The Journal OF Nervous and Mental Disease

An American Journal of Neurology and Psychiatry, Founded in 1874

Original Articles

PHENOMENA OF NEUROBIOTAXIS AS DEMONSTRATED BY THE POSITION OF THE MOTOR NUCLEI OF THE OBLONGATA¹

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What laws govern the arrangement of the elements of the nervous system is a question which has frequently puzzled the minds of neurologists. So long as the embryology and the phylogeny of the nervous system were still very insufficiently known, only suppositions could be made concerning such laws. From comparative embryology has come the first impetus to a systematic study of this question.

It is, however, only the determination of the growth of axis cylinders and dendrites that has been taken into consideration by embryologists. The determination of the position occupied by the ganglion cells is a problem which is scarcely mentioned by them.

Among the first whose researches led him to give considerable attention to the outgrowth of axis cylinders was His, senior. This author, generally prone to consider the purely mechanical factors as the most important in the evolution of the nervous system, was also inclined to see a mechanical problem in the determination of the growth and arrangement of these nervous elements.²

He tried to solve this problem, assuming that the direction of

¹ From the Central Institute for Brain-research of Holland. Amsterdam. Emended and expanded study, first appearing in Seventeenth International Congress of Medicine.

² His, sen., Die Entwicklung der ersten Nervenbahnen beim menschlichen Embryo, Archiv f. Anatomie und Physiologie, Anatomische Abteilung, 1887. See also: Die Entwicklung des menschlichen Gehirnes, 1904.

growth of nervous elongations was determined by the places of minor resistance, which would lead them to form those connections which they finally have.

Ramon y Cajal (see below), who has written a critique on this theory, justly remarks that this assumption does not explain the question, but only displaces its solution.

Accepting that only a general tendency of growth is present in the ganglion cell, and that the direction in which this growth shall be effected only depends on preëxisting spaces and paths in the surrounding tissues, the question remains: what has determined such a typical arrangement of this tissue, so that delicate fiber-tracts are directed in the right way?

It seems also possible that the peculiar arrangement of tissue is originally formed, or at least influenced, by the same forces by which nerves of central fibers are directed, and that afterwards this "path" is inherited and so well preformed that even foreign nerves or foreign central fibers (not present in this path under normal conditions) shall follow its course if they are transplanted in their neighborhood.

Concerning nutrition theory of His, jun.,³ I refer to the original.

The observations of Held⁴ are of more importance. After a full exposé of the history concerning the development of nerve cells and fibers, Held mentions that the cells of the nervous system are already—before the formation of fibrils—in mutual connection by intra-cellular bridges: plasmodesms (cf. also Braus⁵).

In such plasmodesms the fibrils, *i. e.*, the nervous path, are formed. In this process vicinity of cells (p. 47) and axial differentiation (p. 68) act a part.

Held himself is, however, perfectly convinced that the presence of these plasmodesmic forepaths alone cannot explain the *selection* in the fibrillo-formation, since it appears that alone in special plasmodesmic forepaths the definition formation of the nerve takes place. He calls the unknown cause (loc. cit., p. 270) of this *selection* "das Prinzip der Wegstrecke" "principle of the way" and discusses (pp. 270–80) the different possibilities that may explain this selection. He does not believe in a mechanical cause, and Cajal's theory of chemotaxis does not appeal to him since he supposes that diffusion will speedily spread the chemical substances

³ His, jun., Die Entwicklung des Herznervensystems bei den Wirbeltieren, Abhandlungen der Kön. Sächs. Akad. der Wissenschaften, Math.-Phys. Classe, Bd. xviii, 1893

⁴ Held, Die Entwicklung des Nervengewebes bei den Wirbeltieren, Barth, Leipzig, 1909.

⁵ Braus, Die Entstehung der Nervenbahnen, Vogel, Leipzig.

that should act as leading factors. He is inclined to believe—accepted that such chemical substances are produced—that a special absorbing character for these substances in certain paths should be the cause of the selection, but he does not say by which process this special absorption should be caused. More satisfactory to me is his more general expression that the fibrillo-formative substance of the cell must be “receptive for the manifold impulses . . . which work upon it from the structures about it” (p. 273). He thus leaves without discussion the chemical process that might or might not accompany these stimuli.

Very accurate work on this subject has been done by Cajal, who also limited his observations to the process of outgrowth of axis cylinders, collaterals, and dendrites, and hardly alluded to the determination of the localities occupied by the cell-bodies themselves.

In his standard work on the retina, then in his text-book on brain anatomy, in his treatises on regeneration, and finally in his exposé of the neurotropic hypothesis, Cajal has carefully tested the rich material of his personal observations.⁶

A great amount of observations and experiments gave him the conviction that, apart from some mechanical influences (as the central periventricular arrangement of the germinal cells, the presence of a *membrana limitans externa*), the direction of growth is determined by *chemotactic substances* in the central nervous system, and the sensibility for these substances in the outgrowth of cells.

As far as concerns the secretion of chemotactic substances Cajal supposes that this does not take place in all cells at the same time, but that different cells of the central nervous system pass this stage of secretion at different times of their embryological development. The first cells which come in this state of secretion, and consequently have a directing influence on the outgrowth of nerve-cells, would be spongioblasts, especially the external part of their cell-body, which exhibits in early stages a fringed condition. This outer division would cause the proliferating buds of the axis cylinder to grow in external directions. The myotómes and the epithelium of the skin would come next in a stage of chemotactic activity, while the cells of the central nervous system itself would come last in this condition.

⁶ Cajal, *La rétine des vertébrés*, *La Cellule*, t. ix; *Die Regeneration der Nervenfasern* (originally in Spanish; *Trabajos*, &c., t. iv); *Influencia de las condiciones mecanicas sobre la regeneracion de los nervios*, *Sociedad española de Biología*, *Boletino*, 1908; *Algunas observaciones favorables á la teoria neurotropica*, *Trabajos*, t. viii, p. 63, 1908; *Estudios sobre la degeneración y regeneración del sistema nervioso*, t. i, *Degeneración y regeneración de los nervios*, Madrid, 1913.

Although it seems strange to ascribe to so many various elements in an early stage of development, spongioblasts, muscle-cells, epithelium, nerve-cells, this capacity of directing in certain stages of evolution the outgrowths of nervous elements, the fact that proliferating tissue, even non-nervous, is able to exercise such an influence on axis cylinders and collaterals is clearly demonstrated by the experiments published by Cajal himself (*Trabajos*, t. viii) and the observations made by Forssmann,⁷ Lugaro,⁸ the Rossis,⁹ Marinesco and Minea,¹⁰ Dustin,¹¹ and others.

The simplest example of this influence is given by the proliferating connective tissue of a posterior or anterior root after lesion of that root.

Some days after the operation the axis cylinders of the roots are found to send a great quantity of collaterals into this proliferating tissue, which obviously exercises a stimulating and at the same time a directing influence on the axis cylinders.

This stimulating and directing influence, according to Cajal, can be so great that even the axis cylinders of the lateral funiculi are stimulated to send collaterals into the roots or root-fibers to send recurrent collaterals into the spinal cord.

The stimulating and directing influences of proliferating tissue on the outgrowth of nerve-fibers may thus be considered as a matter of fact.¹²

Since, however, these experiments have not directly to do with the normal development of the nervous system, but are observed in transsections, extirpations, cicatrizations, or transplantations of nervous tissue, this short quotation may suffice. For fuller details I refer to the above-mentioned authors, especially to Cajal's article in vol. viii of the *Trabajos*, where also the literature on this subject is collected.

Concerning the development of the central nervous system, Cajal points out in his text-book that we are obliged to accept that each cell of the central nervous system must be considered as being both active and passive, *i. e.*, it attracts and is attracted.¹³

⁷ Forssmann, Zur Kenntnis des Neurotropismus, Zieglers Beiträge, Bd. xxvii, 1900.

⁸ Lugaro, Sul neurotropismo e sui trapianti dei nervi, Rivista di patologia nervosa e mentale, vol. xi, 1906.

⁹ O. Rossi, Processi regenerative, &c., *ibid.*, vol. xiii, 1908. U. Rossi, Per la regenerazione dei neuroni, *Trabajos del labor. de Madrid*, t. vi, 1908.

¹⁰ Marinesco et Minea, Recherches experimentales et anatomo-pathologiques, &c., *Folia Neurobiologica*, i, 1908.

¹¹ Dustin, Le rôle des tropismes et de l'odogenèse dans la régénération du système nerveux, *Archives de Biologie*, t. xxv, 1910.

¹² It may be remembered that this influence is not only exercised on nerve-cells, as the study of regeneration teaches us that also other tissues may be stimulated and directed by localities of regeneration.

¹³ Only the spongioblasts form an exception. In a stage of evolution they attract and direct the growth of axis cylinders, but their own growth is not chemotactically directed.

The stage of attraction should be a temporary one, and coincides with the evolution of the cell, of which also the above-mentioned experiments may be considered as proofs.

Since the evolution of the different cells takes place in different stages of development of the nervous system, the attractive or, as Cajal calls it, the *chemotactic* function of different cell-groups would also take place at different times. The sensibility for this attracting influence would be present as well in the cell-body as in the dendrites and axis cylinders.

This differentiation in two sorts of expansions, axones (with collaterals) and dendrites, depends, according to Cajal, on the sequence of formation of chemotactic sources.

The spongioblasts should cause the first outgrowth of axis cylinders, and their influence as such would be continued by developing muscles, epithelium, cells of skin, and sense organs and nerve-cells, while the end branches of the axones should cause the dendritic expansions to grow in certain directions (p. 558). His histological observations taught him that the latter are, as a rule, only formed if the axone has or has nearly reached its end point (p. 523).

In this interesting exposé—based on a great number of observations—it is necessary to notice that Cajal ascribes a considerable influence to the spongioblasts in the direction of the outgrowth, not only in such a sense that their presence may have a mechanical influence on the shape of the path but specially in a chemotactic sense.

Not only the central outgrowth of various roots but also the commissural fibers (one of the first intra-cerebral tracts) should be directed in their outgrowth by the epithelial cells of the anterior wall of the central canal. Even the first outgrowth of the anterior roots, as long as they have not yet left the cord, should be directed by the spongioblasts.

Apart however from the fact that *Cajal* considers the ependyma cells as the first source of neurotropic phenomena his assumption of “substances attractives”—(accepted even that such substances are secreted in the nervous system) does not explain the matter.

It only means a displacement of the question and its answers, since *Cajal* does not mention which factors determine the secretion of these substances. If such factors are of an engrammatic, hereditary origin—as may be supposed in embryological development (partly at least) than we have to ask—for a complete insight in the whole process—of which determining moments they are an expression. As long as we are not acquainted with the factors that determine these secretions, we know little more, indeed, than we did before.

Cajal himself has felt this and says plainly in his excellent work on the retina (p. 240):

This hypothesis presupposes the existence of certain preliminary chemical and morphological conditions which are wholly inexplicable; for example, the production in the different portions of the centers of the substances, attractive or repellent according to *preëstablished laws*, the suspension or the transformation of the chemotactic state of each element for certain limited periods, etc. One might say that this theory merely defers the difficulty without reaching a solution.

This is also my opinion.

Nevertheless, the facts found by our Spanish colleague keep their value.

Of more importance than Cajal's chemotactic theory, is his remark concerning the *displacement of the ganglion cells themselves* in the ontogenetic development of the nervous system.

This remark, not known to me when I started my own researches on this point, is in perfect harmony with my own observations. Cajal expresses himself like this (t. i, p. 560): "If after a condition of relative rest new axones proceed to some nervous territory, a neurone can approach these axones in two days; either by sending out new dendrites or by a shifting of the cell-body itself, which may be guided by a large dendrite in the direction of the newly arrived axones.

Cajal mentions as examples of this cell-shifting into the direction of a territory of new nervous organization the superficial granular layer of the cerebellum and the spinal ganglia.

It appeared to me in my comparative researches on the oblongata and mesencephalon that *this displacement of nerve-cells in the direction of the place of stimulation is a factor of utmost importance for the architecture of the nervous system*, and that it plays a greater part than even Cajal could suppose at that time. It is a great satisfaction for me to confirm this author's statement as far as regards the shifting of cells, the more since my first observations and deductions on this subject were made before I knew Cajal's short remark on this matter.

I have, however, avoided the word "chemotaxis" in my conception of this process (although the similarity also struck me) because I have not found sufficient evidence for such a name, and I have used the expression "*Neurobiotaxis*" on account of this being a process of taxis or tropism occurring under normal conditions of nervous action, that is, under the influence of reception and propagation of stimuli.

I will emphasize here that *this process cannot be explained by the presence of plasmodesmic "forepaths."*

Since cell-migration in a certain direction is generally preceded by the outgrowth of a large dendrite in the direction in which the shifting of the cell shall take place, we may accept for a moment that the dendritic outgrowth follows a preformed plasmodesmic path, and that consequently the cell, if it follows that outgrowth, does the same. In so far plasmodesms could accompany or even precede the process, but what can never be explained by the presence of such a plasmodesmic forepath is why in one case only the dendrite follows this plasmodesmic way, while in the other case also the cell itself migrates along this path. Or, in other words, the principal question, *the shifting of the cell*, cannot be explained by it, and my studies, now covering all the cranial motor nuclei in all classes of vertebrates, have taught me with certainty that for this phenomenon *only the process of taxis or tropism exercised by the centres from which the majority of stimuli proceed to the cell and its dendrites can be considered as responsible*. It would take too much space if I gave even a short exposé of the phenomena of cell-shifting, or discussed in detail the different stimulating or afferent fiber-systems which in each case have to be considered responsible for the location of the cells. For those details I refer to my former publications on this subject.¹⁴

It is only mentioned here that comparative researches show that the motor nuclei of the oculomotorius, trochlearis, trigeminus, abducens, facialis, glossopharyngeus, vagus, accessorius, and hypoglossus occupy very different places in the brain-stem of the different classes of vertebrates as is shown by the colored plates accompanying this article.

The *oculomotor nucleus* may be located as well dorsally under the mid-brain ventricle (in most cases), as partly dorsally, partly ventrally (Petromyzon and Teleostei).

¹⁴ Specially to: 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-fiber, 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, 1911.

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

See also: The arrangement of the motor nuclei in the brain of Chimaera monstrosa, compared with other fishes, Verhandelingen der Kon. Akad. van Wetenschappen, Amsterdam, 1912.

The structure of the autonomic nervous system, compared with its functional activity, Journal of Physiology (Cambridge), vol. xxxvii, 1908.

The *trochlear nucleus* may lie dorsally in the velum cerebelli (Petromyzon) as under the floor of the fourth ventricle (most vertebrates). In Petromyzon it is found far behind the III nucleus, near the level of the Vth; in most vertebrates, however, it is shifted in a frontal direction, lying either very close to the oculomotor nucleus or being continuous with it.

The *trigeminus nucleus* is always situated near the level of its root-entrance, but in some animals (Petromyzon, Amphibia) is found directly under the floor of the fourth ventricle, in others (Teleostei and Reptilia), partly, and again in other animals (mammals) entirely in the middle of the oblongata.

The *facial nucleus* is sometimes found in a dorsal position (Rana and Petromyzon). In others (Selachii, Ganoids and Urodele Amphibia) it has still a dorsal position, but is shifted a long distance behind the entrance of its roots, being continuous with the nucleus of the IX and X columns. In Teleosts a part of the nucleus (sometimes connected with some IX cells) has descended a short distance ventrally along Herrick's anterior gustatory tract.

As a rule the descent of the facial nucleus takes place behind the level of the root-entrance (Reptilia and mammals, with the exception of Monotremes); in birds, however, this descent takes place in front of the root-entrance.

In those animals in which the VIIth cells descend behind the level of the root, the nucleus is either found to lie medially to the superior olive (Alligator), behind it (most mammals), or partly behind, partly laterally to it (Homo).

Only one or two small groups of cells keep a dorsal position.

Similar displacements are found in the *abducens nucleus*. Originally¹⁵ in lower vertebrata it is located behind the VII entrance (Teleostei, Selachii, Amphibia), sometimes lying nearer the VIIth root (Teleostei), sometimes nearer the IXth (several Amphibia). In the Selachii and Amphibia it has a dorsal position next the fascic. longitudinalis posterior in Teleosts, however, it is located very ventrally, mostly divided into two parts, and dorsal cells are scarcely found.

In Reptilia it exhibits a frontal displacement. In water-living Reptilia it extends from the IXth root to the entrance of the VIIth. This frontal elongation is followed by a caudal retraction in land-living Reptilia, so that the greater part of it is found in or near the level of the VIIth. This position is kept in most birds and Mam-

¹⁵ For Petromyzon see: Tretjakoff, Archiv f. mikroskopische Anatomie, Bd. lxxiv, 1909 (Das Gehirn von Ammocoetes).

malia, but in most of the latter the nucleus has acquired a more dorso-lateral position, not under, but next to the horizontal root of the VIIth.

Also the nuclei of the IX, X, and XI suffer considerable displacements.

The motor *glossopharyngeus nucleus* has a dorsal position in Cyclostomes and Selachii, being continuous with the (dorsal) vagus nucleus. In Teleostei it may be separated from the Xth nucleus and more or less shifted ventrally together with the frontal part of the facial nucleus.¹⁶ Lying dorsally in Amphibia and in most birds, it has a more or less ventral position in Reptilia, where it is united with the facial nucleus. Its position is still more ventral in mammals, where it forms the frontal part of the nucleus ambiguus, being connected with the ventral Xth nucleus.

Only some of the cells, those that innervate the salivatory system of the parotis, keep a more dorsal position, together with some dorsal VII cells (Hayama and Yagita), innervating the submaxillary gland.¹⁷

The entire *vagus nucleus* has a dorsal position in all animals with the exception of birds and mammals. In birds the posterior part of the ventral vagus nucleus is formed (posterior part of the ambiguus), and besides this a number of the dorsal cells are shifted in the direction of the XII nucleus of these animals and constitute, with a part of the XII cells, a special phonation nucleus. In mammals only those cells of the vagus column have kept their dorsal position which innervate the esophagus, the stomach, and the lungs. The motor root-cells of the larynx and the heart (Kosaka) have acquired the same ventral position as the glossopharyngeus cells, and constitute the caudal division of the nucleus ambiguus. Apart from the elongation which the posterior part of the dorsal X nucleus: the *accessorius nucleus* exhibits (having only one root in fishes, three in some Reptilia, and up to seven in mammals), it also acquires a ventro-lateral position in the latter, instead of the dorso-medial position present in lower vertebrates.

The most striking phenomena of displacement is however shown by the *anterior spino-occipital nerves*, during their transformation in *hypoglossus roots*.

¹⁶ For Menidia, see Herrick's paper, Journ. of Comp. Neurol., vol. ix, 1899.

¹⁷ Ueber das Speichelsecretionscentrum Neur. Centralblatt, 1908, No. 15; and Weitere Untersuchungen über das Speichelsecretionscentrum, An. Anzeiger, Bd. xxxv.

Originally, in animals without a muscular tongue, the corresponding center of this nerve is simply an elongation of the anterior horns of the cervical gray matter, remaining with its frontal limit far behind the frontal limit of the IX-X nuclei. In animals with a muscular tongue it loses successively its continuity with the cervical horns, and shows a dorso-frontal displacement, so that at last (in mammals) its frontal extremity reaches about as far frontally as that of the IX-X systems.

At the same time the position of the cells has become so dorsal that they lie for a considerable part dorsally to the fasciculus longitudinalis dorsalis.

A careful study of these displacements and a comparison with the other phylogenetic changes in oblongata and mid-brain have given me the conviction that these shiftings are caused by the differences in stimulation, viz., the difference of development of their corresponding posterior roots, and the differences in the sensory, optic, vestibular, acoustic, and other reflexes that influence their function. At the same time changes in the muscular system which they innervate complicate these factors.

The nuclei appear to shift in the direction of the places whence the majority of stimuli proceed to them.

For the *eye-muscle nuclei* the optic and vestibular reflex tracts appear to be the most important factors for the determination of their location, and the changes in position which they exhibit appear to run parallel to changes in the optic, vestibular and coördinative reflex tracts.

The associative function of *oculomotor* and *trochlear* nucleus may be considered as the cause of the close relationship in most vertebrates, although the former is originally found nearer the basis of the mesencephalon, and the latter¹⁸ above the fourth ventricle in the velum cerebelli, lying, moreover, a long way behind the former in the region of the trigeminus in *Petromyzon*. In higher vertebrates they are grouped round the fasciculus longitudinalis dorsalis, a highway of optic and vestibular associative reflexes, and the trochlear nucleus shifts in a frontal and ventral direction to reach the place of reflex action, where also the III nucleus is found (Tretjakoff).

Röthig found in *Bufo* and *Rana* a considerable elongation of the IV nucleus, which points out that in these animals the frontal shifting is not yet entirely completed. In Teleosts, in which this fasci-

¹⁸ Tretjakoff, Das Gehirn von Ammocoetes, Archiv f. mikroskopische Anatomie, Bd. lxxvi, 1909.

culus is less developed, a large part of the oculomotor nucleus has a ventral position on the large ventral tecto-bulbar tract of these animals.

A neuro-biotactic phenomenon of great importance has been described recently by Brouwer¹⁹ who traced the formation and frontal shifting of the central nucleus of *Perlia* which serves convergence and phylogenetically grows forward between the nuclei of Edinger-Westphal, which innervate the internal eye muscles and consequently serve the internal accommodation. Great differences are shown by the *abducens nucleus*.²⁰ In *Selachii*, in which the fasciculus longitudinalis *dorsalis* acquires the largest size known in the comparative anatomy of the bulb, its cells are located next, even partly between the fibers of this tract. In Teleosts, where the *ventral* tecto-bulbar tracts have such an enormous size, the nucleus has a ventral position, and lies close to these tracts. In the higher vertebrata the dorsal position of this nucleus is again found, but its cells shift in a frontal direction, so that instead of lying between the level of the VII and IX root, they are found on the level of the VII root, apparently shifted in a frontal direction.

This frontal displacement of the VI nucleus is introduced in *Chelone* and *Alligator* by a frontal elongation of the nucleus, similarly as Röthig could demonstrate it for the trochlear nucleus of some *Amphibia*. This shifting is apparently caused by the influence of the anterior part of Deiters's vestibular system and the nucleus triangularis vestibuli, which becomes still more obvious in most mammals, where the position next the fasciculus longitudinalis posterior is even left, and the cells shift in a dorso-lateral direction, approaching more the floor of the ventricle, and acquiring a much closer relation to the principal nucleus of the vestibular nerve and Deiters's nucleus, apparently attracted by these centers as well as by other reflex systems that proceed to them from a dorso-lateral direction, as I have specially demonstrated for *Rodentia*, *Ungulates*, and *Man*, in contradistinction to *Carnivora*.

For the displacement of the originally dorsal *trigeminus nucleus* to the mid-ventral part of the oblongata the position of its sensory nucleus may be considered to be responsible. Chiefly in those animals which chew their food (mammals), this typical position next to the sensory nucleus of the mouth, teeth, and jaws, is found.²¹

¹⁹ Brouwer, Klinisch-Anatomische Untersuchungen über den Oculomotoriskern. Zeitschr. f. d. gesamte Psych. und Neur., 1917.

²⁰ According to Tretjakoff in Cyclostomes the VIth nucleus is found in the caudal part of the Vth nucleus.

²¹ In some Teleosts, which do not chew their food but swallow it directly, the nucleus is found to run along a gustatory center and tract.

For the considerable caudal displacement exhibited by the *facial nucleus*, the centers of taste (located on the level of the glossopharyngeus entrance) are of great importance. This explains why in animals with a poor development of the sensory taste fibers of the VII (and IX) nerve (Cyclostomes and especially birds) this caudal displacement fails.

In birds this nucleus, which here chiefly innervates the posterior belly of the musc. biventer, even unites with the Vth nucleus that innervates the anterior belly.

The development of the facial muscle-system from a branchial system to a system of the face itself, and the considerable rôle which this musculature acquires for the organs of vision (eyelid movement), hearing (stapedius and ear-shells), smell (nostrils), with the fact that the musculature of the facialis is chiefly covered by a trigeminus skin, are to be regarded as the causes of the fact that the dorsal facial nucleus leaves its location near the VII-IX taste center, and descends, thus approaching the fibers of the descending Vth, the oliva superior and tecto-bulbar fibers of the visual reflex system, and the spino-bulbar reflex fibers that accompany *Gowers' tract*.²²

From this standpoint it is very interesting to notice that only a small part of the facialis cells keep their dorsal place near the center of taste, and that the researches of Yagita and Hayama have proved that these cells constitute the *salivatory center of the submaxillary and sublingual glands*. It is similarly proved that the only cells of the *glossopharyngeus nucleus* that keep a dorsal place near the dorsal taste center, form the *salivatory nucleus* of the *parotis*. A more striking proof for the determination of the location of the motor-cells by their chief sensory center—that is, by neurobiotactic influences—can hardly be given.

Concerning the *ventral nucleus of the glossopharyngeus*, the front part of the nucleus ambiguus, we may state that, contrary to the salivatory glossopharyngeus nucleus just mentioned, it innervates striated musculature and that it lies next to reflex paths of this musculature.

We know from the researches of Stuurman and those of Kosaka and Yagita that the *dorsal vagus nucleus* innervates the lower part of the esophagus, the stomach, and probably the lungs (in animals with a large stomach, birds, and cows, it is extremely large;²³ in

²² For the VIth nucleus in *Petromyzon*, see the other plate.

animals with a small muscular stomach it is small). This nucleus for unstriated musculature of visceral character keeps its position next to its chief sensory center: its own sensory root fibers, as may be expected from a motor center which acts chiefly on reflex impulses from the viscera—its own sensory root being its chief stimulating center in the medulla.

The *ventral nucleus vagi*, whose constituents originally are in a dorsal position, may have shifted under the influence of the mid-ventral fiber system of the oblongata. It is striking that the formation of this ventral nucleus runs parallel to the development of the larynx-muscles, which are practically only well developed in mammals. It is also only in mammals that the entire ventral ambiguus is found,

That the formation of a center for sound-production has really to do with these cells seems to be proved by the condition found in birds, where a small number of vagus cells has shifted in a ventral direction—only a very short distance however—thus approaching dorsal cells of the hypoglossus column, which innervate the syrinx of these animals: *nucleus intermedius* X and XII.

Since it is well known that the sound-production in birds is effected by the collaboration of larynx and syrinx musculature, we find here a striking case of the arrangement of motor cells to one reflex center (*nucleus intermedius*). That in mammals also this nucleus shifts much farther downwards may be due to a greater influence of ventral reflex paths, probably from the sensory Vth part of the Xth.

The situation of the heart-center in the posterior third part of the *nucleus ambiguus* is very difficult to explain. In harmony with the position of all the other visceral centers in the dorsal nucleus, one would expect to find this also in the same, and I would be seriously inclined to doubt its presence in the ventral nucleus, if amongst others such a careful and painstaking experimenter as Kosaka had not come to this conclusion.

It is strange that this division of the ventral Vagus nucleus is even the first to migrate in a ventral direction. In contrast to the glosso-pharyngeus nucleus (afterwards constituting the anterior division of the ambiguus) it is already found to shift in some Reptilia and in all birds. Whether this shifting has to do with the

²³ Vermeulen, Note on the size of the dorsal motor nucleus of the X in regard to the development of the stomach, *Verhandelingen der Koninkl. Akademie v. Wetensch.*, October, 1913.

transformation of circulation which occurs in higher animals or with homeothermia (temperature tracts lying ventro-laterally) I dare not say.

The ventro-lateral displacement and caudal outgrowth of the *accessorius nucleus* in mammals are more easily understood if we consider the great enlargement of its muscular system in these animals, where it has become a most important element in the movement of the upper limbs. Since the conscious movement of limbs is chiefly effected by peripheral fiber systems in the spinal cord, it is not strange to find the caudal enlargement of this nucleus combined with a ventro-lateral dislocation. That the *accessorius nucleus* has however to be considered as a caudal outgrowth of the dorsal X nucleus is not only proved embryologically in Mammalia, but also by the relations as found in sharks (Davidson Black,²⁴ van der Horst²⁵), and the fact that in many full-grown mammals, chiefly ungulates (Vermeulen²⁶), the *accessorius nucleus* exhibits still connections with the dorsal vagus nucleus.

One of the most easily demonstrated displacements caused by difference of stimulation and reflex action is shown by the *hypoglossus nucleus*.

As long as a muscular tongue does not yet exist, the corresponding musculature is found in the ventral part of the anterior body wall, and its motor roots may possess a corresponding sensory root with a ganglion. The motor nucleus is continuous with the cervical gray matter, and originally does not reach farther frontally than the posterior extremity of the vagus nucleus (see Petromyzon).

The formation of the tongue, and the part which this musculature acts in it, give rise to an entirely different reflex action of these muscles in so far as they take part in it. Deprived of stimuli which act on the body wall, they come entirely under the influence of the sensory innervation of the mouth, and as a consequence of this their motor root-cells shift in a frontal and dorsal direction, thus approaching this center. The displacement in mammals is so considerable that the cells at last reach as far frontally as the anterior extremity of the vagus nucleus, and the place which they acquire is next to the dorsal center of the taste fibers of the VII, IX, and X,

²⁴ Davidson Black, The motor nuclei in phylogeny. A Study in Neurobiotaxis, Journal of Comp. Neur., vol. 26.

²⁵ Van der Horst, Die motorischen Kerne und Bahnen in dem Gehirn der fische, ihr taxonomischer Wert und ihre neurobiotaktische Bedeutung. Sydschr. der Ned. Durk. Vereeniging.

²⁶ Vermeulen, Proc. Royal Society, 1915, Amsterdam.

near which also tactile fibers of the V, VII, IX, and X run (Wallenberg).²⁷

If the opinion of Brun,²⁸ who recently asserted that the nucleus intercalatus of Staderini is a center for mouth reflexes, is confirmed—which I believe it will be—it is not strange to find the nucleus of the tongue closely adjacent to it. A more striking proof can hardly be given for the determination of the place of motor cell by neurobiotactic influence of the centers from which the majority of its stimuli proceed during life, or, in other words, a more striking proof of the important part which is acted by neurobiotaxis for the configuration of the nervous elements is hardly to be found.

It is not possible for me to give a fuller exposé of this process, and a more detailed discussion of the forms in which it appears, in these few pages. I will only add that the neurobiotactic factor is equally found in the arrangement of the sympathetic system, and according to Herrick,²⁹ it can be equally traced in the architecture of the forebrain (septum nuclei). Also the position of the spinal ganglia of most vertebrates outside the spinal cord in which they are originally found (*Amphioxus*) and the peripheral displacement of cells of the ganglion Scarpæ in the direction of the cochlea, when this appears in phylogeny, is a shifting in the direction of stimulation. Similarly the formation of the optic and olfactory bulbs, in the direction of the light and smell, is an expression of it.

Concerning the psycho-chemical way in which this process acts I have given further details in the Journal of Comparative Neurology³⁰ where also the important findings of Bok³¹ concerning the stimulogeneous fibrillation of the axones are mentioned.

In conclusion I may add that I have very rarely found mechanical influence to be of importance in the determination of the places of cells in the central nervous system. Only in some cases large bodies, as the superior olive are seen to have an influence in this way. Their influence is, however, generally surpassed, and eventually annihilated, by that of stimulation.

Referring for details to other publications, I have thought this Journal a valuable occasion for a short communication on this subject, especially since all the authors who deal with taxis or tropism

²⁷ Deutsche Zeitschrift f. Nervenheilkunde, Bd. xi, 1897.

²⁸ Arbeiten an dem Neurologischen Institut in Zürich, 1912.

²⁹ Herrick, The Forebrain of Amphibia and Reptilia, Journal of Comparative Neurology, vol. xx, 1910.

³⁰ Further Contributions on Neurobiotaxis, No. IX, The Dynamic Polarization of the Neurones, Journal of Comp. Neur., vol. 27.

³¹ Die Entwicklung der Hirnnerven und ihrer zentralen Bahnen, Die Stimulogenefibrillation, Folia Neurobiol., Bd. ix.

in or outside the nervous system have hardly mentioned phenomena concerning displacements of the cell bodies themselves; their observations and conclusions—concerning little but the outgrowth of the cells, not the place of the cell itself.³²

As far as regards the outgrowths of the cells I may mention that an impartial judgment of the course of fiber-tracts in the nervous system, especially of lower vertebrates, seems to give us sufficient evidence to say that their arrangement is also determined by associative or correlated stimulations.³³

So we find the interesting fact that the laws which determine the material arrangements in the nervous systems are strictly homologous to the laws of psychology.³⁴

It is the more satisfactory to state this fact, since my researches on neurobiotaxis have not been started with this conception as "*idée préconçue*," but naturally have resulted in this conviction.

³² See amongst others the interesting researches of Harrison, The Outgrowth of Nerve-fibers as a mode of Protoplasmatic Movement, *Journal of Experimental Zoology*, vol. ix, No. 4.

Burrows, The Growth of Tissues of the Chick Embryo outside the Animal Body with special reference to the Nervous System, *ibid.*, vol. x, 1911, and Braus (*loc. cit.*).

³³ For fuller details concerning this special point I refer to my article on Neurobiotaxis in the *Folia Neurobiologica* of 1908, and to a lecture read before the Psychological Congress held in Frankfurt a. M., 1908.

Very interesting facts concerning the influence of correlative function on the formation of fiber tracts are found in Herrick's brilliant paper on The Centers of Taste and Touch in the Oblongata of Fishes, *Journal of Comp. Neurol.*, 1906, and Bok's paper on Stimulogeneous fibrillation.

³⁴ For further details see *Journ. of Comp. Neur.*, vol. 27.