurs (some glia cells and lymphocytes are found richly provided with myelin-like or fatty granules), but when its formation becomes more abundant it prevents by its nonconducting character the anodal

Fig. 6 Sagittal section of the habenular ganglion of *Scyllium canicula*, showing the position of unmyelinated fibers surrounding the myelinated fibers.

current from extending its course and consequently its conveying influence (kataphoresis) beyond the wall of myelin which thus thickens more and more.

An induced anodic condition of the direct periphery might then also cause lecithin substance of surrounding tissue (Ranvier cells) to gather on the sheath.

Why we do not find an accumulation of the same substance at the apex of the axis-cylinder, why the telodendria remain free from it, is difficult to explain. Perhaps that the conveying character of the current for this substance is so considerable there that it does not remain there when formed.

In connection with the accumulation of myelin in the periphery of the axis-cylinder I wish to mention a fact which struck me repeatedly in the study of the cerebral commissures of lower animals, where (e.g., in the commissura superior habenulae of plagiostomes fig. 6) we frequently observe that the medullated fibers are arranged in the decussating bundle on the periphery of the non-medullated fibers. The same fact struck me often in the fasciculus retroflexus, especially in *Arius*.

Sheldon,⁵² too, noticed this in his study of the olfactory tracts and centers in teleosts, and he makes the same remark with regard to some thalamic tracts. Whether this is to be explained as a repetition of the same process—an analogy—of peripheral accumulation of myelin in the medullary sheath, I do not venture to say. It seems probable, since we saw that also in another respect (monoaxonism and fasciculation, see above) the principle that holds good for an axon seems to hold good also for a collection of axons.

Here, however, we transgress the limits of a scientific hypothesis, which, though not pretending to be more than a mere hypothesis, must be founded on facts.

I would be perfectly content if this short note might stimulate others to think about these matters. The dynamic polarization of the neurone and its biologic character still require a good deal more light than has as yet been shed upon it, and is worth the attention of our best physiologists and biochemists.⁵³

RÉSUMÉ AND CONCLUSION

From the shiftings exhibited (phylogenetically) by the cells of the motor nuclei it appears that those parts of the neurone that receive the stimuli (dendrites and cellular body) are formed and directed to those stimuli trying to approach their center.

⁵² Sheldon, R. E. The olfactory tracts and centers in teleosts. *Jour. Comp. Neur.*, vol. 22, pp. 177-339, 1912.

⁵³ I have only one more remark to make. Darwin once said that plants think with their roots. He did not mean this in a literal sense, of course, but that there may be some similarities between the sensibility to certain stimuli and the behavior of the roots of plants (or other centers of growth) and parts of the nervous system, chiefly the axons, does not seem so very improbable.

Further researches show that this influence is found only on such nerve cells as have already a certain previous indirect affinity with those impressions, or with the region where those impressions accumulate, and it can be proved that this affinity consists in a simultaneous or successive condition of action (stimulative correlation); and that consequently, in the material arrangement in our brains, the law appears which has been long since acknowledged to be one of the main laws for the development of our mental capacities, viz., the law of association.

The acknowledgment of correlated function as the fundamental factor in the arrangement of the cells and dendrites induced me to investigate whether the same law could be shown in the final course and connection of the axons to lower or higher centers (so-called central-motor paths and higher sensory neurones), and a careful comparison of the regions where such paths begin and terminate, showed, that here too such an associative affinity could be pointed out, that this affinity determines the place where the axon will end, and explains a number of peculiarities in the ending of such paths, e.g., throws a light on the singular fact that the pyramidal tracts do not originally terminate in motor, but in sensory regions.

Under this fundamental law, that *neurobiotactic processes occur between correlated systems*, the tropism of the dendrites and cell body takes place in an opposite direction to the nerve current, i.e., towards the center of stimulation: *stimulo-petal*, whereas the course of the axon conducting the impression farther is in the same direction as that current: *stimulo-fugal* or (more correctly) *stimulo-concurrent*.

That, however, also the development of the axon is a consequence of the stimulus has been proved by Bok, who in an equally convincing and ingenious way showed that at first the axon does not conduct a stimulus irradiating in the nervous system, but that on the contrary, this stimulus forms the axon so that also here a stimulogenous formation occurs, described by Bok in a very important contribution to our knowledge of neurobiotactic processes, under the name of stimulogenous fibrillation.

Taken all in all, we can say that the stimuli which arrive in the nervous system, especially the relation between those stimuli, mold the material substratum of the mind; this correlation is the primary force, and expresses itself in the material arrangements of our nervous system.

This correlation of stimuli thus plays the fundamental part, in all processes of neurobiotaxis, in which, however, the dendrites and the cell body grow towards the stimulus center stimulo-petal, whereas the axon grows away from the stimulus center, with the influence irradiating from it: stimulo-concurrent.

The question is now: how can we explain these different tropisms in the nervous system; how can it be, that one nerve unit, the neurone, shows such a clearly *opposite polar difference*, that one part of its protoplasm approaches the source of stimulation (*stimulo-petal dendrites and cell body*), while the other grows with the direction of the stimulus-irradiation proceeding from it (*stimulo-concurrent axons*)?

In order to find the solution of this problem, we may study the other tropisms in nature, which are more accessible to experimental research, especially the galvano-tropisms.

In galvano-tropisms we find phenomena which remind us most forcibly of the manifestations in the nervous system just described.

By *galvanotaxis* we understand the fact that a living being or part of it, when placed in a constant electric current of certain strength, is inclined to turn towards a certain pole, in most, or in nearly all cases towards the electro-negative pole (the kathode). Thus the root-tips of plants grow towards the electro-negative pole, monocellular animal organisms move in that direction.

The process is however reversible. By putting the object, such as the root-tips of growing plants or the monocellular animals in a stronger solution of chloride of potassium or sodium (which at the same time increases the conductivity of the solution) the tropism is reversed and goes towards the positive pole (anode).

Albumen also shows a shifting in a galvanic current (*kata-phoresis*).

Contrary to the above-mentioned tropism, the shifting of

albumen and lecithine takes place under ordinary circumstances (that is to say in the circumstances in which it usually occurs in animal bodies) generally towards the positive pole. Addition of potassium also enhances the anodic character of this process, and the substance of the axon and myelin sheath of a nerve root, just cut from the body, shows in a galvanic current even a very strong displacement toward the positive pole (Hermann).

By acids the removal of the albuminous substance *may be reversed*, however, and directed towards the negative pole.

There is much evidence that these galvano-tropic and kataboretic experiments are applicable to the formation of the nervous system by the stimuli that reach it and act in it.

We know from the *negative variation* that a part of our nervous system which is stimulated forms a negative pole, a kathode, with respect to its surroundings, which in other words form an anodic field with regard to the center of stimulation.

The nerve-cells which are found in the surroundings of this electro-negative center of stimulation, will first show an anodic offshoot going in the same direction as the radiation from that center of stimulation, on account of the anodotropic character of their protoplasm. This anodic extension, will derive chemical and tropic characteristics of the potassium and chlorides in which it is imbedded.⁵⁴ In consequence a larger quantity of potassium chloride is found in the axis-cylinder than elsewhere in the neurone (as Macdonald and Macallum and Menten showed independently of each other and in different ways). This large quantity of chloride of potassium (conformably to the above-mentioned experiments with root-tips and ameba) will again enhance the *anodotropic, in casu stimulo-concurrent* character of the axon, and besides it increases its conductivity.

Not until much later do the dendrites appear, and somewhat later still the cell body begins to move in the direction of the stimulated electro-negative center.

⁵⁴ Why so much Cl is found in the axonic part of the neurone is unknown. It seems possible to me that this is due to the anodotropic character of Cl, this being an anion. A greater permeability for anions might then be the cause of the enhanced anodotropic character of the colloid substance of the axon. There is much in favor of this, that it would be rather the chlorine than the potassium.

This *stimulo-petal, kathodic tropism of the dendrites and of the perinuclear protoplasm* is probably a more complicated phenomenon, which however is not counteracted by K and Cl, since this does not occur to any considerable amount in those parts. On the other hand, it may be favored by a kathodic kataphoresis since it coincides with the appearance of the nuclear acid derivatives, known as Nissl's bodies, and does not take place until the axon has nearly reached its terminus and the neurone is therefore in a much greater state of perfection (Cajal). This kathodic tropism, followed by a gradual shortening of the dendrite and a displacing of the cell itself (as in most kathodic tropisms), is in accordance with the phenomena of kathodic stimulation, according to Pflüger's law (Loeb and Maxwell, Boruttau), as these become apparent in animal protoplasm susceptible to stimulation (e.g., also in ameba under normal circumstances) and causes these parts of the neurone to find their way to the electro-negative field which is in a state of stimulation.

It is probably accompanied by a facilitation of a stimulus-transition at that place at the moment when the galvanic current which appears in the nervous system makes itself felt (*the enhanced sensitiveness at the kathode well known in neurology*).

Thus we find in the first development of stimulo-concurrent axons a consequence of the enhanced anodotropic character, experimentally proved, of their substance, strengthened by the large quantity of K and Cl, while the formation and contraction which takes place much later of the dendrites, and the displacement of the perinuclear protoplasm to the kathode is a special case of Pflüger's laws, not counteracted by any amount of KCl, perhaps even favored by nuclear acid-derivatives.

Such may be the explanation of the dynamic polarization of the neurone. It does not, however, tell us anything about the final connection of the axis-cylinder.

This final connection is always a territory or cell which has a correlated activity, that is a simultaneous electrolytic dissociation with it. Non-stimulated centers are all equally indifferent to it, i.e., *corpora aliena* to it. We further saw that *monoaxonism* is a result of the *effect on the same pole* (a resultant line of different

forces on the same point of application), while *polydendritism* is possible and even usual on account of the fact that their formation is *not* a resultant line of different forces *on the same pole* (mathematically expressed of different forces on the same point) of the cell body since the perinuclear and dendritic protoplasm is equally sensitive everywhere to the kathodic influence and may respond at several different places to several stimuli of different origin, each of which may affect it on that part of its *ubiquitous receptive surface* that is nearest by.

The ability of the neurone to receive at the same time more than one stimulus by different dendrites and to lead their compound along one axis-cylinder, may be considered as the material expression of the formation of a compound impression from different perceptions, and this compound again acts as a factor in the formation of higher, more complicated compounds, if the axis-cylinder runs in the cerebral direction. If it runs in the aboral direction, the axis-cylinder is the final common path leading to a somatic effector center.

It seems hardly necessary to emphasize that I do not believe that *nervous life* and still less its psychic, conscious realization are, or even could be, explained by such considerations—provided they are right. They may, at the best, give us an idea of some physico-chemic processes that accompany its evolution and explain the form in which our nervous elements appear. After all, “life” and its “*données immédiates*” (Bergson)⁵⁵ remain as self-imposing truths, that are revealed in but not explained by any phenomenon whatever.

⁵⁵ Bergson. *l'Evolution Creatrice*. Felix Alcan. Paris, 1907.