On the Inadequacy of the Cellular Theory of Development, and on the Early Development of Nerves, particularly of the Third Nerve and of the Sympathetic in Elasmobranchii.

By

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It is now more than ten years ago since I first pointed out the inadequacy of the cellular theory of development. That I did so in a very guarded manner need hardly be said; but now, after ten years of mature work, I feel justified in giving a stronger expression to the views which I then formed, and which all my subsequent work has amply confirmed. My words then (in 1883) were as follows:—"In short, if these facts are generally applicable, embryonic development can no longer be looked upon as being essentially the formation by fission of a number of units from a single primitive unit, and the co-ordination and modification of these units into a harmonious whole. But it must rather be regarded as a multiplication of nuclei and a specialisation of tracts and vacuoles in a continuous mass of vacuolated protoplasm." Again, in 1888, in the preface to my "Monograph on the Development of the Cape Species of Peripatus,"[1] I wrote: "It would appear, indeed, that in Peripatus the cells of the adult, in so far as they are distinct and sharply marked off structures, are not, as appears to be generally the case, present in the earliest embryonic stages, but are gradually evolved as development proceeds. In other words, the cell-theory, if it

[1] 'Studies from the Morphological Laboratory of the University of Cambridge,' vol. iv, part 1.

implies that the adult cells are derived from embryonic cells which have been directly produced by the division of the ovicell, does not apply to the embryos of Peripatus."

In the days when these words were written it was a general belief among leading histologists and physiologists that the connections which were known to exist in some cases between adult cells had arisen secondarily, and that the primary condition brought about by the cleavage of the ovum was a complete separation from one another of these units, of which the body was supposed to be composed. There has been, no doubt, a change of opinion since those days, and although many biologists would still maintain that cleavage is complete and results in the formation of separate units which later become connected, there is a constantly increasing number who would consider themselves misrepresented if one imputed to them this belief not long ago universal, and the belief which was supposed to follow from it, that the first stage in the evolution of the Metazoa was a colonial Protozoon. But, as I have said, opinions have changed since those days, and I quote my words, written then, to show that I have long held the view which I am now expressing, and that I was among the first to attack a theory which had even then passed its stage of usefulness, and is now holding men's minds in an iron bondage. For although opinions have changed on this important subject, and although there are some who think that they have escaped from the domination of this fetish of their predecessors, yet as a matter of fact the cellular theory of development is still rampant, still blinds men's eyes to the most patent facts, and still obstructs the way of real progress in the knowledge of structure.

In order that I may not be met with the statement that such a state of things exists only in my own imagination, that I am putting up a dummy merely to knock it down again, it is necessary that I should give some proof that this hypothesis has still the power which I ascribe to it. What is the cellular theory of development? I am not concerned with what its authors held; what we want to know is, what is the present form and extent of it? What is the point of view which it compels its votaries to take?

It is not easy to answer this question; it is, in fact, as difficult to answer as that other question so often asked of the teacher by his pupil—what is a cell? The source of the difficulty is that we are dealing with a kind of phantom which takes different forms in different men's eyes. There is a want of precision about the cell-phantom, as there is also about the layer-phantom, which makes it very difficult to lay either of them. Neither of these theories can be stated in so many words in a manner satisfactory to every one. The result is that it is not easy to bring either of them to book.

To answer the question—what is the cellular theory of development?—the best plan will be to consider for a moment the ideas which are taught to the student of biology, and which influence him in his future work. We tell him that the cell is the unit of structure, that an organism may consist of a single cell, or of several cells in association with one another: we draw the most fundamental distinction between the two kinds of organism, and we divide the animal kingdom into two great groups to receive them. As a proof of the importance which we attach to this feature of organisation we assert that a man is nearer, morphologically, to a tapeworm, than a tapeworm is to a paramœcium. We tell him that the various structures present in a protozoon are all parts of one cell, whereas in a metazoon the various parts are composed of groups of cells which differ from one another in structure. Finally, when we ask him in the examination to tell us the principal differences between hydra and vorticella, we consider that he is very inadequately prepared if he does not sum them up by saying that hydra has tissues composed of definite cells and is multicellular, while vorticella is without definite cellular tissues and is unicellular. Carrying on the idea thus implanted in his mind as to the fundamental importance of the cell, we tell him about the neuro-epithelial cell and the myo-epithelial cell, and we point out their primitive distinctness,—an idea which is still further impressed upon him when he studies the connection between nerve and striated muscular fibre. Finally, when he comes to study embryology, the importance and distinctness of the cell meets him at every step, from the complete cleavage which he is led to believe is primitive, to the development of nerves according to the views of His.

So much for the student in the schools: now for the investigator in the laboratory. He studies the ovum and maintains its absolute isolation in the organism; or he examines epithelial cells and draws them as isolated structures separated by sharp boundary lines; or he labours to prove the continuity between the nerve and muscle, or between the nerve and secreting cell: so much is he dominated by the idea of separate cells that he considers that the burden of proof rests rather with the man who asserts such continuity than with him who denies it. Or, if he be an embryologist, he will talk of, and figure, the proliferation of cells at the primitive streak; he will describe the nascent ganglion cell sending a process from the developing spinal cord into the anterior root, and he will figure it; he will talk of mesenchyme cells, and figure them for the most part separate from one another.

I take it that this is a not unfair account of the training a zoologist receives at the present day, so far as the cell is concerned, and of the ideas which dominate him in his later work. He believes that the cell is the unit of structure, and that it forms the basis of organisation in the Metazoa; it is the functions of the cell and the relations which it enters into with other cells which forms an important subject of current biological investigation. Who, then, can deny that the cellular theory of development is still a living power in the school of biology? That it blinds men's eyes to the most patent facts, and obstructs the way of real progress in the knowledge of structure, it will now be my endeavour to show. For this purpose I shall deal on this occasion with the origin and structure of two tissues of the Vertebrate embryo—the so-called mesenchyme and the system of peripheral nerve-trunks. My results are the product of many years' work, and will, I hope, be published in greater detail and with figures on a future occasion.

The So-called Mesenchyme Tissue of Elasmobranch Embryos.

This tissue is always described as consisting of branched cells lying between the ectoderm and the endoderm. The cells are spoken of as being separate from one another, and from the adjacent ectoderm and endoderm, excepting at points where they are supposed to arise from one of the primary layers. And not only are they described as being separate cells, but they are actually drawn in the author's figures as separate from each other. This is, perhaps, the best instance that can be given of the bondage in which the cellular theory holds its votaries. For what are the facts? The separate cells have no existence at all! In their place we find, on looking into the matter, a reticulum of a pale non-staining substance holding nuclei at its nodes. It is these nodes, with their nuclei, which are drawn by authors as the separate branched cells of the mesenchyme, and they are constrained by this theory, with which their minds are saturated, not only to see things which do not exist, but actually to figure them. Another erroneous view due to the same cause is the view that this mesenchyme tissue is not continuous with the ectoderm or with the endoderm; whereas, as a matter of fact, the opposite is the case, for the primary layers are simply parts of this reticulum in which the meshes are closer and the nuclei more numerous and arranged in layers. These are facts of which anyone with an unbiassed mind can convince himself by the simple inspection of a Selachian or an Avian embryo, and they would have been recognised long ago had it not been for the dominating influence of the cellular theory of development.

The current views as to the origin of this tissue show just as conspicuously the influence of the same theory. It is said to arise by the budding-off and migration of cells from the walls of the embryonic cœlom, from the primitive streak, and from the neural crest; and the space between the ectoderm and endoderm into which these cells migrate is described as being empty of structural elements. What are the facts? The space between the layers is never empty; it is always traversed by strands of a pale tissue connecting the various layers, and the growth which does take place at the places mentioned is not a formation of cells, but of nuclei which move away from their place of origin and take up their position in this pale and at first sparse reticulum which exists between the layer. As this reticulum, which has always existed, becomes infested with nuclei it increases in bulk, and forms the conspicuous reticulate tissue which is by some authors called mesenchyme. The primitive streak, the walls of the cœlom, and the neural crest, and, as Goronowitsch[1] has shown, parts of the ectoderm, are growing points where nuclei, not cells, are produced. These facts I described long ago in the development of Peripatus, and it is the recognition of the same processes taking place in the Vertebrata in an even more conspicuous manner that has induced me to again call attention to their importance.[2]

The Origin of Nerve-trunks and the Fate of the Neural Crest.

If there is one point more than another on which the cellular theory of development has led anatomists completely astray, it is upon this one. We may take it that the new views upon the origin of the peripheral nerves began with Balfour's discovery of the structure which is generally called the nerve crest. Before that discovery nerves were supposed to develop in situ in the mesoderm; after it, there were two principal views as to the origin and growth of nerves: one of these was that cells of the central organ grew outwards as strings to the periphery; while, according to the other, nerve-fibres are the elongated

[1] 'Morpholog. Jahrb.,' Bd. xx, 1893.

[2] At the same time Peripatus shows certain features more clearly than the Vertebrate; I would refer especially to figs. 24 *d* and 26 *d* on pl. v of my Monograph, in which, while the so-called ectoderm and endoderm are obviously parts of the same layer, or tissue : they are separated by a region in which the vacuoles are larger, the protoplasmic strands less numerous, and nuclei are conspicuous by their scarcity.

processes of cells either of the central organ or of the ganglia. Both these views are erroneous; and if both were not inspired by the cellular theory of development, they were both promulgated at a time when that theory was at its zenith. The earlier view, that nerves were developed *in situ* from the mesoderm, was much nearer the truth.

The nerve crest does not, as was first stated by Balfour and afterwards by all authors on the development of nerves, give rise exclusively, or even principally, to nerves and ganglia. It gives rise to nuclei which spread out in, and add to the mesoblastic reticulum, which at all times, i.e. from the very beginning, exists between the layers, and to nuclei which become the nuclei of the rudiments of nerve ganglia. The nerves are developments of the reticulum; they are elongated strands of the pale substance composing the reticulum, with some of its nuclei; and their free ends branch out into the fibres of the reticulum, and are added to by the latter falling into the line of the growing nerve. Neither they nor the ganglia appear until the nerve crest is breaking up. The reticulum further gives rise certainly to smooth muscular fibres, connective tissues, and blood-vessels, and probably also to striated muscle. It is also continuous with all the so-called epithelial tissues of the embryo; *indeed this latter substance is to be regarded as consisting only of one or more layers of nuclei embedded in the outer part of the reticulum, which is rather denser than elsewhere in correspondence with the greater density of the nuclei.* Nerves are a gathering up, so to speak, of the strands of the reticulum into bundles, and are formed in that way; or, to put the matter in another way, nerves are a special development of the reticulum along certain lines. These special developments are generally marked by an increase in the number of nuclei, such increase being particularly great in the neighbourhood of the ganglia.

To sum up the matter, the nervous and muscular tissues are, as they were in *Peripatus* (see my Monograph, p. 131), special developments of the same primitive reticulum, a community of origin which renders their adult relations perfectly intelligible. Further, I have no hesitation in saying that His' descriptions of the development of nerve-fibres as processes of central or ganglionic nerve-cells, does not apply to Selachians; inasmuch as nerves are laid down long before any trace of nerve-cells can be made out. The neuroblasts of His and of other authors are nuclei lying in a substance which, after death caused by the ordinary reagents, has usually a fibrous structure. This substance is continuous with, and therefore a part of, the reticulum outside. The cell-processes which have been described as growing out from the neuroblasts are merely parts of this reticular substance, the fibres of which become arranged more or less in the direction of the long axis of the nuclei, and the meshes correspondingly drawn out and narrowed. Many of His' drawings even show that this is so, and an inspection of the specimens leaves no doubt at all about the matter. In short, the development of nerves is not an outgrowth of cell-processes from certain central cells, but is a differentiation of a substance which was already in position; and this differentiation seems to take place from the medullary walls outwards to the periphery, both in the anterior and posterior roots, and to precede, or to proceed pari passu with, the development of other tissues. The nerve crest is, then, to be regarded as a centre for the growth of nuclei, which spread into the body of the embryo and become concerned in the formation of many tissues, nervous tissues amongst the rest. There are many other such centres for the production of nuclei; for instance, I may mention the walls of the cœlom, the caudal swellings, and in the Amniota the primitive streak. All these centres of growth are in so-called epithelial tissues. This is, of course, necessitated by the fact that Selachian embryos are at one stage composed entirely—or almost entirely—of these so-called epithelial tissues; as are many embryos, e.g. those of Peripatus and of Amphioxus.[1] These facts will be dis-

[1] The significance of this epithelial structure of the young embryo—this

puted by many morphologists, but they are easy of proof by the simple inspection of good preparations to minds not warped by the cellular theory as ordinarily taught. In fact, had it not been for the undue persistence of this hypothesis beyond the time of its fruitful life, they would have been recognised long ago, and much needless waste of labour in trying to make the facts of nerve-development conform to the theory would have been saved.

The nerve-crest in Selachians (Scyllium, Acanthias, Raia, and Pristiurus) is, as I pointed out some time ago ("Notes on Elasmobranch Development," 'Quart. Journ. of Micr. Sci.,' vol. xxxiii), from its first appearance, in three pieces.[1] The first of these pieces reaches from the region of the fore-brain to the hind brain. The posterior limit of it is marked in older embryos by the root of the trigeminal nerve. It gives rise to the reticulum of the front part of the head, and contributes to that of the mandibular arch. The following nerves are formed within its limits:—The trigeminal and its branches, which include the so-called ramus ophthalmicus profundus with the ciliary ganglion and the third nerve (see below). Very possibly other nerves, viz. the fourth, the sixth, and the olfactory, may be also developed from this part of the reticulum, but I have no observations on this point.

The manner in which these nerves are laid down may be described as follows:—When the nerve-crest, which in this region of the head very early spreads ventralwards on each side of the brain, is breaking up into the reticulum, certain tracts of it remain unaltered and characterised by a greater density of nuclei. These tracts mark the course of the future nerves and the sites of the future ganglia. They them-

collection of the nuclei at the surfaces, as it may be described—I hope to consider in another place. Now, I may merely hint that it is probably due to the impress of some well-marked larval phase in earlier stages of evolution (see my article on "von Baer's Law, &c.," in 'Quart. Journ. Micr. Sci.,' vol. xxxvi).

[1] Goronowitsch ('Morph. Jahrb.,' Bd. xx) has recently found the same fact for the bird, but he makes no reference to my results on this point.

selves continue to break up, but a kind of core remains which constitutes the foundation of the future nerve and ganglion. The Gasserian ganglion, the ophthalmicus profundus, the mandibular branch of the fifth, and the ciliary ganglion thus gradually emerge from the remains of the nerve-crest—are, so to speak, crystallised out of it. At first they have the form of dense cords of nuclei; but they soon acquire some of the non-staining fibrous substance, which makes its appearance as a rule in their central portions, so that for a time sections of these nerves exactly resemble in appearance sections of the nerves of Invertebrata, e. g. Peripatus, Chiton, &c. This description holds for an embryo of 35 mm., beyond which stage I have no observations. The nuclei which have peeled off, leaving the nerve-trunk below, give rise to the muscular and connective tissues of the parts concerned, the reticulum of which is freely continuous with that of the nascent nerve, especially at the free end of the latter. It thus becomes apparent that these tissues—nervous, muscular, connective, and vascular—are all developed in continuity.[1]

While the Gasserian ganglion, the mandibular branch of the fifth, the ophthalmicus profundus, and the ciliary ganglion all crystallise out of the nerve crest; the third nerve does not do so. It arises as a differentiation of the reticulum formed by the breaking up of the nerve crest, and it first makes its appearance as a forward projection of nuclei from the ciliary ganglion. This, by a gradual differentiation of the reticulum, extends itself until it reaches the base of the mid-brain, with which it becomes continuous by means of an increase in the pale fibrous strands which pass between the medullary wall and the reticulum. The third nerve is at first a cord of nuclei and rather dense pale substance. The third nerve,[2] there-

[1] The continuity of the embryonic tissue which will give rise to the nervous and muscular tissues is well seen in the embryo of Peripatus capensis, and I have already hinted at this fact in my Monograph on the development of that species at pp. 131 and 133, and figured the tissue as nerve musc., pl. x, fig. 5.

[2] It will be evident, if my observations are correct, that I have found an earlier stage of the third nerve than Dohrn describes in his sixteenth study. In

fore, presents this interesting and remarkable peculiarity in Scyllium and Acanthias; it grows or is differentiated from the ciliary ganglion to the floor of the mid-brain, and not in the opposite direction, as has hitherto been supposed. The proof of this is to be found in the fact that in a Scyllium and Acanthias embryo of 10 to 11 mm. the third nerve can be seen projecting forwards from the ciliary ganglion, and ending in front in the reticulum, short of the floor of the mid-brain. The ciliary or profundus ganglion is at one time—when it is first laid down—in contact with the ectoderm. Later it is shifted inwards, but remains connected for a time with the ectoderm by a cord of cells, which eventually disappears. This point has been seen by van Wijhe.

The embryonic medullary wall[1] is connected with the reticulum by pale fibres similar to those which compose the reticulum, and the nerve-roots, both anterior, posterior, and cranial, are special enlargements of such connecting strands. They are formed at a time when no structures which could be called cells by any but a fanatical devotee of the cellular theory are present, either in the medullary wall or in the ganglionic rudiments, and in a manner which, if closely followed, renders it quite impossible to speak of growths one way or the other, excepting that one can make one assertion—the pale fibrous substance which marks the nerve appears both in the anterior and posterior roots and in the cranial nerve-roots next the central organ, at a time when the white matter (which is composed of this pale fibrous substance) first appears as a thin layer, and in continuity with such white matter. The differentiation outwards proceeds from this point, and the free end of the nerve-rudiment always ends by branching out into the fibres

my fuller paper dealing with this subject I hope to examine Dohrn's results in detail.

[1] Inasmuch as the nerve-crest is derived from the medullary wall and gives rise to mesodermal structures, the medullary wall itself gives rise, in part, to mesoderm.

of the reticulum. The only exception to this rule is the third nerve of Scyllium and Acanthias (and probably others), which is undoubtedly differentiated from the ciliary ganglion to the floor of the mid-brain; but this is, perhaps, more an apparent exception than a real one, because the ciliary ganglion belongs to the fifth nerve and the order of fibrous differentiation is normal, viz. from the root of the fifth nerve, through the ciliary ganglion, to the floor of the mid-brain. I commend this observation on the development of the third nerve to the physiologist, with a view to a renewed investigation of its functions. It is rendered the more interesting by the fact that in Lepidosiren it is commonly stated that the area of the third nerve is supplied by the ophthalmic branch of the fifth, the third nerve being absent.[1]

I have already, in my 'Notes on Elasmobranch Development,' stated my reasons for believing that the views put forward by Hensen as to the origin of nerves were nearer the truth than those of any other zoologist. I have, in this paper, shown not only that the network required does exist, but also how it arises, and how it gives rise to the rudiments of the peripheral nerve-fibres. Minot, in his 'Human Embryology,' p. 624, says that Hensen's theory of the origin of nerves "cannot be adopted because the outgrowths of the nerve-fibres have been observed; moreover, Altmann has pointed out that the fibres seen in the embryonic mesoderm are really processes of the mesoderm cells, and, as shown in the excellent fig. 2 of his plate, are quite distinct both from the ectoderm and endoderm." (The italics are mine.) This passage is, according to my work, full of errors; for I maintain, as the result of long and careful observation, extending over many years, that the outgrowth of nerve-fibres from cells in the ganglia and medullary wall not only has not, but cannot

[1] This statement rests on Hyrtl's work. It must, however, be remembered that his specimen was confessedly rotten in its nervous tissues, and by the fact that v. Wijhe ('Nied. Arch. f. Zoologie,' Bd. v, 1882) has found the third nerve in Ceratodus. Parker does not deal with the brain and nerves in his memoir on Protopterus.

be observed; that the fibres in the embryonic mesoderm are not processes of mesoderm cells (as they are always figured), which have no existence, but are parts of the reticulum which has always existed from before cleavage onwards, connecting together the various parts of the developing ovum, and that this reticulum is not separate from ectoderm and endoderm, but freely continuous with both, they being but parts of it. The almost universal practice of drawing this reticulum as composed of separate branched cells is a most remarkable instance of the manner in which a theory can blind men's eyes to the most obvious facts.

Before concluding this general account of my work, I may mention one or two other points of general interest which I have noticed. Firstly, I may mention that in Scyllium there are a number of anterior roots next the head, varying in number from three to five, according to the age of the embryo, without posterior roots. They no doubt give rise, as has been suggested by others, to the so-called anterior roots of the vagus. Secondly, Balfour was quite correct in the account he gave of the origin of the sympathetic ganglia in Elasmobranchs.[1] The ganglia arise as swellings on the posterior roots of the spinal nerves, and soon become removed from the latter, so as to form isolated masses connected with the spinal nerves by a cord. These masses eventually become united longitudinally into a chain. I may add to Balfour's account this fact, viz. that no sympathetic ganglia are found within the area of extension of the vagus ganglion. Or, if I am not correct in applying the term "vagus ganglion" to the posterior part of the vagus—the part which lies dorsal to the gill-slits and gives off the branchial nerves, it would be better to say that sympathetic ganglia are not found in the region of the branchial slits, but begin immediately behind these structures. Thus, in an embryo of 22 mm. the vagus ganglion and branchial

[1] I have not examined mammals on this point, but I think Paterson's memoir ('Phil. Trans.,' 181) does not carry conviction. On the contrary, there is, I think, in it internal evidence which inclines me to the view that he has not got to the bottom of the matter.

region of the fore-gut ends at the level of the fifth anterior root, and the first posterior root and the first sympathetic ganglion occur at the level of the sixth anterior root. In older embryos, in which the branchial region extends much further back and overlaps a number of fully-formed spinal nerves, the original sympathetic ganglia which were formed in connection with the ganglia of these spinal nerves thus overlapped are found to have disappeared. The first sympathetic ganglion appears always to be just behind the branchial region, as in the adult, and sympathetic ganglia are formed in Scyllium in connection with nerves which are without a posterior root.

Gaskell reproaches v. Wijhe with not knowing the true meaning of a sympathetic ganglion, and one is tempted to ask, does Gaskell himself know much more about it, or throw any light upon the question? He says ('Journal of Physiology,' vol. x, p. 162) that a sympathetic ganglion is the ganglion of the anterior root of a spinal nerve which has travelled to a variable distance from the central nervous system. As Dohrn (seventeenth study, 'Naples Mit.,' Bd. x) very properly insists, this view is at variance with the known developmental history of the ganglion—which I am able to confirm so far as its nuclei are concerned, and with the reservations necessitated by the views set forth in this paper—and I am now able to state that it is at variance with the fact that sympathetic ganglia are entirely absent from those spinal nerves in which the posterior root fails to reach its full development. In fact, one may say of these ganglia that they are always absent when the posterior roots are not developed.

With regard to the fate of the neural crest described in this paper, I should mention that I strongly hinted that it gave rise to nuclei which entered the reticulum in my 'Notes on Elasmobranch Development,' p. 581, published in 1892; and that Goronowitsch arrived independently at the conclusion that it broke up into mesenchyme in the bird, and published his results at some length in 1893 ('Morph. Jahrbuch,' Bd. xx); but Goronowitsch failed to recognise the reticulum, and he was unable to appreciate the full significance of the facts he described in their bearing on the question of the origin of nerves. Platt approximated to the truth with regard to the third nerve in her account of it as growing from the ciliary ganglion to the brain, but retained the error of her predecessors in regarding it as a cellular object, and not as a differentiation of the reticulum.

Minot has a characteristic comment on Platt's statement. He says ('Human Embryology,' p. 639), "This view rests probably on erroneous interpretation of observation, for it cannot be admitted that a motor nerve is formed by ganglionic fibres"! (The italics are mine, as is also the note of admiration.)