THE CROONIAN LECTURES

ON

DEGENERATION OF THE NEURONE.

Delivered at the Royal College of Physicians of London

By FREDERICK W. MOTT, M.D.LOND., F.R.S.,

Pathologist to the London County Asylums; Physician in Charge of Out-patients, Charing Cross Hospital.

LECTURE I.

MR. PRESIDENT AND GENTLEMEN,—Allow me to thank you for the great honour you have done me in asking me to give these lectures. I feel the responsibility all the more in lecturing upon the subject I have chosen when I look back upon the eminent neurologists who have given these lectures on previous occasions. I cannot hope to attain to the philosophy of Hughlings Jackson, nor the epoch-making researches of Ferrier, but I will endeavour to put before you some thoughts, experiments, and observations relating to degeneration of the nervous system which have occupied my attention during the past three or four years.

DEFINITION OF THE NEURONE AND THE NEURONE THEORY.

Before considering the neurone under pathological conditions it is necessary to define the term, to make a few general remarks upon the neurone theory, and to describe our present knowledge of the structure of the neurone. The term "neurone" was introduced by Waldeyer for the nerve cell and all its processes, including the protoplasmic processes or dendrons and the single axis-cylinder process, with its cone of origin, its collaterals or side branches, and its terminal arborisation. The theory of the neurone put forward by Waldeyer is that the nervous system consists of innumerable such anatomically independent nervous units in contiguity, but not in continuity. There is interlacing of the processes, but no nerve network.

THE NETWORK OF GERLACH.

In 1871 Gerlach, by the gold method of staining, showed an intricate network in the grey matter; he came to the conclusion that the protoplasmic processes of the nerve cells were all connected in a delicate network, and that out of this network strands of fibrils joined together to form fibres which passed out of the posterior roots and became sensory nerve fibres. For fifteen years this theory was accepted; then Forel and His, by their studies respectively of degeneration and of the development of the nervous system in the embryo, completely overthrew the doctrine of Gerlach. Forel pointed out the limitation of secondary degeneration; and by the Gudden atrophy method showed that degeneration or atrophy did not pass beyond a cell station when the fibres which arise from those cells are cut through; and he claimed that the nervous system consisted of independent cellular units. Forel also called attention to the remarkable work of Golgi, and although he opposed the diffuse nerve network theory put forward by that authority, yet he recognised the great value of the researches made by his new chrome-silver method.

About this time, also, Professor His published his researches upon the development of the nervous system, and he showed that the axis-cylinder and the other processes of the nerve cell were outgrowths of the cell protoplasm, and the apparent nervous network was really only an interlacing of innumerable cell processes.

The chrome silver method of Golgi was later adopted by Ramón y Cajal, Retzius, Kölliker, Lenhossek, Van Gehuchten, and many others, and their researches apparently demonstrated the fact that the whole nervous system consists essentially of independent anatomical units, and the neurone theory seemed indisputably established. No matter how multitudinous and complex the branches of the cell might appear, yet they never anastomosed with the branches of other cells; like the trees of a forest there is contiguity, but not continuity. Within the last few years, however, owing to the researches of Apáthy, Bethe, Dogiel, and Nissl, there is a tendency on the part of some authorities to go back to a diffuse network theory. Some important researches by Held also have been put forward to disprove the neurone theory. In my opinion, however, one can still accept the neurone

theory and admit the truth of Held's observations, namely, that the terminal arborisation of the axis-cylinder process of one neurone forms protoplasmic concrescences by fusion with the cell body and dendrons of another. This of course implies continuity of the protoplasm of one neurone with another, but trophically and genetically the two are independent, and it is merely a question of degree of contact of the protoplasm of one with the other. Held agrees with other investigators that in embryonic tissues, and even in early life, the neurones are entirely independent of one another. This independence he can determine by a line of demarcation at the points of contact due to a difference in refraction. This refractive limiting line is, however, not demonstrable in the adult, and he comes to the conclusion that during the process of growth the protoplasm of related neurones fuses. Turner and Hunter, by the *intra vitam* methylene blue method, however, come to a different conclusion to that of Held, for they have shown that the terminal arborisations of the axons of one set of neurones end in a basket work around the cells of functionally related neurones, but do not form protoplasmic connections.

The neurone theory has always been opposed by Golgi, who maintained that his method demonstrates a diffuse network formed by the collaterals of the axons; but it is especially the work of Apáthy and Bethe which has led authorities such as Nissl to renounce the neurone theory. Lugaro, Lenhossek, Barker, Van Gehuchten, and many other authorities, on the other hand, maintain that the observations of Apáthy and Bethe do not warrant the general conclusion that nerve cells are connected with each other by means of their primitive fibrils. Moreover, Apáthy has only demonstrated a continuous network of elementary fibrils outside the nerve cells in invertebrates; such an arrangement has not yet been proved to exist in vertebrates; in fact, there is the strongest histological evidence that it does not exist. The study of the development of the nervous system and secondary degeneration to my mind show the genetic and trophic independence of the nervous units; and in spite of the opposition which the "neurone theory" has lately met with in some quarters it is still acceptable.

THE STRUCTURE OF THE NERVE CELL AS REVEALED BY THE NISSL METHOD.

The Nissl method is generally used for demonstrating the internal structure of the protoplasm of the nerve cell and its processes, but, before referring to pathological conditions as studied by this method, it is necessary to make a few remarks upon the method itself, and the appearance presented by normal nerve cells.

Nervous tissue, which has been fixed in 96 per cent. alcohol, formol solution, or corrosive sublimate solution, and of which sections have been cut and stained by basic aniline dyes—for example, methylene blue, toluidine blue, thionine, and by many other modifications of the original method, shows pictures of the nerve cells stained in a characteristic manner. If we take as a typical structure an anterior-horn cell stained by this method, we shall observe the following characteristics. The body of the cell is stained a deep blue, but not uniformly, for the staining presents a mosaic appearance, due to little stained polygonal areas disposed more or less concentrically round the nucleus, and separated one from another by an unstainable substance. Towards the periphery of the cell these polygonal stained areas become elongated, and upon the dendrons they are fusiform, their long axes being parallel to the processes. At one portion of the cell, if it is entire, a process—the axon—will be observed which does not possess any stainable substance; so that we see this method differentiates two substances—a chromatic stainable substance and an achromatic substance.

Researches, to be afterwards alluded to, have shown that the stainable substance is a nucleoprotein—a substance which contains phosphorus, but in less proportion than the nucleic acid of the nucleus, and the fact that the stainable substance is found around the nucleus may indicate that it is a result of the active metabolism of the nucleus on the surrounding protoplasm. By some authorities it is considered to be a store of nutriment; by others, a store of energy; and on this account it has been termed by Marinesco "kinetoplasm." The changes which this substance undergoes, as studied by the

Nissl method, show that it has some important functional relationship to the metabolic activity of the neurone; it is, however, not the essential substance. The unstainable substance, on the other hand, is essential, and consists of an organised network of delicate fibrils, which extend into the dendrons, forming a network in the cell substance, and passing out again in the axis-cylinder process. Consequently there is probably a direct protoplasmic fibrillary continuity between the dendrons and the axons. This was originally stated to be so by Max Schultze. The nucleus is apparently of simple structure, and is permeated by irregular strands of karyoplasm, which form a coarse network. It is apparently situated in the centre of the cell, and contains a nucleolus or several nuclear bodies, which, together with the nuclear membrane, are stained with a basic dye.

THE SIGNIFICANCE OF THE NISSL GRANULES.

There is a vast amount of literature concerning the stainable bodies called "Nissl granules." They were at one time believed to be an essential constituent of the living cell, but the researches of Hardy have shown that there is a great difficulty in deciding to what extent structure demonstrable in the fresh or fixed state is the product of the chemical and physical changes which constitute the death changes, or due to the action of fixatives; moreover, Held has shown that the *intra-vitam* methylene blue method does not reveal Nissl granules in the cells. The stainable (chromatic or chromophilous) substance, therefore, is probably not present in the living cell in the definite form which we see it when the tissues are fixed and stained by the Nissl method. It must not, however, be assumed, therefore, that the method is unreliable as a means of studying the biochemical changes occurring in the protoplasm of the nerve cells, for providing certain precautions are taken, it has proved most valuable in demonstrating functional and organic changes occurring in the nerve cells as a result of injury of the axon or of toxic substances in the blood.¹

The large motor cells of the cord and brain are the best to study the changes in the cell protoplasm, because in these structures the stainable substance appears in normal tissues as if it consisted of formed elements (Nissl granules) in the body of the cell and in the dendrons. I have always looked upon these elements as being due to a death change of the fluid plasm of the cell whereby the nucleo-proteid substance contained in it is thrown down as a fine precipitate, much the same as myosin is precipitated from myosinogen. If this substance is abundant in the fluid plasm it produces, when precipitated, these definite forms, because it fills up the spaces of the unstainable intracellular fibrillary reticulum.

Chromatolysis is the term which is frequently applied to designate the disappearance or disintegration of these Nissl granules, and there may be various stages of chromatolysis. Usually the process begins at the periphery of the cell and on the dendrons. The stainable substance may be greatly diminished or entirely lost in these situations; or, again, the granules may be seen to consist of fine particles, their definite outline being lost, and in advanced chromatolysis the whole cell may be so affected.

The condition and amount of the stainable substance may be an indication of the functional activity of the cell, and it is conceivable that diminution of the nucleo-proteid colourable substance is the expression of the diminution of the vital interaction of the highly phosphorised nucleus upon the surrounding cell protoplasm. I do not consider that chromolytic changes alone are indicative of cell destruction; for, as I shall show later, most marked chromolytic changes may occur in the cells of origin after section of a nerve, and yet the cells completely recover.

Changes of the cell in form and size may be recognised; for example, swelling or shrinking, due no doubt to an alteration of the vital osmotic reaction of the cell protoplasm to its fluid environment; likewise the nucleus may be clear and swollen, or shrunken—the nuclear membrane in the latter case being thrown into folds. Very frequently the nucleus becomes eccentric in position instead of being situated in the centre of the cell and owing to abnormal osmotic relations and protoplasmic change it may even be extruded, and this of necessity would cause death of the cell. Another indication of death

of the cell protoplasm is revealed by uniform staining of the whole cell and its processes. It occurs in hyperpyrexia and in coagulation necrosis resulting from obstruction of the blood supply for a sufficient length of time to cause the death of the protoplasm.

The importance of the chemical and histological changes occurring in the myelin sheath in degeneration of the nervous system, the difference of opinion as to its origin, and the important discoveries which have been made by Flechsig, Bechterew, and others, with regard to correlation of structure and function necessitate a somewhat full account of the myelin sheath and the nucleated sheath of Schwann.

THE MYELIN SHEATH AND NUCLEATED SHEATH OF SCHWANN.

Nerve fibres are of two kinds, grey and white. The grey sympathetic fibres differ essentially from the white fibres by the existence in the latter of a complex phosphoretted fatty substance lying between the nucleated sheath of Schwann and the axis-cylinder process. The white fibres of the central nervous system differ from the peripheral white fibres by not possessing a nucleated sheath of Schwann; the myelin is probably contained in a neuro-keratin reticulum, and this reticulum is much more abundant in the white matter of the central nervous system than in the peripheral, for Kühne and Chittenden have shown that there is about eight times as much neuro-keratin in the white matter of the central nervous system as either in the grey matter of the central nervous system or the white matter of the peripheral nervous system. In 1884 Weigert introduced his hæmatoxylin method for staining the myelin sheath, and by means of this Flechsig and his pupils were able to show that certain tracts of fibres of the central nervous system were developed earlier than others. This method and its various modifications (Pal, Marchi-Pal, and Schäfer) have yielded the most valuable results. The different tracts of the posterior columns of the spinal cord were found to be myelinated at different periods, and it was owing to Flechsig's studies that those of endogenous origin (that is, arising from cells within the spinal cord) were differentiated from those which are exogenous (that is, have their trophic and genetic centres in the cells of the posterior spinal ganglia). The practical outcome of this research was the modern idea of the pathology of tabes, for it was shown that the exogenous fibres were alone atrophied in tabes, while the endogenous—namely, cornu commissural zone of Westphal and the median oval area of Flechsig—were spared, these tracts having their trophic and genetic centre in cells within the grey matter of the cord. These facts were recognised as being incompatible with the prevalent view that the degeneration was caused by a sclerosis or overgrowth of glia tissue in the posterior columns or by vascular changes; but they pointed especially to a nutritive failure in the trophic and genetic centre by which the outlying projections of the axis-cylinder processes and their myelin coverings underwent degeneration; in fact, a metamorphosis of the neurones occurred—the inverse of their development.

CORRELATION OF FUNCTION AND MYELINATION.

Again, the researches of Flechsig have demonstrated the different centres of the central nervous system in which tracts of nerve fibres have their origin or termination; and it is to the application of this method by Flechsig that we owe one of the most exact and one of the most valuable contributions to the structure and functions of the human brain. The method depends upon the fact that there is a correlation between the functions of systems, groups, and communities of neurones and the myelination of their axons; thus, in the brain and the spinal cord of the fetus, the newborn child, and the developing infant, tracts of fibres are myelinated with definite regularity at successive periods of time, indicating ontogenetically their functional and structural development. The myelin sheath appears three or four months after the development of the axis-cylinder process; for example, a bundle of axis-cylinder fibres demonstrable by the Golgi chrome-silver method at the ninth month would not show a myelin sheath until three months or more after birth. When the myelination of a nervous system is complete, further information by a study of the condition of the myelin sheath can only be obtained by observations made upon secondary degenerations, produced either by disease or experimentally,

and to this subject I shall refer later on, with especial reference to the Marchi method. To return, however, to the process of myelination: in the central nervous system the afferent projection fibres are myelinated before the efferent, and it is a fundamental principle that bundles of fibres of different physiological functions are myelinated at different periods of time; the whole afferent tract conducting tactile, articular, muscular, and visceral sensations by the posterior columns, fillet, thalamus, and corona radiata, is myelinated at birth; and these bundles of fibres have already (while the fœtus was *in utero*) been exercised in conveying impressions to the appropriate receptive centres in the Rolandic region of the cortex—the stimuli being provided by contact of the teguments with the maternal structures, and as a result of reflex movements which commence at quickening; for every movement must necessarily be associated with alterations in tension of muscular, tendinous, and cutaneous structures, giving rise thereby to kinæsthetic impressions.

Moreover, the myelination commences first in those parts of the occipital lobe situated around the calcarine fissure, which we know corresponds to the function of vision; the relays of neurones which proceed to the cortex forming the afferent projection systems are earliest myelinated, as they are the first to be acted upon by stimuli which excite the nerve terminations in the skin, joints, tendons, and mucous surfaces of the developing fœtus. Thus, as shown in the diagrams, in the newborn child, only the lower centres of the spinal cord, medulla, pons, corpora quadrigemina, optic thalamus, and certain areas of the cerebral cortex are myelinated; the cortical areas, which are so myelinated, are situated around the primary fissures, and correspond to areas, which are the end stations of the afferent projection systems; for example, the tactile motor area is situated around the fissure of Rolando; the olfactory, gustatory, and auditory around the Sylvian; the visual around the calcarine. (See Figs. 1 and 2).

Fig. 1.—Diagram of vertical section through the brain of a newborn child stained by a special method to show myelination of the fibres. All the parts which are dark contain myelinated fibres. Attention is particularly called to the rather faint staining about the central fissure which corresponds to the tactile motor area. It will be observed that the association centres are not myelinated as in Fig. 2, nor is the pyramidal tract.

Flechsig has shown that at least two-thirds of the cortex cerebri consists of neurones of association; and, according to him—although this does not meet with general acceptance—these association centres possess no neurones belonging to the afferent or efferent projection systems. In the fœtus of eight months the pyramidal fibres of the motor-efferent system are still without myelin; but Ambron and Held have shown by a new method of examining the condition of the myelin—by the effect produced on polarised light—that the motor fibres of the anterior roots are myelinated earlier even than the posterior roots.²

In a second paper Held has shown the important influence stimulus has upon myelination, thus establishing still more

fully the correlation of function and myelination. Cats, dogs, and rabbits (animals which are born blind), were experimented upon in the following way: Light was admitted for varying periods to one eye by opening a lid, the other remaining closed. Examination of the optic nerve on the two sides under the same conditions showed a more obvious myelination on the side exposed to light than on the other. The irritation, which might be produced by opening the lid, was not the cause of this difference, for an animal which had had the lid opened on one side and not on the other, but which was kept in darkness, showed no difference in myelination of the two sides. The obvious inference is that transmission of light impulses along the optic nerve had stimulated the process of myelination. This experiment agrees with the observations of Flechsig: that a child born at eight months showed at nine months more marked myelination of the optic nerves than a child born at full time. Still there must be a primary innate tendency of the axis-cylinder to produce myelin, for a dog kept absolutely in the dark had, on the eighth day, orange-tinted optic nerve fibres by the polarisation method, showing that myelination had commenced. Elinger states: The discoveries of Kaes show the cerebral cortex increases in richness of myelinated fibres for a long time, even to the fortieth year or longer but diminishes in old age. The correlation of function and myelination is proved both by positive and negative results; the myelin appears to be necessary for the functional activity of nerve tracts, at least in animals which possess a nervous system with myelinated fibres, for the development of the myelin along particular tracts of fibres in the central nervous system proceeds in a manner *pari passu* with the development of function. Atrophy and degeneration of the myelin sheath in pathological processes, whether due to disuse atrophy, or to primary or secondary degeneration, are associated with marked disturbances appertaining to the functions of particular systems, groups, and communities of neurones.

THE HISTOGENESIS OF THE SHEATH OF SCHWANN.

This has been studied by many observers, and a paper has recently appeared by Gürwitsch reviewing the work of previous observers, and giving his own observations upon

Fig. 2.—Diagram of vertical section of the brain of a child aged 5 months. The greater part of the brain now shows by the staining myelination of the white matter, showing development of the association centres. The corona radiata and the pyramidal tract are now well myelinated.

this subject. Kùpffer, Beard, and Gegenbauer believed that the axis-cylinder is developed from a chain of cells of ectodermal origin arranged in a series. Such an idea would conform with the researches of Apáthy upon invertebrates, and is opposed to the axis-cylinder being an outgrowth of a nerve cell situated either in the anterior cornua or the posterior spinal ganglia. If this hypothesis be true, the three constituents of the nerve fibre—axis-cylinder, myelin sheath, and sheath of Schwann—must be formed by a differentiation of

protoplasm of these cells. If, however, it be admitted that embryological, morphological, and experimental researches have demonstrated that the axis-cylinder of a nerve fibre is a prolongation of a nerve cell, then the sheath of Schwann is genetically foreign and extraneous to the axis-cylinder; but the question arises, How, then, is the myelin sheath formed? Is it developed by the axis-cylinder, as in the central nervous system, where the sheath of Schwann is absent, or is it formed by the nucleated sheath of Schwann? Another alternative is that it is developed by a metabolic interaction of the axis cylinder upon the protoplasm of the series of mesoblastic cells which are wrapped round it.

Fig. 3.—Diagram to show reflex arc. A, skin with sensory endings. B, end organ, Pacinian corpuscle. C, end organ of tendon (Golgi). D, sensory nerve fibre. (Only one sensory nerve fibre is represented as conveying impulses from those above-mentioned structures, but it must be clearly understood that there are separate neurones for each.) E, cell of posterior spinal ganglion, with fine granules scattered through the body of the cell; these are the chromophil granules. Emerging from the capsules is the axis-cylinder process, forming a 'T'. The central process passes to the spinal cord, and at F the chain of tubular cells representing the sheath of Schwann ceases, but the axis-cylinder process is still covered with myelin; it breaks up at G into a terminal arborisation with H. H, the motor efferent neurone. The lower part of the cell is represented showing polygonal granules (Nissl); the upper part of the cell shows a fibrillary reticulum. The granules exist all over the cell and on the dendrons, except at the emergence of the axis-cylinder process; but they are not represented in the upper part, in order that the fibrillary reticulum of the achromatic substance may be clearly shown. The axon becomes coated with myelin; it acquires a sheath of Schwann on emergence from the spinal cord, and terminates at K in the motor end plate.

Ranvier and his pupil, Vignal, compared the formation of the myelin to the formation of fat within a fat cell. Vignal's description of the process of myelination is as follows: At a particular stage of development, when the nerve fibre consists of non-nucleated bundles of fibrils, mesoblastic cells migrate into the interior of the fibre, and apply themselves closely to single groups. Their cell protoplasm increases in length and in breadth, until some of the primitive fibrils are enclosed. The definite intervals in the enclosing sheath, corresponding to the nodes of Ranvier, coincide with the spaces between the ensheathing cells; consequently each internode represents a

segment of the continuous axis-cylinder wrapped round by a mesoblastic cell. At the same time, according to Vignal, the myelin appears in the cell protoplasm, in the form of minute droplets; these become more numerous, and run together to form a general thin covering of the axis-cylinder. Vignal does not deny the possibility that the axo-plasm may share in the formation of the myelin, but in quite a subordinate manner. The observations of Boveri, which recently have been confirmed by Bethe, show that the sheath of Schwann is reflected inwards at the nodes along the axon; if this be true, there is (as in a serous membrane) a parietal and central layer, and between the two the myelin is contained. This would prove Vignal's hypothesis. Gürwitsch has studied the development of peripheral nerves in embryo sheep, fixing the sciatic nerve with Apáthy's solution, and employing various staining reagents used by that observer. He came to the following conclusions: (1) That the nerve fibre is a prolongation of the ganglion cell; (2) the sheath of Schwann arises from the surrounding mesoblast; (3) the myelin sheath has nothing in common with the sheath of Schwann, and probably arises only as a product of the metabolism of axo-plasm. Time will not allow me to give you more than this very brief outline, and to those who are further interested in the subject I would refer them to an admirable digest on the *Histology and Pathology of the Nerve Cell*, by Ford Robertson, or to the splendid new work of Barker on the *Nervous System*.

It would take too long here to describe the normal structure of the various forms of neurones, but, to make myself more clear in speaking of degeneration and the changes which occur in the nerve cell and its processes, I represent here diagrammatically a spinal reflex arc, showing a sensory and motor neurone (Fig. 3). Each portion has a brief description appended, so that I need not detain you further with the details. I would call your attention, however, to two facts—namely, (1) the difference in the myelin sheath as it surrounds the axis-cylinder process and its fibrils within the spinal cord, as compared with the myelin sheath outside the same—in the latter, the axis-cylinder is surrounded with a chain of tubular cells containing the myelin, whereas in the former there is simply a continuous coating of the phosphoretted fat; and (2) the different arrangement and appearance of the stainable substance in the motor and sensory cell.

THE DEGENERATION OF THE NEURONE.

Brief Historical Introduction.

New methods of experiment, observation, and technique mark the successive stages in our knowledge of the structure and functions of the nervous system in health and disease. Fifty years ago Waller gave his memorable communication to the Royal Society, which was the commencement of our knowledge of the degeneration of the neurone. In his paper, *Experiments on the Section of the Glosso-pharyngeal and Hypoglossal Nerves of the Frog, and Observations of the Alterations produced thereby in the Structure of their Primitive Fibres*, he pointed out that Günther and Schön had ten years before stated that the primitive fibres, at the end of a week after division of the nerve, and when it had lost its irritability, showed changes indicating degeneration; likewise Nasse and Steinrück had described changes following division of nerves. Waller's researches showed that a change took place throughout the whole of the nerve below the point of section, extending to its terminal fibrils. Original pictures are here reproduced from Waller's monograph (Figs. 4, 4a, and 5). He concludes his paper with this very apposite statement: "We cannot suppose that this is a local phenomenon and that the nerves do not participate in similar alterations, and that the brain itself, composed in great part of tubular fibres, must be excluded. It is impossible not to anticipate important results from the application of this inquiry to the different nerves of the animal system; but it is particularly in reference to nervous diseases that it will be most desirable to extend these researches." How much light the extension of these researches during the last fifty years has afforded neurology can be best appreciated by reviewing the enormous strides which have been made in our knowledge of the anatomy, physiology, and pathology of the nervous system. Waller had anticipated that degenerative processes would be found to occur in the central nervous system as in the peri-

pheral nerves. He had not long to wait, for in 1852 Türck published a paper showing secondary degeneration of the spinal cord after a transverse lesion, and in 1854 he published his classical paper on secondary degeneration of tracts in the spinal cord and their prolongations in the brain, based upon 21 cases. As Waller's observations form the basis of our knowledge of secondary degeneration of the peripheral nervous system, so Türck's observations are the basis of our knowledge of secondary degeneration of the central nervous system. Waller extended his researches, and formulated the three following fundamental laws, which are given in italics in an appendix to the work quoted, consisting of fifty-two important statements bearing upon the results of his experiments.

Fig. 4.

Fig. 5.

As a general rule the sensory fibres develop by starting from the peripheral and radical poles of the ganglion corpuscles, and extend from them into the peripheral organs, and in the spinal cord to a height undetermined.

The ganglion corpuscle is, in consequence, the central organ for the formation and nutrition of its peripheral and central fibres, and accordingly we shall call it the neurogenotrophic corpuscle, and the ganglion the neurogenotrophic body. (The neurone doctrine foreshadowed. F.W.M.)

Considering the ganglion in its simplest state as a bipolar corpuscle we are able to assert that every part of the radical and peripheral poles which is separated from the corpuscle disorganises, while the whole of the poles in connection with the corpuscle remains normal.

His son, Dr. Waller, gives on page 352 of his *Textbook of Human Physiology* an unpublished drawing of these very points.

Fig. 6.

Figs. 4, 5, and 6.—Drawings from the original monograph of Dr. Waller (*Phil. Trans.*, 1850) to show the degeneration of the terminal fibrils of the nerves in the papillae of the tongue of the frog after section of the nerves.

Fig. 4.—Papillary nerve of frog six days after ligature.

Fig. 5.—Papillary nerve, three weeks after section, with muscular fibres in the interior of the capillary coil at the summit of the fungiform papilla.

Fig. 6.—Disorganised muscular nerve, from the inferior surface of the tongue, five days after section. The muscular fibre has been omitted in this drawing.

Numerous observers since have claimed that the law formulated by Waller that every part of a nerve which is separated from its cell origin undergoes degeneration whilst the central portion remains normal, although fundamentally true, may require some modification; and the first observer whom I find to suggest this is Dr. W. H. Dickinson, who in a very interesting paper on the Changes in the Nervous System which follow the Amputation of Limbs stated as a result of his observations that the posterior roots may atrophy, though still in connection with the ganglia; the anterior, though still in connection with the cord; and it appears that long disuse of a nerve is sufficient to lead to its atrophy, although those nervous structures which immediately regulate its nutrition are complete (Figs. 7, 8, 9). (Bérard in 1839 had noticed atrophy of the ventral roots in an amputation case). The degeneration described by Waller and Türck are degenerations secondary to injury, and that described by Dr. Dickinson and numerous other observers since may be looked upon as a *disuse atrophy*. A little later Gudden commenced his celebrated work upon atrophy of the cells of origin of a nucleus by tearing out the nerve in young animals, and this method threw great light upon the anatomy of the nervous system. It was adopted with striking success by Forel and von Monakow. There is another form of degeneration which, excepting the

cellular theory of Virchow—that the whole organism including the nervous system is made up of an aggregation of cells, each cell being a living unit having an independent existence—is a *primary* degeneration of the complex nerve cell or neurone. Every cell of the body nourishes itself and is not nourished—

Fig. 7.—A transverse section of the normal sciatic nerve magnified 300 diameters. From an article by Dr. W. H. Dickinson, published in the *Journal of Anatomy and Physiology*, November, 1868.

Fig. 8.—A transverse section of the sciatic nerve from the stump of the same person 53 years after amputation, also magnified 300 diameters. From an article by Dr. W. H. Dickinson, published in the *Journal of Anatomy and Physiology*, November, 1868.

Fig. 9.—A transverse section of the cervical part of the spinal cord from a man whose left arm had been amputated twenty-three years before death. The left posterior column (L) is smaller than the right. From an article by Dr. W. H. Dickinson, published in the *Journal of Anatomy and Physiology*, November, 1868.

that is to say, every cell behaves as a unicellular organism, possessing a specific energy; and by the vital reaction of its protoplasm upon the lymph environment, metabolic exchanges, constructive and destructive, are continually taking place correlative with functional activity. We have no evidence to show that regeneration of nerve cells can take place in the higher vertebrates, but there is some evidence in favour of the view that all the nerve cells of the adult body are present in a rudimentary form at birth. The growth of the nervous system depends, not so much upon an increase in number of the nervous units, but of their size, by multiplication and complexity of the processes. Cajal (and I reproduce his diagram—Fig. 10) has shown that this growth in complexity during the process of development is not only true ontogenetically, but also phylogenetically. Wallerian degeneration proves that the nerve cell is the trophic centre, and the embryological researches of His have shown that it is the genetic centre. If then we admit the generally accepted view that the nerve cell in the higher vertebrates is incapable of regeneration when destroyed, the corollary is that

every nerve cell of the human body is endowed with a specific durability, whereby in the healthy perfect organism every neurone possesses an equally adjusted vital energy, so that not only is functional equilibrium maintained in the physiological processes of active life, but also of decay, the regressive metamorphosis incidental to old age being manifested by a gradual and general enfeeblement of the functions of the whole nervous system. Lucretius says: "When the body has been shattered by the mastering weight of Time, and the frame has drooped, with its forces dulled, then the intellect halts, the tongue dotes, the mind gives way, all faculties fail, and are found wanting at the same time. It naturally follows that the whole nature of the 'soul' is dissolved like smoke into the high air, since we see that it is begotten along with the body and grows up along with it, and as I have shown breaks down at the same time worn out with age." In contradistinction to this normal senile decay are premature pathological processes of decay, attacking groups, systems, or communities of neurones subserving special functions, whereby functional equilibrium is destroyed, symptoms of disease manifested, and according to the functional relations of the system selected characteristic symptoms are presented, constituting clinical groups. The neurones of a particular system die prematurely owing to an *inherited* or *acquired want of durability*, and the regressive process of decay may be looked upon as a nutritional failure on the part of the same cells to maintain that metabolic equilibrium essential and correlative to functional activity; consequently, *those parts most remote from the trophic and genetic centre of the complex cell (neurone) degenerate*. The process may be regarded as the inverse of development, the fine collaterals and terminal arborisations being the first to disappear. Dr. Hughlings Jackson in his Croonian Lectures, March, 1884, states: "I have long thought that we should be very much helped in our investigation of diseases of the nervous system by considering them as reversals of evolution, that is, as dissolutions." Morphologically, I conceive that the process of primary degeneration is an evolutionary reversal, commencing in the structures latest developed, namely, the myelin sheath and the terminal arborisations and collaterals of the neurone.

Every point of the central nervous system is in physiological if not in anatomical connection with every other point, and resistance to the spread of excitation is variable.

Fig. 10.—Diagram after Ramón y Cajal to show the autogenetic and phylogenetic development of a psychomotor neurone. A, frog; B, newt; C, mouse; D, man. It will be noticed that as we rise in the zoological series there is an increase in the complexity of the neurone and in the multitude of points of contact, produced by an increase in the dendrons and side branches of the axon; a, b, c, d, e show ontogenetic development of a psychomotor cell in the human embryo.

The nervous system may be said to consist of three systems of neurones—afferent, efferent, and association systems (Fig. 11). Before entering into a detailed account of my own observa-

tions upon the degeneration of the neurone, which will occupy most of the other three lectures, I will give a few illustrations relating to the neurone theory as regards the transmission of impulses and certain physiological problems connected with variable resistance to transmission of the spread of excitation. Every excitation can spread over the whole nervous system, but it is difficult to understand how there may be a variable resistance to the spread of an excitation, if we accept the diffuse, continuous network theory of Gerlach or of Golgi, or how use may lead to opening up of paths so that the time occupied by transmission of impulses may be diminished by repetition. Facts seem to show that there is a delay in the transmission of impulses in the passage from one neurone to another in the central nervous system. Does this delay occur at the junction of the terminal arborisations at the axon of one neurone with the dendrons of another? or does the resistance occur in the protoplasm of the cell body?

Fig. 11.—Diagram to show the three systems of neurones, illustrating the path of sensory impulses to the cerebrum and cerebellum, the path of outgoing impulses from the brain in a voluntary movement and the association of the afferent and efferent projection systems in the grey matter of the brain. This diagram also illustrates the path of a simple spinal reflex and of a psychical reflex.

Bubnoff and Heidenhain found that the strength of stimulus was related to rate of transmission in the central nervous system, for one stimulation of the cerebral cortex of the dog the reaction time is shortened by increase in the strength of the stimulus, whereas the peripheral nerves are influenced as regards rate of conduction only to a comparatively trifling degree by the same increase of stimulus.

It would therefore appear that a stimulus passes from the upper neurone to the lower more rapidly when the stimulus is strong than when weak—that is to say, the excitation in the upper neurone must reach a certain intensity before it is capable of flowing over and exciting the next in the series. Is the resistance to the passage of the impulses in the physiological junction of the upper and lower neurones, or in the

protoplasm of the cell body? According to the neurone theory, it would be at the junction.

DIAGRAM.

A stimulus which is insufficient to rise into consciousness may, by repetition, lead to summation, and the opening up of a path (*Bahnung*) by breaking down resistance; thus Urbantschitsch has shown that very weak sounds, at first not audible, become so by repetition. This effect can be explained by the stimulus opening up the path to the auditory perceptive centre. The same effect can be produced by an effort of the will and concentration of attention, by which the auditory perceptive centre becomes more excitable. That an excitation may spread over the whole nervous system is not to be wondered at when we consider the length of some of the projection system neurones; for example, the posterior spinal sensory neurones, which have their cells of origin in the first sacral ganglion, extend from the nape of the neck to the sole of the foot. The central projection of the T-shaped process gives off a branch, which extends in the column of Goll the whole length of the spinal axis, and the peripheral portion as a sensory fibre extends to the sole of the foot. It is probable, therefore, that the central projection establishes connections by delicate collaterals with the grey matter of the whole spinal axis. The reason why excitations do not spread is probably dependent upon the condition of the bio-chemical stability of the neurones. In strychnine and tetanus poisoning the most localised peripheral excitation will cause general muscular spasm; in both toxic conditions the spread is probably due to a bio-chemical change in the protoplasm of the spinal motor neurones, to be referred to later on, whereby the excitability is greatly increased and a slight impulse is sufficient to fulminate the whole system of motor neurones. In epilepsy and other paroxysmal neuroses and psychoses it is possible that some altered condition of the blood associated with an inherited bio-chemical instability of certain groups, systems or communities of neurones may act as a *fulminating agent*. In neuralgia and local hyperæsthesia, the slightest general or distant local irritation suffices to produce pain; thus coughing, the vibration of a passing train, or a slamming door may produce pain by the stimulation of the hyperexcitable neurones.

If a skin reflex is increased on one side of the body, then sometimes a slight excitation on the normal side is sufficient to produce the crossed reflex, while perhaps the excitation is not sufficient to bring about the normal reflex on the sound side. It sometimes occurs that associated sensations (in part of a painful nature) arise from pressure upon spots which cannot be explained upon any known anatomical basis. This condition can be understood only by supposing that certain groups of neurones are in a state of hyperexcitability, and that the neurones which are stimulated have fortuitously opened up the connection by association neurones, and it has been fixed and made easier by each successive stimulation. The excitation spreads, but is not of sufficient intensity to arise into consciousness, except in the hyperexcitable area. (Goldscheider.)

Besides hyper-excitability, there may be diminished excitability affecting groups, communities, and systems of neurones having special functions. It will be seen later that this lowered excitability is usually the result of the selective action of various poisons producing either functional depression or degeneration, whereby paralytic or other symptoms of loss of function arise in certain definite functionally related systems of neurones, thus causing correlative groups of clinical symptoms, due, on the one hand, to perverted function or loss of function, and, on the other hand, producing other groups of symptoms, as pointed out by Hughlings Jackson, "due to over-activity of nervous arrangements which are perfectly healthy." This disturbance of the functional equilibration of the neurones may best be studied by a consideration of the nervous mechanism concerned in voluntary movement. Fig. 11 shows that three nervous circles—spinal, cerebral, and cerebellar—are engaged, and all three systems of neurones take part, for in every voluntary movement impulses are passing up the afferent channels and down the efferent, and these two systems are brought into physiological harmony by the association systems.

DISTURBANCE OF THE FUNCTIONAL EQUILIBRATION OF THE NEURONES.

The perfection of a voluntary movement is brought about by the association and equable adjustment of systems and communities of neurones presiding over groups of correlated antagonistic muscles in such a way that the desired movement is produced with the least expenditure of nervous and muscular energy. Interference with the functions of any one system will disturb the normal functional equilibration that must of necessity exist in the action of the whole.

Dr. Hughlings Jackson emphasises the fact that the symptoms of nervous disease are due as much to normal physiological functional activity, imperfectly applied, as to the actual loss of function occasioned by the disease. He pointed out that in paralysis of the external rectus, strabismus caused less trouble to the patient than the double vision occasioned by the physiological activity of the two retinae, upon which the images were prevented by the paralysis from falling upon corresponding points. Again, the importance of the integrity of one set of neurones having a specific function upon all the rest of the functionally related neurones was strikingly shown in some experiments by Sherrington and myself; for we found that if the upper limb were rendered *apasthete* by section of a number of the posterior roots (third cervical to third dorsal inclusive), not only was the limb of the animal rendered insensitive, but it was unable to perform the finer voluntary movements; although stimulation of the cerebral cortex in appropriate regions produced every movement, showing that the efferent path for voluntary movement was still open, but the animal was unable to ideate the movement. Another marked effect of section of the posterior roots was the immediate loss of tonus in the muscles, showing that peripheral stimulation is the important reflex agent in its production.

Again, the experiments of Bubnoff and Heidenhain show the intimate relation which exists between the functionally related neurones. They found that a weaker stimulus was required to produce a movement of the limb by faradisation of the cortex cerebri if the limb were gently stimulated, thus showing that not only in a movement do impulses pass from the cortex to the periphery, but that each successive movement and alteration in tension of the skin, muscles, tendons, and articular ligaments cause a transmission of kinæsthetic impulses (Bastian) from the periphery to the cortical centre with an increase of its excitability; thus there is a continuous molecular vibration occurring in all these circles, and this is of importance with regard to the metabolic exchange and nutrition of the neurones themselves; for stimulus is essential to function and bio-chemical action.

In discussing later the changes which occur in motor nerve cells, when their axons are cut, we shall better appreciate the changes which take place by remembering that if a muscle is paralysed changes in tension of the related structures, namely, muscle, tendon, skin, ligaments, etc., cannot occur, and that normal succession of kinæsthetic stimuli which travel up the afferent system *pari passu* with the stimuli that travel down the efferent no longer take place. Warrington, indeed, has shown that section of posterior roots causes chromolytic changes in the anterior horn cells of the same side, indicating that this loss of stimulus produces a depression of the metabolic functions of the spinal motor cells, a fact quite in accord with the physiological results above described.

ANATOMICAL CORRELATION OF ASSOCIATED SYSTEMS OF NEURONES.

The correlation of associated functionally related systems, groups, and communities of neurones finds an anatomical proof in regressive associated atrophy of correlated structures. A good instance of this has lately been investigated in my laboratory by Mr. Tredgold, the Technical Scholar. Cases have previously been published of a similar nature, but there are some points in this case which have not previously been noticed. The man suffered with right congenital hemiplegia, affecting especially the hand and foot. The lesion was primarily in the optic thalamus on the left side; it caused atrophy of the left hemisphere, the right half of the cerebellum, and the spinal motor neurones of the cervical and lumbar enlargements, and

descending degeneration of the right crossed pyramidal tract and the left antero-lateral tract. We thus see, referring to the diagram, that all the functionally associated efferent tracts of the three nervous circles engaged in voluntary movement had undergone atrophy in consequence of the disuse occasioned by the primary lesion preventing the development of that normal association of correlated neurones necessary for perfect voluntary movement. There are certain very interesting points in this case which will be fully published in next number of *Brain*.

BIBLIOGRAPHY.

- Apáthy, *Das leitende Element des Nervensystems und seine topographischen Beziehungen zu den Zellen*: Mittheil. aus der zoologischen Station zu Neapel, Bd. xii, 1897. A. Barker, *The Nervous System*. Beard, *Anat. Anzeiger*, 1892. Bethe, *Ueber die Primitivfibrillen in den Ganglienzellen von Menschen und anderen Wirbelthieren*. *Morphol. Arbeiten*, herausgegeben von G. Schwalbe, Bd. viii, s. 95, 1898. Bubnoff and Heidenhain, *Pflüger's Archiv*, Bd. xxvi, 1884. Ramón y Cajal, *Croonian Lectures, Proceedings Royal Society*, 1894; vide Barker's *Nervous System* for later publications. Dickenson, *Journal of Anat. and Physiol.*, 1868. Dogiel, *Archiv f. Microsc. Anat.*, 1893, 1895, 1896. Edinger, *Anatomy of the Central Nervous System*, translated by Hall, p. 233. A. Forel, *Einige hirnanatomische Betrachtungen und Ergebnisse*, *Archiv f. Psychiat. und Nerven*, Berl., Bd. xviii, 1887. Flechsig, *Ist die Tabes Dorsalis eine system. Erkrankung?* *Neurol. Centralbl.*, v. iii, 1890. Gegenbauer, *Lehrbuch der vergleichenden Anatomie*, 1893. Van Gehuchten, *Anatomie du Système Nerveux*. Gerlach, Stricker's *Handbook of Histology*, The Spinal Cord. C. Golgi, *Sulla Struttura della Sostanza grigia del Cervello*, *Gaz. Med. Ital. Lombarda*, t. vi, 1873. Von Gudden, *Ueber die Kerne der Augenbewegungsnerven*, *Neurol. Centralbl.*, 1882. Alex. Gürwitsch, *Die Histogenese der schwannischen Scheide*, *Archiv f. Anat. u. Phys.*, 1900, *Anat. Abth.* 1 u. ii Heft. Goldscheider, *Die Bedeutung der Reize für Pathol. u. Therapie im Lichte der Neuronlehre*, 1898. Hardy, *Structure of Cell Protoplasm*, *Journal of Phys.*, vol. xxiv, No. 2, 1899. H. Held, *Beiträge zur Structur der Nervenzellen und Fortsätze*, *Archiv f. Anat. u. Phys.*, *Anat. Abth.*, 1897; *Ueber experimentelle Reizung des Nervenmarks*; (und Ambron), *Ueber Entwicklung und Bedeutung des Nervenmarks*, *Archiv f. Anat. u. Phys.*, *Abth.*, 1896. Alexander Hill, *The Chrome-Silver Method*, *Brain*, 1896. W. His, *The Nervous System*. Barker. Hughlings Jackson, *Post Epileptic States*, *Journal of Mental Science*, October, 1888. Kölliker, *Handbuch der Gewebelehre des Menschen*, 1896. Kühne and Chittenden, *Ueber das Neurokeratin*, *Zeitschrift f. Biol.*, Bd. viii, 1890. C. Küpfer, *Studien zur Entwicklungsgeschichte des Koppes der Krantoten*, ref. Gürwitsch. Von Lenhossek, *Neurol. Centralbl.*, 1899, No. 3. Lucretius, H. J. Munro's translation, p. 124. Lugaro, *Riv. di Patologia*, p. 500, 1898. G. Marinesco, *Pathologie Cérébrale de la Cellule Nerveuse*, *Presse Méd.*, 1897. Nasse und Steinrück, ref. Waller. F. Nissl, *Nervenzellen und graue Substanz*, *Münch. med. Wochenschrift*; Eine kritische Besprechung, etc., *Deutsche Zeitschrift f. Nervenheilk.*, Bd. xiii, 1898. Nothhaft, ref. Huber. Ranvier, *Leçons sur l'Anatomie du Système Nerveux*, 1898. Ranvier et Vignal, *Sur le Développement des Éléments du Système Cérébro-Spinal*, Paris, 1889. G. Retzius, ref. Barker. Ford Robertson, *Normal and Pathological Histology of the Nerve Cell*, *Brain*, 1899, part lxxxvi. Sherrington and Mott, *Experiments upon the Influence of Sensory Nerves upon Movement and Nutrition of the Limbs*, *Proc. Roy. Soc.*, vol. lvii, 1895. Max Schültze, *Stricker's Manual of Histology*. Tuckett, *On the Structure and Degeneration of Non-medullated Nerve Fibres*, *Journal of Phys.*, vol. xix, No. 4, 1896. L. Türck, *Akad. der Wissenschaft, Sitzungsberichte*, Wien. Bd. ii, 1855. Turner and Hunter, *Brain*, 1899. Urbantschitch, ref. Goldscheider. Virchow, *Cellular Pathology*. Waldeyer, *Deutsche med. Wochenschrift*, Bd. xvii, 1891. Warrington, *Journal of Physiol.*, 1898, vol. viii, 1 and 2. Aug. Waller, *Minute Structure of the Papillae and Nerves of the Tongue of the Frog and Toad*, *Phil. Trans.*, 1849; *Experiments on the Section of the Glossopharyngeal and Hypoglossal Nerves of the Frog*, *Phil. Trans.*, 1850; *Nouvelle Méthode Anatomique pour l'Investigation du Système Nerveux*, 1me partie, 1852; *The Nutrition and Reparation of Nerves*, Lecture Royal Institution, 1861. Westphal, ref. Goldscheider.

NOTES.

¹ Since the method is a comparative one great care must be exercised in practising the same details of method of fixation, cutting and staining the morbid tissues and the normal tissues, with which they are to be compared. Again, it is absolutely essential that the tissues examined should be fresh and free from any chance of *post-mortem* decomposition.

² This method is a very ingenious one; as it is not generally known I will describe it a little more fully: Method—Held and Ambron take nerves of newborn animals, tease them in normal saline solution, and examine them in the following manner with polarised light: They place the two prisms at right angles and put the nerve in the same line as the "quartz plate," when it gives a purple colour. The myelinated nerve will appear red, orange, or yellow, according to the stage of myelination (red being the most advanced)—these are the subtraction colours; whereas non-myelinated nerve and connective tissue give the addition colours, violet, indigo, and blue. In this way they have examined all the nerves, and have arrived at the conclusion that the peripheral motor nerves are more advanced in myelination than the sensory at early periods of development. Flechsig has shown, as I have remarked, and they confirm this, that the reverse is the case for the central nervous system. They offer no explanation, but possibly it may be found phylogenetically that in the evolution of specialised reflex acts in the zoological series the motor fibres have acquired first the myelin sheath: or it may be that the sensory bundles are made up of fibres having different functions, and that these are myelinated at different periods of time; again, we know that a large number of fibres entering a muscle (Sherrington) are afferent in function.

The German Anthropological Congress will hold its annual Congress this year at Halle from September 24th to 27th.