



BRAIN.

PART 1, VOL. 44.

THE INNERVATION OF STRIPED MUSCLE-FIBRES AND LANGLEY'S RECEPTIVE SUBSTANCE.¹

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LET me try to give you in this lecture in broad outlines the results of recent investigations on the mode of innervation of the striped muscle-fibres of vertebrates, the origin of the nerve-fibres which reach the muscle-fibres, their mode of ending on them, the manner in which the nerve-endings are connected with the muscle-fibres and the path by which the stimuli arriving by the nerves may reach the contractile substance of the muscle-fibre.

In the time at my disposal I must necessarily treat the subject somewhat dogmatically, and I fear that I shall not be able to do much more than express my own views about this subject without giving you a full historical account of the questions or stating the authorship of the large number of investigations carried out in this field and bearing on the innervation of the striped muscle-fibres of vertebrates and in general on the relation of the nerve-endings to their surroundings, on which these views are founded.

For a morphologist like myself it is only natural that morphological details will come in the first place to call our attention. But it seems to me that in general (apart from questions of phylogeny and comparative anatomy) morphological details derive their full value in the first place from the physiological and functional insight they are able to furnish us. For only when we are able to give a physiological interpretation of a given morphological detail can we say that we understand it, that it has given us some new insight into the ways of Nature.

But first let me state some general principles.

It cannot be denied that animal histology nowadays is in a period

¹ Lecture delivered at the University of London, on February 16, 1921.

of unrest, of evolution, of reform, that it is passing through a crisis, which is shaking its very foundations. The old conception of the cell as an elementary organism, established as the basis of all our researches after years of strife and an incredible amount of labour—this conception of the cell, on which generations of our teachers had built up the entire splendid structure of our knowledge of the animal body and its component parts, must be revised. And this process of revision has met with frequent and often serious opposition.

Obviously the cytologist, when studying and analysing the structure of the smallest elements that build up the living body, the cells and their derivations, is strongly tempted to regard these cells as units, as indivisible self-propagating independent elementary organisms, originated in a direct line from the dividing egg-cell and remaining independent units until their death or the death of the organism which they helped to build up.

This is not to be wondered at. It is not only that we have learned, since the time of Robert Brown, of Schleiden and Schwann, of Max Schultze, Huxley, Ranvier and Virchow, that all living bodies are composed of those small units, the cells, and their differentiation products. But afterwards there has been brought to light inside these cells themselves a distinct organization, a world in itself, a number of independent self-propagating structures, the nucleus, the amyloplasts, the tonoplast of de Vries and Went, the chlorophyll-bodies, the elaioplasts of Wakker, the centrosome, the mitochondriae and their differentiation products, and in the nucleus the chromosomes with their outfit of chromomeres, which during the last years have become of such enormous significance, especially through the work of Morgan and his school on the physical basis of hereditary phenomena.

And we are here still standing on the threshold. Every new line of research started reveals to us unknown wonders of organization of the cells. But, on the other hand, when by the use of the more and more accurate and subtle methods of present-day histology, we penetrate farther and farther into that wonderful organization of the cells, the cell itself loses a part of its independence as an elementary organism. Many of them we see in the course of development losing their boundaries, and fusing together to form a syncytium. And even when, as seems to be the case in the myocardium of mammals, this syncytium in a later period of development is again differentiated into cells, even here the lines of junction of the cells are bridged across by the muscle-fibrils, and we are by no means sure

that the cellular elements, which we are able with tolerable accuracy to make out in the full-grown myocardium, are the selfsame elements which were seen to constitute the heart muscle tissue before the coalescing period.

The cross-striated voluntary muscle-fibres with their immense number of nuclei, formerly supposed generally to be formed by the elongation of a single enlarged cell, have now been shown to be the product of more than one cellular element.

In the first place they are built up by the joining together, end to end, of a number of cells of the muscle-plate, so as to form a syncytium, within which the striated fibrils make their appearance. But, secondly, even more than one segmental muscle-plate may contribute to the formation of a single muscle-fibre, as Godlewski and Sunier have shown and Agduhr was able to prove by their mode of innervation, and thirdly, as Sunier has shown, even mesenchymatous elements may take a part in the formation of the muscle-fibres.

As to the smooth muscle-cells, what we know about their development tends in the same direction. According to the observations of McGill the smooth muscle-cells of the alimentary canal of the pig, seemingly so distinctly separate as true cellular organisms in the adult animal, are developed from a syncytium of mesenchymatous cells surrounding the entoderm tube. Here too the myofibrils developing in their protoplasm need not be confined to the limits of a single-cell territorium, but may extend over two or even a number of cells. In the adult smooth muscle-cells the intercellular substance is bridged across by filaments passing from cell to cell, so that even the fully formed smooth muscle-tissue retains something of its syncytial character.

The same holds true for the follicle-cells of the ovary, for many forms of connective tissue, and, last and not least, for the elements of the nervous system. For, according to the observations of Held, during their development they seem to pass through a syncytial period that leaves them by no means the selfsame elements that went into it. And during their later development and in the course of the process of regeneration, as we shall see more clearly later on, the growing axons make use of conducting cells and other "mesenchymatous" or "nervous" elements to reach their destination.

In short, wherever we study the elements of the tissues more closely, and especially histogenetically, we get the impression that the cell-lineage of the cellular elements of the full-grown body is in

most cases by no means clear. Everywhere new elements are being formed, not always entirely independent of each other, and out of a syncytial stage these elements appear as new cells, independent of the old ones, which originally went into it.

Viewed in this light, the relation of the cell to the organism as a whole, to the individual, is changing too. The embryological experiments of recent years, for instance, the experiments in which two egg-cells were made to fuse together to form one giant individual of normal form and proportions, the brilliant experiments of Fischel, of Spemann and Lewis on the formation of the eye-lens out of different tissues, the experiments on regeneration and so many more splendid achievements of the most subtle latter-day operative technique, have placed this relation entirely on a different footing. We are everywhere struck with the exquisite harmony of the living organisms, a harmony between the different tissue elements, which demonstrates the domination of the individual over the elements which compose it, the cells.

And it is this harmony which alone can guarantee that equilibrium of the different parts of the organism which Nature is always and everywhere trying to establish or to re-establish when it was lost.

The conception of a struggle for life of the cells in the organism, worked out by Roux years ago to form the basis of his theory of functional adaptation as an analogon to the idea of a struggle for life in Nature, which Darwin revealed to us by turning upon it the full light of his genius, cannot be true, because it does not sufficiently take into account this harmony of the organism.

In Nature, the individual itself is fighting for its life and for the maintenance of its species. In this fight every individual is destroying remorselessly everything that is weaker, and only the fittest survive in the struggle. What we call the harmony of Nature is founded on our own artistic view of the things around us. In Nature itself it is only the elementary forces and energies that exist, which together build up that mighty symphony that the lover of Nature hears everywhere around him. When we speak of the unity in Nature, either we unconsciously transfer the idea of the individual organism to the conception of the universe, or we feel behind the forces and phenomena of Nature a Divine power, before which we can only bow our heads in profound submission, without trying to explain it.

But in the organism this harmony is a distinct reality. Every organism is a unity in itself, and the elements which compose it are

in the first place a part of the whole, deriving their full value not from themselves, but from the individual to which they belong. The individual, the organism as a whole, dominates the cells which compose it. It blends them together, so to speak, subjugates them, to form that unity of the living organisms, that harmony of their organization, which is the greatest wonder and mystery of Nature, and fills us with such a profound admiration.

It is not to be wondered at, that among the different parts of the organism it is the nervous system, which, if this conception is true, must in the first place exhibit phenomena in harmony with this view. And we do not look in vain.

It is not only that the neurone theory, the nerve-cell a distinct unity, even embryologically, histologically, functionally, a separate, independent organism, a true cell of the old school, has to be revised. It was shown by Held and his school, and afterwards I was able to confirm his statements in a series of admirable preparations by Dr. Heringa, that the fibres of the neuroblasts do not run free in the interstices between the cells, but that they everywhere follow distinct protoplasmatic paths either of migrant medullary elements or of mesenchymatous cells, until they reach their destination. In the adult animal too we never find free "naked" nerve-fibres running in the interstices between the cells of the tissues, not even inside the epithelium, as I hope to show you later on. Wherever we find a suitable object (as for instance the corpuscles of Grandry or of Meissner, the organ of Eimer in the mole, the muscle-spindles of the cross-striated muscles of different mammals, &c.) that enables us to study the course of the end-ramifications of the nerve-fibres, we can state definitely that nowhere does a neurofibrillar strand run free, independent of the surrounding elements. And in regeneration the same fact stands out clearly, amidst the often bewildering pictures we get in our preparations of the exuberance of the regenerating nerve-fibres.

Nor is this all. As I hope to show you in the course of this lecture, during the process of nerve regeneration after a nerve has been cut there exists, or is established, a perfect harmony between the elements of the different tissues which build up the path that has to be followed by the regenerating nerve-fibres. It is not only the nerve-fibre that is growing out and seeking its way to re-attain its original destination, but all the surrounding elements, the sheath-cells, the connective-tissue cells, the elements of the original end-

organs (either the sensory end-organs or the muscle-fibres) are seen taking a part in the regeneration process in perfectly harmonious co-operation, none remaining passive, none predominating in its action. And so the re-establishment of the nervous function in regeneration is not due to the simple outgrowth of the axon processes of the nerve-cells as independent units, but to the combining together of the forces of all the surrounding elements, to restore the harmonious equilibrium of the organism, which was disturbed by the degeneration of the peripheral end of the severed nerve.

But now to return to the subject of our lecture, the innervation of the striped muscle-fibres.

About the general structure of the motor end-organ of the higher vertebrates I need not enter into detail here. We know that the end branches of the myelinated motor nerve-fibres having reached

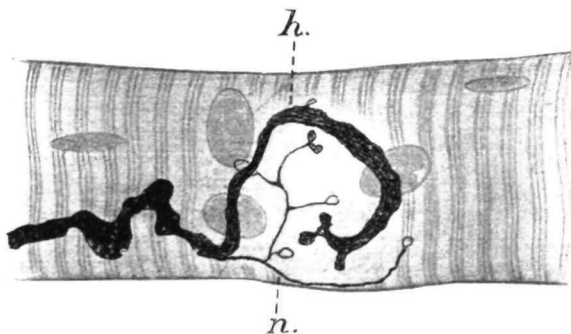


FIG. 1.—Normal motor endplate on a striped muscle-fibre of the hedgehog.

the muscle-fibres pass through the sarcolemma. The neurilemma of the nerve-fibre fuses with the sarcolemma and the axis-cylinder of the fibre is seen ending in a close terminal ramification with varicose expansions on its branches, which when appropriately fixed and stained show a fibrillar structure with reticulated or loop-like expansions. Having passed the sarcolemma, this ramification of the neuro-fibrillæ lies embedded in a layer of granular protoplasm (the sole), which is collected in a small mass at the place of the nerve-ending, and contains a number of nuclei.

Is this hypolemmal position of the nervous end-ramification only to be regarded, as Heidenhain contends, as an arrangement to attach the end-organ more strongly to the muscle-fibre ("Verankerung") and to prevent it from being torn from the muscle-fibre by a violent

contraction? I do not think so. There is no stronger mode of attachment of one element to another imaginable than that of the ends of the muscle-fibre to the tendon. And yet it is easy to demonstrate that, contrary to the well-known views of Oscar Schultze, the sarcolemma extends over the end of the fibre, the tendon-fibrils are attached to the outer surface of the sarcolemma (van Herwerden, Péterfi), and there is no actual continuity between contractile substance and tendon. Why then should such a continuity between the nerve-ending and the muscle-fibre be needed, only to prevent the nervous end-plate from being torn from the muscle-fibre by its contraction? In my opinion this hypolemmal position is only another example of the insufficiency of the old cellular conception, of the continuity of the different cellular structures with each other. And, as we will see further on, it is here of the utmost importance for the regular function of the motor end-organs.

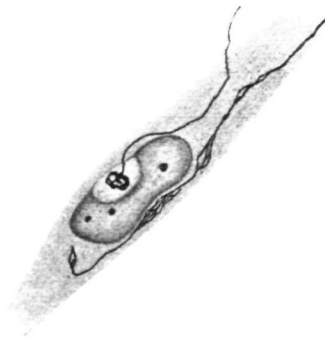


FIG. 2.—Intraprotoplasmic ending of a nerve-fibre on a smooth muscle-fibre of the musculus ciliaris of the human eye.

In this connection it may be of interest to state, that in smooth muscle-cells the same peculiarity is met with. Here too the terminal nerve-fibrils pass into the cell, ending within the protoplasm with loop-like expansions, which often are seen lying so close to the nucleus of the muscle-cell, that they even make an indentation and thus are found lying in a shallow cavity in the side or on the top of the elongated nucleus, thereby proving their intraprotoplasmic position (fig. 2).

About the form of the neurofibrillar end-ramification I will say here a few words only. We know that the muscle-fibres of the different

classes of vertebrates possess characteristic forms of nerve-endings, from the curious spade-like expansion on the muscle-plates of *amphioxus* to the complicated ramifications of the mammalian motor nerve-endings. But this is not all. In every animal the end-ramification seems to represent a distinct type, so that the motor nerve-endings of a rabbit may be distinguished from those of a hedgehog or a bat; and, for instance, the nerve-endings on the muscle-fibres of a crow are of a coarser structure and form than those of the canary. Even in so

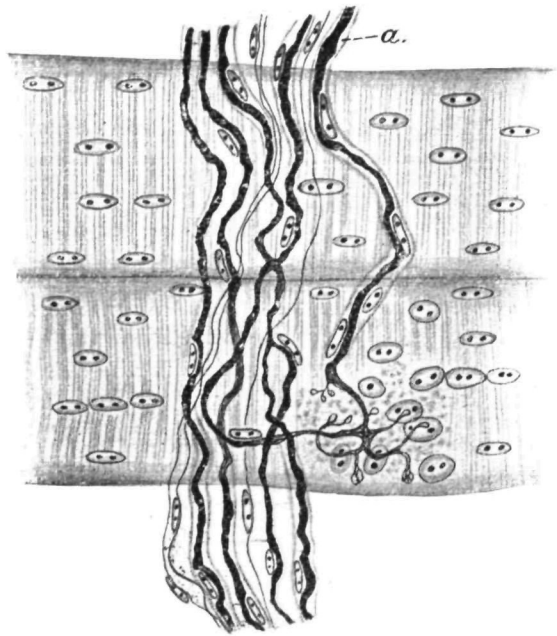


FIG. 3.—Regeneration of the motor endplates of the hedgehog, sixty-two days after the section of the nerves.

insignificant a detail as the form of the neurofibrillar network the nerve-ending appears to be in exquisite harmony with its surroundings, a part of the whole and not a thing in itself. A striking example of this harmony is again furnished by the regeneration process. When a motor nerve has been severed, after a certain lapse of time functional continuity between the cut ends may become re-established by an outgrowth of new fibres from the central stump, the newly sprouting fibres finding their way through the scar tissue between the cut ends of the nerve. After having traversed this tissue, they pass towards the periphery along the course of the degenerated fibres, the sheaths of

which serve as guides for the down-growing axons, until they reach their destination, the muscle-fibres deprived of their innervation by the cutting of the nerve. Then there are formed on those muscle-fibres end-ramifications (fig. 3); these show an exuberance of delicate nerve-fibrillæ, growing out between and on the muscle-fibres, forming end-organs of the most bizarre and complicated structure, entirely different from the normal motor-endings, of which they are the substitutes, especially in their exuberance of form and abundance of ramifications. In this way functional continuity is re-established, nerve-impulses are able to reach the muscle-fibres, contractility and voluntary movement is restored.

But the process of regeneration is not finished yet. When we keep the animal alive some months after functional activity is restored, we find the regenerated motor nerve-endings again changing their form. The complicated, aberrant end-plates, with their exuberance of branches, so totally unlike the normal end-plates, are gradually disappearing. Superfluous expansions of the neurofibrillar structures seem to be drawn in. New smaller branches are formed, and by degrees we see, in the course of a few months, everywhere reappear the normal form of the nerve-endings, characteristic for the species studied, until the equilibrium of form between the different elements constituting the muscle is restored. Only then does the regeneration process come to an end. It is this equilibrium of form, this perfect harmony between the elements, that Nature aims at, and not only the restoration of function.¹

To this end, as I have mentioned before, all the elements of the surrounding tissues are acting and striving together. It is not only the nerve-fibre that is growing out and trying to reach its original destination. The scar tissue developing between the cut ends of the nerve, especially in the beginning of the regenerative phase, is built up of delicate, elongated, branched cells, fused to form a syncytium; about these cells we are not sure whether they are entirely of nervous origin (cells of the nerve-sheaths, lemmoblasts), or derived from the connective tissue, of mesenchymatous origin. These syncytial cells are found to enclose the growing axons, direct them towards the peripheral end of the nerve, and so form a conducting tissue for the outgrowing fibres. The delicate neurofibrillar strands are, as far as can be made out, always

¹ For further details in these matters I may refer the reader to the article: "Nervenregeneration und anverwandte Innervationsprobleme," in the *Ergebnisse der Physiologie*, xix Jahrgang, 1921, where the literature bearing on the subject is to be found.

found inside these elements, running intraprotoplasmically from one cell of the syncytium to the other, until they reach the peripheral nerve-end. Here again a syncytium is formed, the cells of the neurilemmal sheath of the degenerated nerve-fibres having proliferated and fused together into long protoplasmic strands occupying the old nerve-sheaths. The regenerating outgrowing nerve-fibres are drawn towards these protoplasmic strands or conducted to them by the elements of the scar tissue ("hodogenesis" of Dustin), and enter them, here again running intraplastmically. When the regenerating nerve-fibres have traversed the peripheral nerve-end, and have reached their destination, they again are drawn towards the muscle-fibres. We must suppose that the sarcoplasmic soles of the old degenerated endings exercise a neurotropic and neurocladic influence upon the ingrowing nerve-fibres,

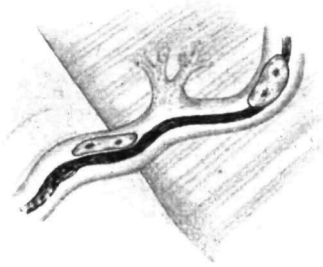


FIG. 4.—Formation of collateral outgrowths of the sheath-cells of a regenerating motor nerve-fibre on a muscle-fibre of the hedgehog.

owing to which they are drawn towards them, enter them and immediately form a number of branches. These branches, collateral and terminal, form together the new nerve-endings described above. It is obvious that the most valuable phase of the regeneration process is the formation of these new end-organs, for without them no functional continuity ever can be obtained. And it is wonderful to see how all the forces of the organism are called into play here, acting together in harmonious co-operation to restore the lost equilibrium. It is not only that the outgrowing nerve-fibres are conducted towards their destination by the protoplasmic strands of the old nerve-sheaths, and that the sarcoplasmic soles attract them and cause them to form their terminal ramifications on the muscle-fibres. First, we see the cells of the nerve-sheath of the nervous plexus between the muscle-fibres beginning to proliferate, to form collateral protuber-

ances, outgrowths, reaching the muscle-fibres (fig. 4), establishing new connections into which and through which the outgrowing nerve-fibres pass to their destination. Secondly, the connective-tissue elements appear to build up a new syncytial conducting tissue throughout the atrophied muscle to the same purpose, the formation of new ways for the outgrowing nerve-fibres. It is true that this last-named proliferation of the connective-tissue elements is by no means easy to follow with sufficient clearness in the sections through the close-packed muscle-fibres of the common muscles. But let us examine places where we find the muscle-fibres more loosely arranged, as is the case, for instance, in the muscle-spindles. Here, as it was described so well by Sherrington, we find the axial spindle-fibres completely surrounded by a large lymph space, bridged across and partially subdivided in

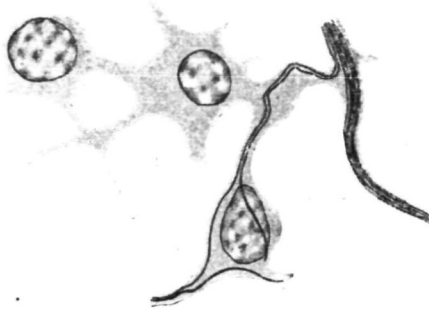


FIG. 5.—Conducting tissue of the periaxial space of a muscle-spindle of the hedgehog, with neurofibrillar strands.

many points by extremely tenuous membranes, filaments, and strands of syncytial connective-tissue elements. And here we can state definitely, not only that the end-ramifications of the normal nerve-fibres are everywhere enclosed within the protoplasm of these mesenchymatous cells (fig. 5), but that during the degeneration phase of the regeneration process these syncytial cells proliferate, branch and form numerous new connections, so that a typical conducting syncytium is formed which catches up the ingrowing fibres, encloses them and enables them to reach their destination, the axial muscle-fibres.

And now, after having studied these things in the muscle-spindles, when turning again towards the ordinary muscle-fibres, we detect everywhere traces of the same process going on here, of the same conductive tissue forming between the muscle-fibres. And I can imagine no other

process which affords us such a striking example of the harmonious co-operation of the elements of the different tissues as subordinate parts of the whole, to reach a given end, the restoration of the equilibrium of the organism, than this mode of regeneration of the motor nerve-endings.

The most prominent feature of the motor nerve-endings of vertebrates (and, as far as they have been studied, the same holds true for those of invertebrates) is the expansion of the neurofibrillar structure. As soon as the axis-cylinder passes through the sarcolemma we see the bundle of neurofibrillæ, after a momentary constriction, broaden out, disperse and expand into branched networks or looplike structures. A typical example of this expansion is exhibited in the figures. Now it is well known that ever since these neurofibrillæ were described by Apathy, who succeeded in staining them in his preparations with the most wonderful accuracy, not only their arrangement, connections and other morphological details have been under constant discussion, but morphologists and physiologists alike have been discussing the question of the function which we have to ascribe to these peculiar fibrils, which are found without exception in all parts of the ganglion-cells and their processes. Apathy himself regards them as the sole conductors of the nerve-impulses, and, in the lecture delivered at Cambridge in 1898, gave a number of arguments in support of this conclusion. In later years it was chiefly Bethe who took up the idea and carried out several interesting experiments to furnish proofs for it. A number of investigators agreed with him. Others, such as Wolff, von Lenhossek, Verworn, Jenkins and Carlson, Cajal, are convinced that the nervous impulses are also conducted by the neuroplasmic substance enveloping the neurofibrillar structure, either by the two substances together or by the neuroplasm alone. In this case the neurofibrillæ only play the part of supporting filaments of the nervous elements. It would lead us too far to review all the different statements and arguments of the numerous authors who have contributed to the question under discussion. In my opinion there is only one conclusion to be drawn from the different observations on this point, and that is, that we have to see in the neurofibrillæ the actual conductors of the nerve-impulses.

But if this assumption be true, we are confronted with a real difficulty. In general there seems to be no connection between the neurofibrillar structure of the motor-endings and the contractile substance of the muscle-fibre. Even Kühne, who advocated so strongly the hypolemmal position of the motor-endings, pointed out (in the Croonian

Lecture) that properly stained hypolemmal branches terminate usually in rounded ends sharply marked off from the muscle substance. According to Langley, even in the simplest case, that of the nerve-endings of amphibia, where the ramifications spread over a considerable length of the muscle-fibre, the substance which has been described as continuous with the endings is clearly the sarcoplasm of the muscle, which stretches throughout the muscle-fibre, and not the contractile substance itself. And indeed, as far as my experience goes, I know of only one case in which the neurofibrillar structure (or something akin to it) is found to be continuous with the myofibrillæ. That is in amphioxus, where I found the extremely delicate terminal meshes of the neurofibrillar network to be continuous with the anisotropic discs of the muscle-plates, each anisotropic disc receiving a small branch

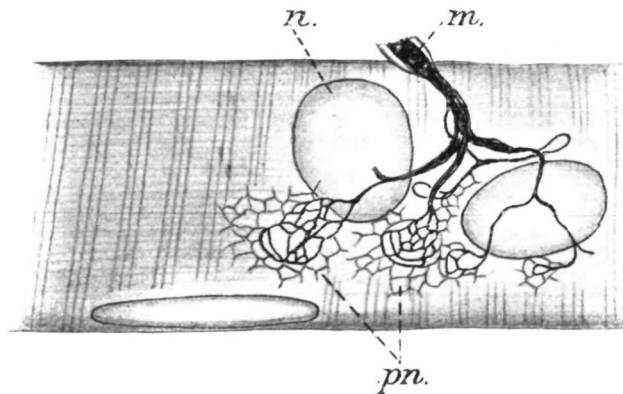


FIG. 6.—Normal motor endplate of the bat, with periterminal network;
pn. = periterminal network; *n.* = nucleus of the sole.

from the neurofibrillar structure running along it. In all the other vertebrates there lies, when studied in ordinary preparations, a stretch of undifferentiated granular sarcoplasm between the terminal ramifications of the neurofibrillæ and the contractile substance, the myofibrillæ.

But let us study these things in carefully stained and differentiated Bielschowsky preparations, in which not only the neurofibrillar network stands out very clearly, but the adjoining tissues and elements have taken the stain, too, so as to be visible in the sections. Then there appears in the sarcoplasm surrounding the neurofibrillar end-ramifications a reticular differentiation, extremely delicate, on one side attached to the neurofibrillar ramifications, on the other side losing itself in the sarcoplasm. In my first publication I proposed for it the name of

"periterminal network," and by this name I will call it in the following pages. Enclosed in the finely granular sarcoplasm we find this periterminal network as extremely delicate fibrils, forming a reticulum with small meshes and somewhat thickened knots, which is continuous with the neurofibrillar ramifications (figs. 6, 7). Especially around the end-loops and end-nets of this structure the meshes of the periterminal network are very distinct; they appear here either as small regular, polygonal meshes of about the same size, or those surrounding somewhat larger end-loops or end-reticula of the neurofibrillar structure are of somewhat larger dimensions, slightly elongated, crescent-shaped or cup-like in appearance. But even where the innermost meshes, surrounding

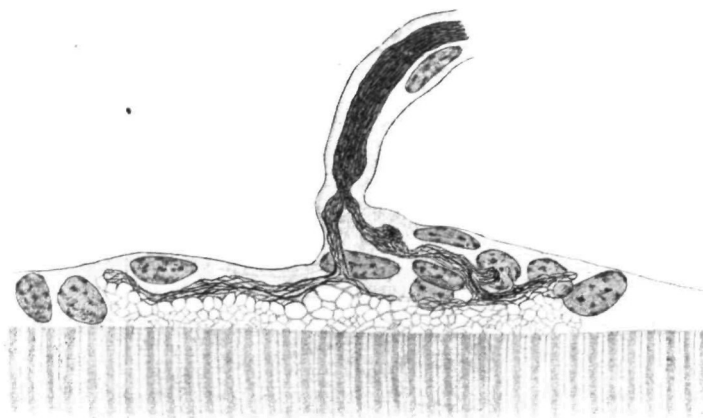


FIG. 7.—Normal motor endplate on a muscle-fibre of the *m. obliquus sup.* of the cat, with periterminal network, seen "in profile."

the end-loops of the neurofibrillar structure, appear in this way, the second layer of meshes generally shows the polygonal, regular form, mentioned above. There where the reticulate neurofibrillar end-loops are not spread out in one plane, but are three-dimensional, more or less pear-shaped, the meshes of the periterminal network are seen surrounding them on all sides.

But it is not only with the end-loops and end-reticula of the neurofibrillar structure that the periterminal network is found to be in connection; it may be seen as clearly surrounding the more or less varicose branches of the motor-ending, and here too it is always found in close connection with the neurofibrillar structure (fig. 7). Often, when examined under the highest power, the neurofibrillar strands give the impression

of being covered with extremely tenuous spines. With these tiny spines the fibrils of the periterminal network are seen to be in connection. The meshes of the periterminal network appear to be continuous throughout the sarcoplasm of the sole, and although it is wont to take a stronger stain in the immediate neighbourhood of the axial neurofibrillar ramification, in several cases I could follow the fibrils of the periterminal network throughout the sarcoplasmic sole to the myofibrillæ; here they seem to pass into the anisotropic discs of the myofibrillæ, and to form an extremely delicate network throughout the whole thickness of the discs (fig. 7).

As to the morphological value of the periterminal network I need not enter into details here. The time at my disposal prevents me from going too far into historical details. Suffice it to say that traces of this network seem to have been seen by Retzius, Koelliker and Rollett, that it makes the impression of being an element *sui generis* and that in my opinion it is not identical with the reticular differentiations inside the muscle-fibre described by Veratti, Cajal-Fusari and Holmgren.

The periterminal network is an element *sui generis*. But is it to be regarded as of a neural nature, a continuation of the neurofibrillar structure, or is it a differentiation of the sarcoplasm itself? This is a difficult question to answer. It is always found in close connection with the neurofibrillar structure. During the development of the motor end-plates it is always found to appear as a continuation of the neurofibrillar structure. Even in properly stained sections it always takes the darkest stain where it is attached to this structure, and it is often only visible in this part of the sarcoplasm and gradually disappears from view farther on. And yet its features are so different from the neurofibrillar structure, and it gives so clearly the impression of a protoplasmic reticulum, that I do not hesitate to assert that in my opinion it is of protoplasmic (sarcoplasmic) origin, but that it develops only in connection with and under the influence of the neurofibrillar structure of the motor nerve-ending. This is important for the accurate conception of its physiological and functional significance.

An interesting point is its behaviour during degeneration and regeneration of the motor nerves. The most characteristic feature of the degeneration of the motor nerve-endings, after cutting of the nerve, is the gradual disappearance of the neurofibrillar network. Within a few hours after the operation the fibrils begin to swell, to fuse together, and the mass thus formed, in the course of one or two

days breaks up into portions and disappears. During the first stages of the process of degeneration the periterminal network may still be distinguished, but it disappears from view together with the neurofibrils, and only the granular sarcoplasm of the sole remains visible. When, after a lapse of time, the regenerated motor nerves again reach the muscle-fibres, their ends ("cônes de croissance") pierce the sarcolemma, come again in contact with the sarcoplasm and develop into new nerve-endings. As soon as the muscle-fibre is reached and the first neurofibrillar loops have entered it, the periterminal network makes its reappearance (as is shown in fig. 8) as a reticular

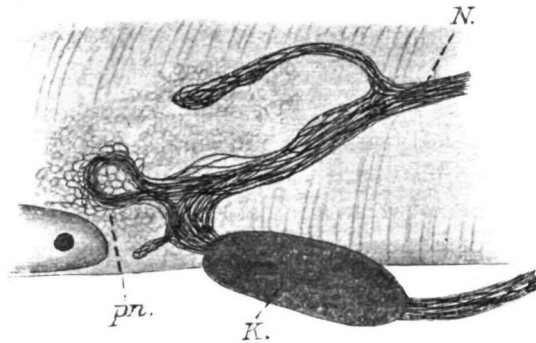


FIG. 8.—Regeneration of a motor endplate of the hedgehog, with formation of the periterminal network (*pn.*); *K.* = nucleus.

differentiation of the sarcoplasm surrounding the neurofibrils, at first only in the immediate neighbourhood of the neurofibrillar strands, but gradually spreading and growing out. So its disappearance and its reappearance are absolutely connected with and dependent on the presence or absence of the neurofibrillar structure.

All this seems to indicate that the periterminal network (whether as a sarcoplasmic reticulum or a continuation of the nervous structure) is intimately connected with the functions of the neurofibrillar structure of the motor-endings. And thus, when we have every reason, as I have mentioned already, to regard the neurofibrillæ as the actual conductors of the nerve-impulses, the assumption seems to be justified that the neurofibrillar structure, not being continuous with the contracting substance of the muscle-fibre, the impulse is carried on by the periterminal network and in this way transmitted to the contracting substance of the muscle-fibre, the myofibrillæ.

This may be brought into connection with some well-known physiological facts. In his brilliant Croonian Lecture for 1906, Langley has shown that there is every reason to suppose that in the case of a connection of the peripheral end of an efferent nerve with a cell there must be present in the cell one or more substances (which Langley calls "receptive substances") capable of receiving and transmitting stimuli and capable of isolated paralysis. According to Langley it is this substance which is stimulated or paralysed by poisons ordinarily taken as stimulating or paralysing nerve-endings (curari, nicotine, strychnine, and others). Probably not only the function of reacting to numerous chemical bodies, but also the special liability of both afferent and efferent nerves to fatigue, must be transferred from the nerve-endings to the same constituent of the cell. The nerve-ending itself is, according to Langley, physiologically not essentially different from the nerve-fibre. Therefore the special action of the poisons mentioned above must be due to the presence of one or more receptive substances in the cell. These substances are, Langley considers, radicles of the protoplasmic molecule, which reminds us of the haptophoric groups of the "Seitenketten" theory of Ehrlich; and indeed, I think that the general opinion amongst physiologists is, that a morphological substratum of the receptive substances (or the "neuroplasmatische Zwischensubstanz" of Asher) is not to be looked for in histological preparations. And not only physiologists. Even in morphological work, as for example the study of Sutton on the development of the neuro-muscular spindle in the extrinsic eye-muscles of the pig (1915), the conclusion is drawn, that until now there does not exist a morphological basis for the receptive substance.

And yet the later work of Langley and the work of Keith Lucas on the different behaviour of the neural region of the muscle-fibre, and the aneural region as regards the action of poisons, lend support to the view that such a substance exists in proximity to the nerve-endings in muscle. And it was shown by Noel Paton and Findlay in 1916 that after the efferent nerves have been cut and the nerve-endings have degenerated, the receptive substance in the muscle-fibre seems to degenerate secondarily to the neural endings. It seems to remain unaltered for some time after the nerve has ceased to act, and in some cases have its excitability modified during the process of degeneration of the nerve; after some time, however, it degenerates also.

Now all this seems to me to point to the conclusion that we may look for a well-defined, sharply localized morphological basis for the

receptive substance, that it has to be looked for inside the sarcoplasm, between the nerve-ending and the contractile substance, and that all the conditions for it are satisfactorily fulfilled by the "periterminal network" described above. It lies embedded in the sarcoplasm and indeed seems to be a part of it, it is in close connection with the neurofibrillar structure of the nerve-ending and is especially visible in the immediate neighbourhood of it, but extends to the contractile substance. It has a morphological aspect different from that of the neuro-fibrillar structure of the nerve-ending, and seems to be of a finer texture in highly developed active muscle-fibres (as the extrinsic eye-muscles of the cat for instance) than in the muscle-fibres of slower action (as the muscles of the tongue of the hedgehog). And last not least, it degenerates secondarily to the degeneration of the motor-endings, and again makes its appearance as soon as the regenerating nerve-fibres have reached the muscle-fibres and are forming new end-ramifications in the sarcoplasma.

But, as a physiological conception, the receptive substances of Langley are not confined to the striated muscle-fibres. And indeed, one is tempted to ask whether in every case of a synapse, at least of a connection of a nervous end-ramification with a peripheral element, either of an efferent or an afferent nature, a receptive substance, capable of receiving or transmitting stimuli, has not to be localized as an intervening medium between the undifferentiated protoplasm and the neurofibrillar structure of the nerve-ending.

There are several histological phenomena that seem to point in this direction. In the first place I have to mention the connections of the sympathetic nerves with the striated muscle-fibres. Some years ago it was shown that besides the endings of the spinal motor nerves on the muscle-fibres each fibre receives a branch of bundles of fine non-medullated nerve-fibres running between the muscle-fibres. These fibres clearly belong to the automatic nerve-system. For it could be shown that when the eye-muscle nerves (for instance the trochlearis nerve) are sectioned as near as possible to their origin from the mid-brain, before they receive a branch from the autonomic nerve-plexus, the motor nerves and their endings and the sensory nerves degenerate and disappear, but the non-medullated sympathetic nerve-fibres and their endings on the muscle-fibres remain unaltered. Later on it was shown by Dusser de Barennes and Boeke for the trunk muscles, and by Agduhr for the muscles of the extremities, that, when the spinal roots are cut and the spinal ganglia removed without injuring the sympathetic roots (*ramus communicans albus et griseus*), the common motor-

endings and the sensory endings disappear, but the fine non-medullated nerve-fibres with their small nerve-endings on the muscle-fibres remain unaltered. The sympathetic fibres for the muscles of the tongue seem to run, not in the hypoglossal, but in the chorda tympani (Boeke). Their endings on the muscle-fibres present the same aspect as the sympathetic endings in the muscles mentioned above. So the sympathetic innervation of the striated muscle-fibres seems to be put on a solid morphological basis.

Now these sympathetic nerve-endings have the same hypolemmal position as the common motor-endings, and indeed are often found embedded in the same mass of granular sarcoplasma. Moreover it is certainly of interest that surrounding the end-loops and end-nets of these sympathetic nerve-endings there may be distinguished exactly the same regular protoplasmic network as was described for the motor-endings. And indeed, where these sympathetic endings were found embedded in the sarcoplasm of the motor-ending itself, the same periterminal network was seen surrounding them both.

For smooth muscle-cells too, as I mentioned above, it was not only possible to show that the end-loops of the nerve-fibres enter the cell and lie embedded in the protoplasm, but here too they seemed to be in connection with a distinct reticulum.

As to the sensory nerve-endings, there are at least two different kinds of tactile end-organs which exhibit the same features. In the first place the corpuscles of Grandry in the skin covering the duck's bill (figs. 9, 10). As is known, these corpuscles consist of two (or three) large, flat, disc-like cells within a capsule, with the axis-cylinder terminating in a flattened expansion between the cells. In the numerous papers dealing with the histology of the corpuscles of Grandry the tactile disc is always regarded as being entirely independent of the two cells between which it is lying. But Gasirowsky saw these cells degenerate after section of the nerve, and in a set of admirable Bielschowsky preparations of the skin of the duck's bill made by Dr. Heringa in my laboratory, not only the tactile disc could be seen in a syncytial connection with both cells, but inside the protoplasm of these cells there was visible a distinctly stained, sharply defined network in absolute continuous connection with the neurofibrillar structure of the tactile disc. It is seen extending throughout the whole thickness of the two adjoining cells, in short, it exhibits all the features so characteristic of the periterminal network surrounding the motor nerve-endings.

In the second place I have to mention the tactile discs in the epi-

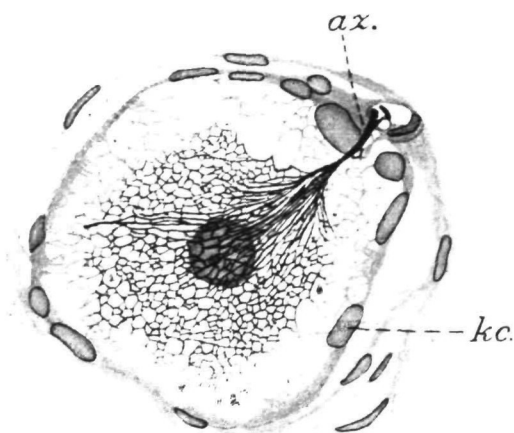


FIG. 9.—Tangential section of a corpuscle of Grandry of the skin of the duck's bill, with intraprotoplasmic network.

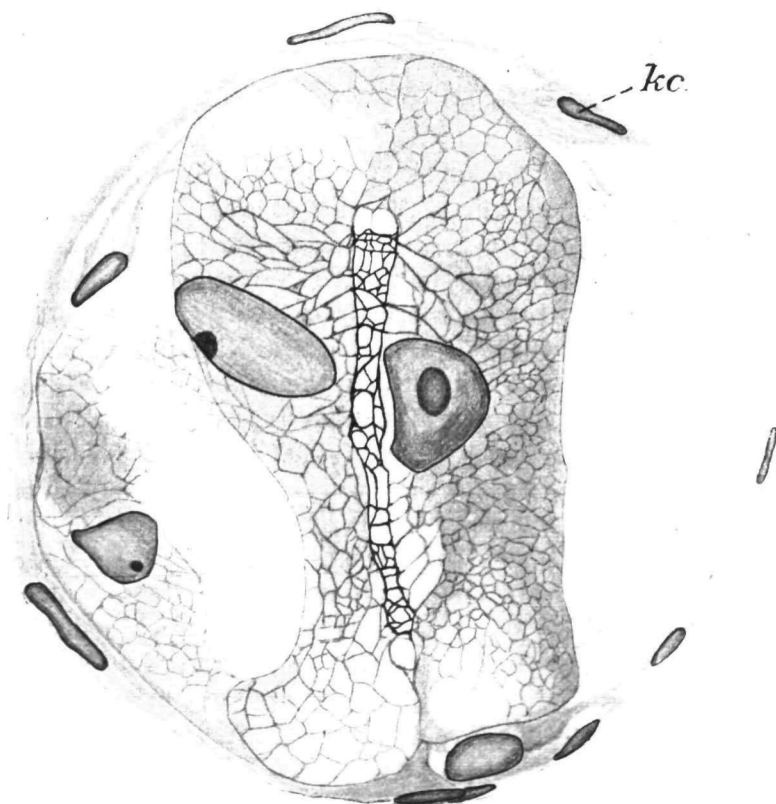


FIG. 10.—Cross-section of a corpuscle of Grandry of the skin of the duck's bill, with intraprotoplasmic network; *kc.* = capsule-cells.

dermis. It is generally assumed that these curious flattened or crescentic nervous expansions lie in the interstices of the deeper epithelium cells, for example, of the pig's snout, or in the organ of

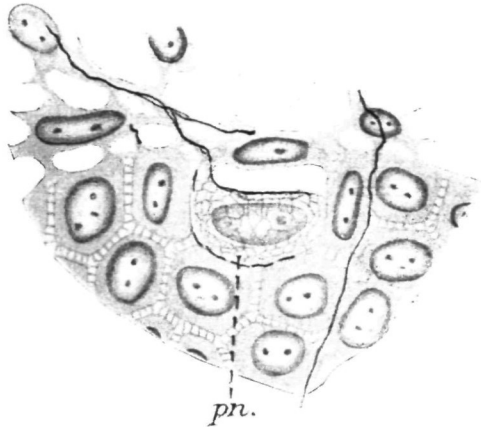


FIG. 11.—Cross-section of the epithelium of the organ of Eimer of a mole, with nerve-fibres entering the skin and a tactile cell with nerve-fibre and intraprotoplasmic network (*pn.*).

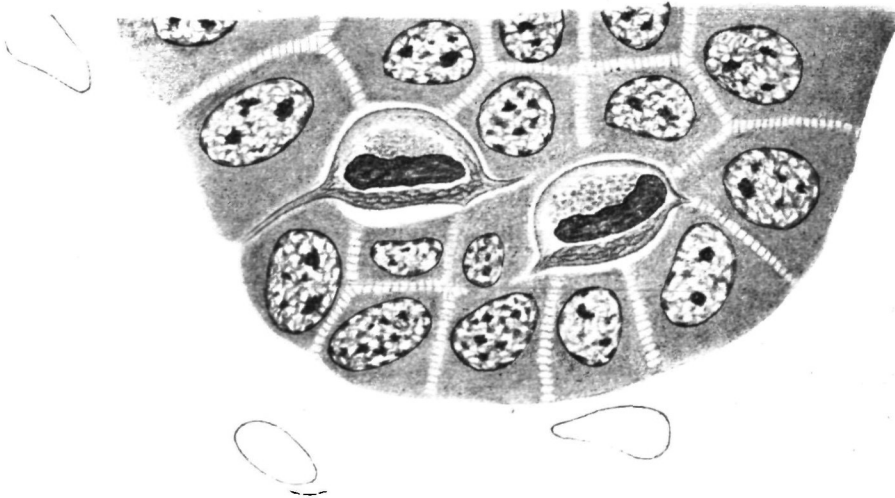


FIG. 12.—Transverse section through the epithelium of the skin of the pig's snout with two tactile cells of Merkel, showing the intraprotoplasmic position of the neurofibrillar network.

Eimer in the snout of the mole, and they may be shown to consist of a fine network of neurofibrillæ. From the earlier investigations of Merkel and Ranvier to recent times almost all writers on the subject agree on

this point, that they are lying between the cells of the epidermis. And yet, when we study them in very thin sections treated, fixed and stained with the utmost care, we come to the conclusion that they are not lying between the cells with a somewhat differentiated cell of the epithelium covering them, but that the neurofibrillar expansion, the tactile disc, lies inside the protoplasm of a differentiated cell of the epidermis. And, moreover, we see that the neurofibrillar reticulum is continued into a distinct protoplasmic network with fine regular meshes, extending throughout the cell (fig. 11) and exhibiting just the same features, characteristic of the periterminal network, as in the case of the corpuscles of Grandry.

These points, which can only be seen in the most carefully made preparations and with the use of the highest magnifying power, are not at all easy to study, and although I was able to make several observations on other sensory endings, as, for instance, the corpuscles of Herbst and the cells of the taste-buds, which seem to tend in the same direction, I do not think it advisable to give here the further details of these investigations.

But it seems to me that the observations recorded give us reason for supposing that not only in the case of the motor-endings but also in the different forms of the sensory nerve-endings there exists in the first place a close connection between the nerve-endings and the surrounding "lemmoblastic" elements that gives us a right to speak of a syncytial arrangement. And, secondly, we may assume that everywhere between the neurofibrillæ of these nerve-endings and the protoplasm is inserted a distinct reticulum, which seems to be the histological substratum for the receptive substance of the physiologists.

This may furnish a solid base for further study in this direction, and for the present-day histologist it is another proof of the inadequacy of the old cell theory, which regards the cells as independent self-sustaining units, and of the wonderful harmony in which all those units combine and act together to build up and sustain the higher organism, the individual.
