The Role of Medullary Cells in the Formation of the Ventral Roots of Spinal Nerves

The Rôle of Medullary Cells in the Formation of the Ventral Roots of Spinal Nerves.

by

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THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

Roscoe Conkling Main,

ENTITLED The Role of Medullary Cells in the Formation of the Ventral Roots of Spinal Nerves.

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE DEGREE OF Bachelor of Arts.

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The Rôle of Medullary Cells in the Formation of the Ventral Roots of Spinal Nerves.

I. Introduction.

In May, 1905, Dr. F. W. Carpenter called my attention to the fact that there was variation in the opinions of embryologists regarding the origin of the sympathetic ganglia of vertebrates, and suggested that this would be a good field for thesis investigation. The original purpose was to determine whether the results obtained by physiologists in experiments upon the sensory and motor functions of the sympathetic ganglia are what may be expected when we consider the source from which the cells composing these ganglia come. Unfortunately the task proved too large for the time to be devoted to it, and the question became primarily one of the migration of cellular elements from the ventral portion of the neural tube into the ventral roots of the spinal nerves. The fate of these migrant cells was also considered. The questions pertaining

to the histogenesis of nerves in general are important because of their bearing on the problem of degeneration and regeneration of the same structures.

Two types of vertebrates, the chick and the pig, were chosen for the work. I am indebted to Mr. R.T. Roney for the use of some very valuable pig embryo material, and to Dr. Carpenter for references to literature, for numerous suggestions and for his very close supervision of the entire work.

2. Observations.

A. Material and Methods.

The materials used were some pig embryos, which were on hand in the laboratory, and chick embryos, which were obtained by incubating hens' eggs found upon the market.

Incubations were made varying from 60 to 120 hours, and it was found that the stages of development best adapted to the purposes of this study were those resulting from about 96 hours' incubation. Serial sections were made in different planes, but the drawings are all from cross sections, as these showed all that could be seen in sections made in any other plane.

The stains used were borax carmine, picro-haematoxylin, Dulafield's haematoxylin, Heidenhain's iron haematoxylin, eosin and von Rath's fluid. The methods found most satisfactory for this study were double stains of Heidenhain's iron haematoxylin and eosin and Dulafield's haematoxylin and eosin.

B. Facts Observed.

At the time of closure of the neural tube its walls are composed of ectodermic epithelial cells. These germinative cells (Keimzellen, His), undergo rapid division, giving rise to indifferent cells. Indifferent cells in the neural tube were first described by Schaper ('97). These cells migrate from a position near the lumen of the tube, where proliferation takes place, toward the periphery of the tube, where at least part of them differentiate into neuroblasts and spongioblasts. On this point practically all the later embryologists are agreed.

The motor roots of the spinal nerves develop in the various segments from about the fourth myotome, caudad and cephalad, either before (Harrison '01) or after (Balfour '75) the appearance of the corresponding dorsal roots. The chief constituents of a differentiated ventral root are the midulus of ganglion-cells in the neural tube, the nerve fibres, (consisting of neuraxones, Schwann's sheaths, and medullary

substance) and the epi- and peri- neurium of connective tissue.

In chick embryos which have been incubated 94 hours, one will find in portions of the neural tube in the region of the middle somites cells which lie near the origin of the future ventral roots of spinal nerves, and which have descended from the indifferent cells.

Pl. 6, Fig. 14 (chick) shows some of these cells (n. bl.) with processes which have pierced the external limiting membrane of the neural tube and extend out into the mesenchyme. The growth of the processes takes place very rapidly. These cells, now called neuroblasts, together with others still in the indifferent condition, form at the ventro-lateral angle of the tube, compact clusters, the niduli (Pl. 1 Fig. 2 and Pl. 3 Fig. 9., nid l. [Fig]) which correspond to the mesodermic somites.

The process of a neuroblast is compact near the cell body from which it arises, but soon breaks up into fibrils which cannot be traced far. This

condition has been described for mammals by Bardeen (03) who thinks that this splitting into fibrils is caused by a migration of cells into the substance of the axis cylinder process.

Pl. 1, Fig. 3, (pig), Pl. 2, Fig. 5, (chick), Pl. 4, Fig. 11, (pig), and Pl. 5 Fig 12 (chick) (cl. comit.) show cells lying along the nerve strands. To such cells the name "accompanying cells" will hereafter be applied. Each consists of little more than its nucleus, the amount of cytoplasm being exceedingly small. The nuclei of these accompanying cells resemble closely in form, size, and staining qualities, the nuclei of the indifferent cells in the midulus.

Pl. 1, Figs. 1 & 2, Pl. 3, Fig. 9, (pig) and Pl. 7, Fig. 17, (chick) (cl.) show several indifferent cells of the midulus near and a few actually in contact with the external limiting membrane; while every figure, but one, of those drawn shows these indifferent cells lying in gaps in the external limiting membrane through which the nerve

strands extend in some instances.

In Pl. 2, Figs. 4, 6, & 7, (chick) there are no nerve fibres, but there are cells outside the tube which are very like the indifferent cells of the nidulus, and are easily distinguishable from the surrounding mesenchyme cells. These figures are taken from regions in which nerve fibres have not yet developed. Pl. 2, Fig. 7, shows that this cluster of cells outside has a tendency to remain in contact with the tube when the mesenchyme has been accidently broken away, although there are as yet, in the cluster, none of the cell processes from the neuroblasts within the neural tube.

Such conditions as these described above are not very wide in extent. If sections be taken a few somites caudad or cephalad, there will be seen in the first case nothing to suggest the presence of fibres or accompanying cells, and in the second case, while many fibres are present, only a few accompanying cells can be made out. None of these lie against or near the external limiting

membrane. If the incubation period be a few hours too long or too short, these conditions will not be met with.

Pl. 3, Fig. 9, and Pl. 8, Fig. 19, (pig) show some accompanying cells (b) like those in the nidulus, and others (g) which resemble those of the nidulus in everything but shape. In this respect they are quite different, being much elongated with their long axes parallel to the direction of the fibres. These cells lie both along the edges of the bundle of fibres (Pl. 3, Fig. 9,) and mingled with the fibres themselves (Pl. 8, Fig. 19, g). They lie at all points from the nidulus inside to a region well out on the nerve.

There is uniform gradation in the shape of the nuclei from the round ones (the indifferent cells) inside the tube to the much elongated ones lying among the nerve fibres (Pl. 4, Fig. 11, pig cl. med. mig.)

Pl. 4, Fig. 10, (pig) and Pl. 8, Fig. 18, (pig), (a) show distinct breaches in the external limiting membrane where the nerve fibres make their exits from

the neural tube, These gaps are large enough to permit cells or even clusters of cells to pass through them. They are not filled up with fibres.

Many instances were noted of round accompanying cells in various stages of mitotic division. (Pl. 2, Figs. 4 & 5, and Pl. 3, Fig. 13, [chick] cl. mit.)

From these observations the following conclusions have been drawn.

1. Medullary cells migrate out from the neural tube into the mesenchyme at those points where the ventral roots of spinal nerves are to develop.

2. In the chick this migration take place before as well as after the cell processes from the neuroblasts inside have pierced the external limiting membrane.

3. These migratory cells are of the indifferent type, that is they are like the cells which form neuroblasts and spongioblasts in the neural tube, and therefore have the same origin as those cells which send out axis cylinder processes, and those which

form neuroglia.

4. Migration takes place quickly, and, at any one stage of development, in a limited region of the neural tube.

5. As the indifferent medullary cells pass out into the nerve root, the nuclei of part of them become much elongated. This change probably does not result from compression in passing through the breach in the external limiting membrane.

6. Broad breaches are made in the external limiting membrane by the exit of cells, and these are not quickly closed again but remain open for a time.

7. Mitotic division is of frequent occurrence among those indifferent medullary cells lying along the nerve. These conclusions will be discussed in the order given.

3. Historical Review and Discussion

1. Medullary cells migrate out from the neural tube into the mesenchyme at those points where the ventral roots of spinal nerves are to develop.

The old question of the presence of cellular elements within embryonic ventral nerves has long since been settled, and His has been forced to admit (though not very gracefully, according to Beard '89) that cells do exist among the fibres. The origin of these cells is, however, still in doubt. His ('89) after admitting their presence claimed that they were derived from a specialized kind of mesoderm cells which lie between the neural tube and the undifferentiated mesenchyme, his whole idea being embodied in what he calls the Zwischenstrang Theorie. His is supported in the case of Selachii by Kölliker ('89) and von Lenhossék ('97)

The theory of the escape of medullary elements from the spinal cord was first advanced by Balfour ('75), and has been supported by

Beard ('89), who has ridiculed the "Zwischenstrang Theorie" from the beginning. The work of Lohrn ('88, '91) upon Selachii contradicts that of Kölliker ('89) and von Lenhossék ('90) upon this same form.

After a long and spirited controversy with His, Lohrn ('91a) finally admitted that His was probably right in case of spinal nerves but still maintained that migration took place in case of the oculomotor nerve.

The migration of medullary cells out into the ventral roots of spinal nerves has also been noted by Herrick ('93) for amphibians, reptiles (and mammals), by Harrison ('01) for Salmo salar, by Neal ('03) for Squalus acanthus, and by Bardeen ('03) for mammals.

Thus while observers agree that embryonic nerves contain cells, the source of these cells is in dispute.

The considerations which have led me to believe that migration does take place in the case of ventral spinal nerves are three.

First; One may find in the central root, cells which are like the undifferent cells of the neural tube. With suitable staining methods it is not very hard to distinguish between the medullary cells and the mesenchyme cells. The difference lies not only in the size and shape of the cells but also in an indescribable staining property which one learns to recognize after a little practice.

Second. Numerous sections have been found where cells possessing the characteristics of medullary cells are distributed along the nerve path from the midbrus inside to the region outside, where large numbers of these cells lie. In some instances this distribution was quite uniform, the cells lying in contact and forming a continuous bridge across the marginal velum and the external limiting membrane, and appearing to be in the very process of passing out.

Third, The first medullary cells to appear outside, either among the fibres or before the fibres have been

seen, are found at the base of the nerve where it joins the external limiting membrane.

2. In the chick this migration takes place before as well as after the cell processes from the neuroblasts inside have pierced the external limiting membrane.

As regards the time of migration of cells from the neural tube into the mesenchyme, relative to the time of appearance of nerve fibres, it may be said that this migration was noted before the appearance of fibres in only a few instances. From such data one might conclude that nearly all migration take place after the nerve fibres have grown out, and that only in very rare instances do the cells pass out first. Such a conclusion I believe however is unwarranted. One is not so likely to recognize medullary cells when a few of them lie loosely aggregated in the mesenchyme as one is when they form clusters of consider-

able size and are accompanied by fibres. The fibres themselves attract the attention and occasion a comparison of the cells among them with the medullary cells and with the mesenchyme cells. For this reason then, I believe the identity of the cells which first migrate out is overlooked. My attention was first called to this matter by a peculiar accident in the preparation of a series of a chick embryo. In a region of the neural tube which did not yet show evidences of ventral nerves, one of the sections was injured in such a way as to brush away the mesenchyme cells from one side of the neural tube. At the ventro-lateral angle of the tube, a few cells remained adhering (Pl. 2 Fig. 7). These were identified as medullary cells, and examination of corresponding regions in adjacent sections showed similar cells which could be distinguished from the mesenchyme. The reason why these cells should thus adhere to the neural

tube is uncertain. There seemed to be a sort of delicate reticulum continuous with that in the tube, but the absence of neuraxones in this region is certain.

Carpenter ('06) saw migrant medullary cells in the root of the oculo-motor nerve before the appearance of fibres there. This condition has been denied by Neal ('03) who says "In embryonic amniotes ventral nerves in their early stages are purely fibrillar structures to which cells are secondarily added. The presence of medullary cells in the embryonic ventral nerves gives rise to the 'cellular structure' in these early stages of development and thus obscures, in preparations made by the conventional embryological methods, their fibrillar structure. Suitable methods show that neuraxones are present in the earliest as in all later stages." Balfour ('75) also claims that from the very first, the rudiments of the anterior roots have a somewhat fibrous appearance. Harrison ('01) says, "Not until the motor root is strongly developed do

certain cells pass through here from the spinal cord"; and he gives a detailed account of the manner in which this takes place.

3. These migratory cells are of the indifferent type, that is they are like the cells which form neuroblasts and spongioblasts in the neural tube, and therefore have the same origin as those cells which send out axis cylinder processes and those which form neuroglia. This resemblance is quite easily recognized and is due to the size, shape, and peculiar staining qualities of the nuclei of indifferent cells.

In speaking of the ventral roots of spinal nerves in Elasmobranchii, Beard ('89) says, "The fibrous nature of the nerve is very obvious, but one also observes a vast number of nuclei within the nerve which one cannot regard, from their form and characters, as otherwise than offsprings of the nuclei which have passed at earlier stages, and even still continue to do so from the anterior cornu of the cord."

His has repeatedly denied this assertion, and Harrison (.31) agrees with His that the first cells arriving in the neighborhood of the origin of the nerve and lodging themselves in the young nerve fibres are mesenchyme cells. He says it is this compressed plug of sclerotome mesenchyme cells in each segment which led Hoffmann in his addition to the well-known work of Balfour, to derive the motor spinal nerves from a cellular outgrowth of the neural tube. It is interesting to note that Hoffmann considered them medullary cells.

4. Migration takes place quickly and, at any one stage of development, in a limited region of the neural tube.

The cause of the beginning of this migration may be a definite power of locomotion possessed by the cells as Dohrn ('91) declares, or it may be due to the rapid division and crowding of the cells of the neural tube. The most rapid multiplication takes place in the epithelial cells about the lumen of the

tube. While the products of this mitosis are migrating peripherally to form the nidulus and thence out into the ventral nerve, other changes are taking place. The neuroblasts are developing dendrites, and neuroglia cells with their processes begin to appear. According to Ris ('89) the formation of this network is the cause of the cessation of migration inside the tube. Other observers, as Neal ('03), have noted a correlation of the appearance of these two phenomena but doubt the causal effect of the one upon the other.

As regards the cessation of migration from the nidulus into the nerve root, it is quite probable that when the nidulus ceases to increase so rapidly in size, the resistance offered by the thickening external fibre tracts and the external limiting membrane is sufficient to prohibit the passage of cells.

5. As the indifferent medullary cells pass out into the nerve root, the nuclei of part of them become much elongated. This change probably does not result from compression in passing through

the breach in the external limiting membrane.

Demonstrations of this phenomenon are not uncommon. In Plate 4, Figure 11, it is very well shown. It has usually been ascribed to the resistance which the cells meet in passing through the orifice in the external limiting membrane. Harrison (,01) says the breach in the outer limiting membrane is so narrow, that the nucleus of the migrant cell cannot pass without becoming compressed, and accordingly one finds such nuclei quite remarkably formed.

On the other hand, this change does not appear to me to be due to pressure. In the first place the orifices in the external limiting membrane are often large enough to allow several cells to pass through, and yet a single nucleus in this region will sometimes become elongated. (Pl. 3, Fig. 9, cl. med. mig.). Moreover this change is gradual, and not sudden as it would ~~be~~ if the cell were passing through a small

hole. Then, too, some of the migrating cells do not change their shape but remain nearly round as far as one can trace them.

6. Broad breaches are made in the external limiting membrane by the exit of cells, and these are not quickly closed again but remain open for a time.

This point has just been discussed and I need only refer to Pl. 3, Fig. 9, a, and Pl. 4, Fig. 10, a, to recall the fact.

7. Mitotic division is of frequent occurrence among the indifferent medullary cells lying along the nerve.

Neal (03) saw cell division of such migrant cells, but thought that multiplication was not very rapid in them. In my preparations I have seen relatively abundant instances of migrant medullary cells in different stages of mitosis.

General Considerations; — Much of the work which has been done upon the histogenesis of spinal nerves has been occasioned by attempts to determine the morphology of the eye-muscle nerves, which have so often been compared with them. This work has resulted in the formation of two opposing theories which have been combating each other for a quarter of a century, ever since the work of Remak, Schwann and Balfour ('75').

The oldest theory is that neuraxons are formed by the fusion and differentiation of the axial protoplasm of chains of spindle shaped cells. This has had the support of Balfour ('75'), Beard, Dohrn ('91'), Gegenbaur, and Herrick ('93')

According to the second theory of neuraxon histogenesis, the neuraxon is an extraordinarily long process of a ganglion cell, and every nerve fibre from beginning to end is to be considered a product of a single cell. His, von Lenhossék and Neal are advocates of this theory. The "process theory" seems to have had the more support recently,

and is regarded by Neal (:03) as settled for Amniota, although he and Beard both claim it is by no means settled for Selachii.

My observations have led me to believe that the cellular elements which migrate from the ventral part of the neural tube take some part in the formation of neurons of the motor chain. Potentially they are very important, and a priori reasoning would warrant great expectations as to their destiny. They resemble the indifferent cells which remain in the tube and develop, some into spongioblasts and some into neuroblasts. From their ancestry then, we may expect that these cells are destined to form either supporting cells, (Schwann's sheath cells) or that by migration and multiplication they form nerve cells from which develop the motor neurons in all peripheral ganglia including the chain of sympathetic ganglia.

Harrison (:01) says, "It seems apparent to me that they represent motor elements of the sympathetic which wander along the visceral branch of the spinal nerve in order to take part in the

formation of the peripheral ganglia. A large number of the sympathetic ganglion cells are certainly motor, and it is only reasonable that these are in genetic relation to other motor cells."

This idea has been supported by Beard ('89) who believes that they wander in early stages down to form the end plates of muscles. Thompsen ('87) believes that degenerate ganglion cells are to be found in the roots of the third and fourth cranial nerves in man, and Carpenter ('06) suggests that these may have had their origin as indifferent cells migrating out from the mid-brain into the roots of these nerves in an early embryonic stage. However, the most generally accepted view of this is that of Rhodi ('86), Otis Jun. and Romberg ('90) and Ovis, Jun. ('91), who agree that the cells composing the sympathetic system are derived entirely from spinal ganglia.

It is doubtless true that the Golgi method employed by von Lenhossék will show motor fibres growing from neuroblasts inside the tube, but this is no

proof that the cell chain mode of nerve development may not also occur. It is hard to understand how a nerve fibre several meters long could be conducted from the ventral root by some mysterious motive to terminations in glands and muscles, and from the dorsal root to sense organs.

Obrrick ('93) has made this pertanent remark, "So long as the dogma of nervous conduction by continuity prevailed, this (referring to the process theory) seemed to physiologists a natural if not a necessary postulate. When, however, we discovered that within the neuraxis the tracts of nervous conduction are frequently composed of series of continuous neurons, the necessity, at least, of the primitive continuity of a nerve fibre no longer maintained;" and in another place, "Study of the growth of nerves in embryos of serpents, amphibians and mammals has convinced the writer that, in some cases at least, the growth is by moniliform adhesion of neurons. The nerve grows by intrinsic proliferation due to karyokinetic multiplication of the

neurons. Such proliferation may take place anywhere in the nerve. The nuclei of the neurons at first lie in the fibre thus produced and only subsequently are 'side-tracked' and are connected with the sheath. They probably retain a vital connection with the fibre. The sheath is to be regarded as a peculiarly modified cell-wall of the neuron." The part played by these nuclei in regeneration is most simply explained as a mere repetition of that part which they originally took in the formation of the nerve.

That the migrating cells participate in the formation of Schwann's sheath seems almost certain when we see how some of them become elongated and take up positions lying along either side of the nerve tract. They thus begin to resemble Schwann's sheath cells in form and position. Moreover, the great number of migrant cells and the common occurrence of mitosis in them warrants the assumption that enough of them are produced to form all the Schwann's sheath cells.

Neal ('03) believes that the migrant medullary cells form only a small proportion of the neurilemma sheaths and take no part whatever in the formation of the neuraxons or ganglia of ventral nerves. Most other observers (as Bardeen '03, for mammals), who admit the migration of medullary cells, deny the participation of these in the formation of nerve sheaths, which have usually been considered as derived from the mesenchyme. Dohrn ('91) does not attempt to say what rôle the cells play in further development after they have migrated out along the nerve.

4 Summary

Whatever may be the fate of cells which leave the neural tube by way of the ventral roots of spinal nerves, the fact that they do so migrate seems to me to be established. I have endeavored to show (1) that such migrant cells are capable of locomotion, and (2) that they do not require the growing fibres to drag them from the tube, (3) that some of them can change their shape without being compressed by surrounding tissues, and (4) that much is to be expected of them if they are potentially equal to the indifferent cells which remain in the tube, and with which they have a common origin.

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6. Explanation of Plates.

All the figures are made from cross sections of chick or pig embryos and with the aid of the camera lucida. In three instances (Plate I, Figs. 1, 2, & 3.) the magnification was that obtained by a Bausch and Lomb $\frac{1}{4}$ objective. All the other drawings are made from a magnification of about 900 diameters.

Abbreviations.

cl. Indifferent cell.
cl. comit. "Accompanying cell"
cl. gn. Ganglion cell.
cl. med. mig. Migrant medullary cell.
mb. lim. ex. External limiting membrane.
ms'ench. Mesenchyme.
n'ax. Neuraxon.
n.b'l. Neuroblast.
n'l. Nucleus.
nid'l. Nidulus
cl. mit. Indifferent cells in stages of mitosis.

Plate 1.

Fig. 1. Cross section through region of ventral root of developing spinal nerve of pig embryo eleven m.m. long.

Fig. 2. Same as Fig. 1.

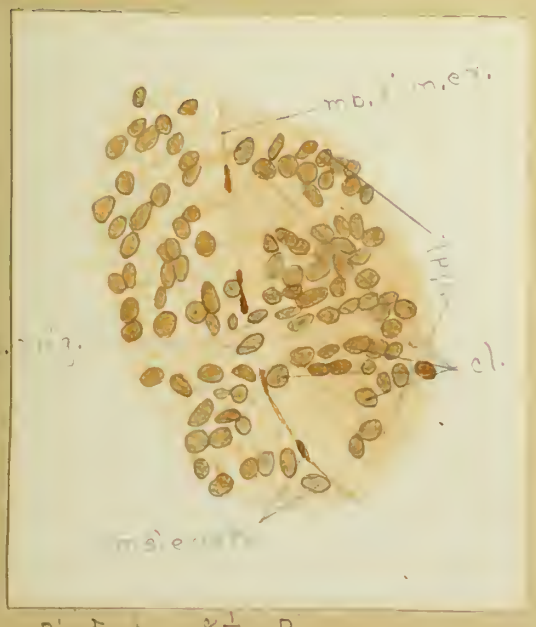
Fig. 3. Section through spinal ganglion and ventral root of spinal nerve in pig embryo 11 m.m. long.

sp. gn. .. spinal ganglion.

Plate 1.

Pig Embr. 9 2/3 R

Figure 1.



Pig Embr. 8 1/1 R

Figure 2.

Figure 3.

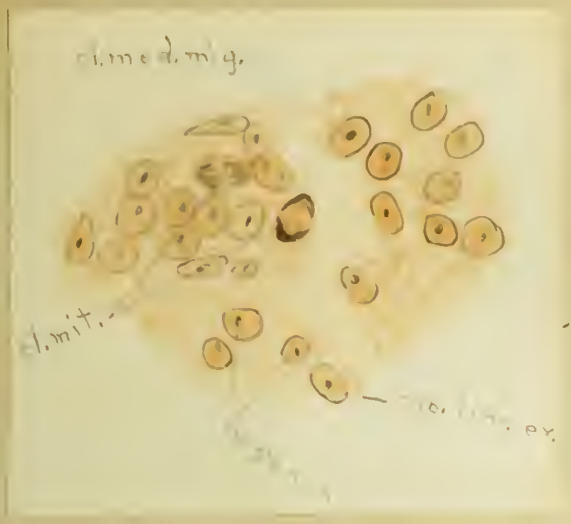
Plate 2.

Fig. 4, Section through region of future ventral root of spinal nerve of chick embryo of 95 hours' incubation. This section shows cells which have migrated out before nerve fibres have been found in the root.

Fig. 5; Section through ventral root of spinal nerve in 96 hours' embryo (chick).

Figs. 6 & 7. Same as Fig 4. Fig 7 shows cluster of migrant medullary cells adhering to the neural tube when the surrounding mesenchyme has been broken away.

Plate 2.



4: 10 $\frac{1}{4}$ M.

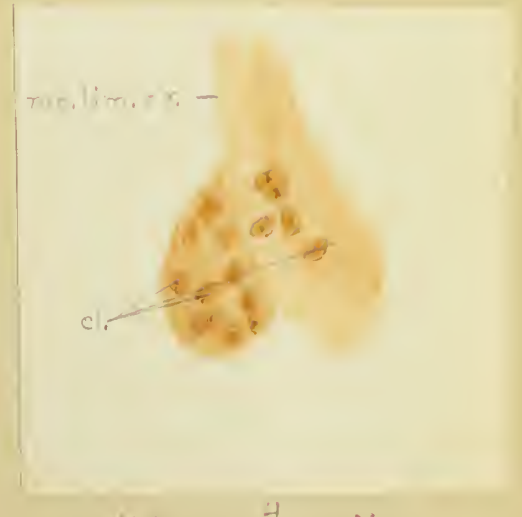
Figure 4

Chick 5'8 in 4 $\frac{2}{3}$

Figure 5

4a 6 $\frac{1}{8}$ M

Figure 6



4 4 $\frac{4}{2}$ M

Figure 7

Plate 3.

Fig. 8. Section through ventral root of spinal nerve of pig embryo 11 mm. long.

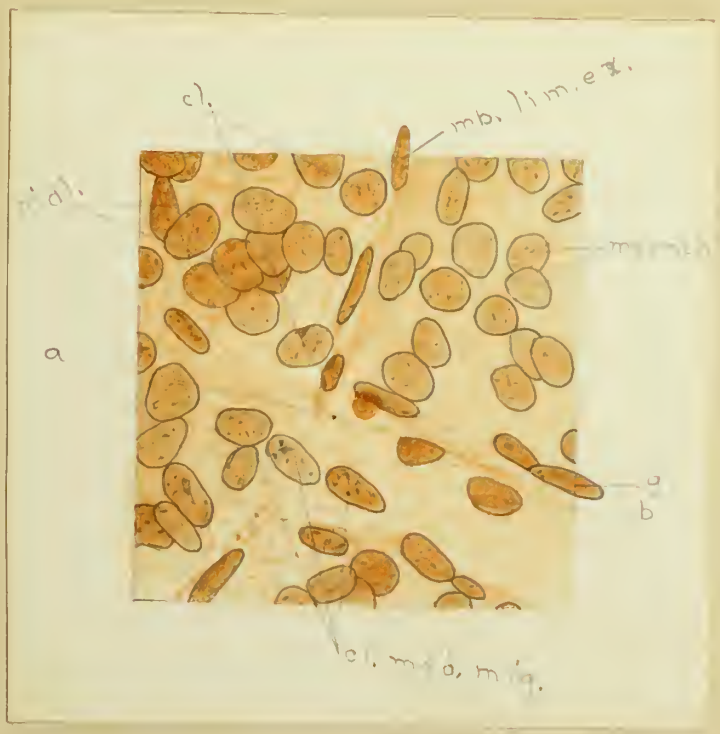
Fig. 9. Section through ventral root of spinal nerves of pig embryo 11 mm. long.

a. breach left in the external limiting membrane by the cells which have passed through it.

b. indifferent cell remaining surrounded by nerve fibres.

Pig Embr. 7 $\frac{5}{6}$?

Figure 8.



Pig Embr. 9 $\frac{5}{7}$?

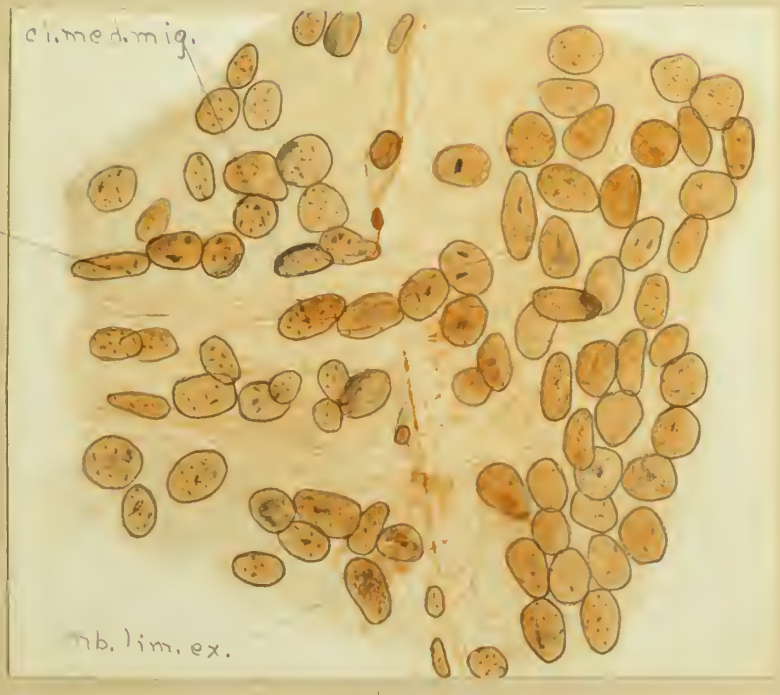
Figure 9.

Plate 4

Figs. 10 & 11. Sections through the ventral roots of developing spinal nerves in pig embryo 11 m.m. long.

Pig Embr. $\frac{2}{2}$

Figure 10.



Pig Embr $\frac{1}{1}$

Figure 11.

Plate 5.

Fig. 12. This section through the ventral root shows how the migrant medullary cells form a cluster in the fibre strand just outside the external limiting membrane

corp. = blood corpuscles.

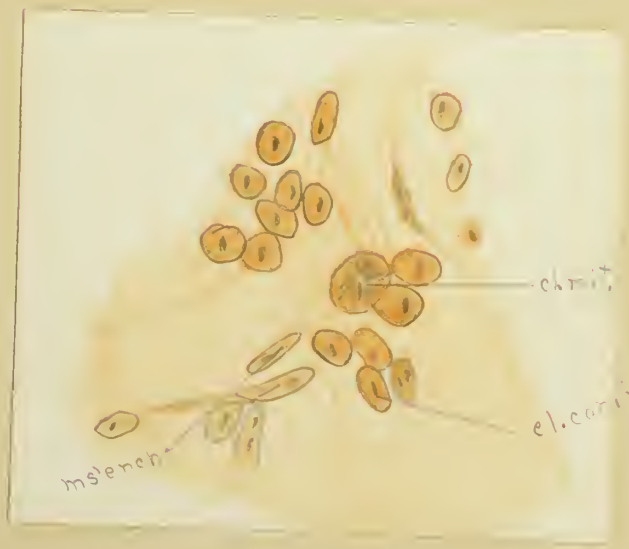
(chick embryo, 96 hr. incubation)

Fig. 13. Section through ventral root of spinal nerve in 96 hr. chick embryo.

cl. mit. = indifferent cell in mitotic division as it migrates across the fibre tract.

chick 5 7 a 4 1/2

Figure 12.



chick 5'8 a 4 1/6

Figure 13.

Plate 6.

Figs. 14 & 15. Sections through the ventral roots of spinal nerves of chick embryo (96 hrs. incubation)

Plate 6.

2 12 621 Lab.

Figure 14.

x 12 6/6 Lab

Figure 15

Plate 7.

Figs. 16 & 17. Sections through ventral roots of spinal nerves in chick embryos (96 hrs. incubation)

Figure 16.

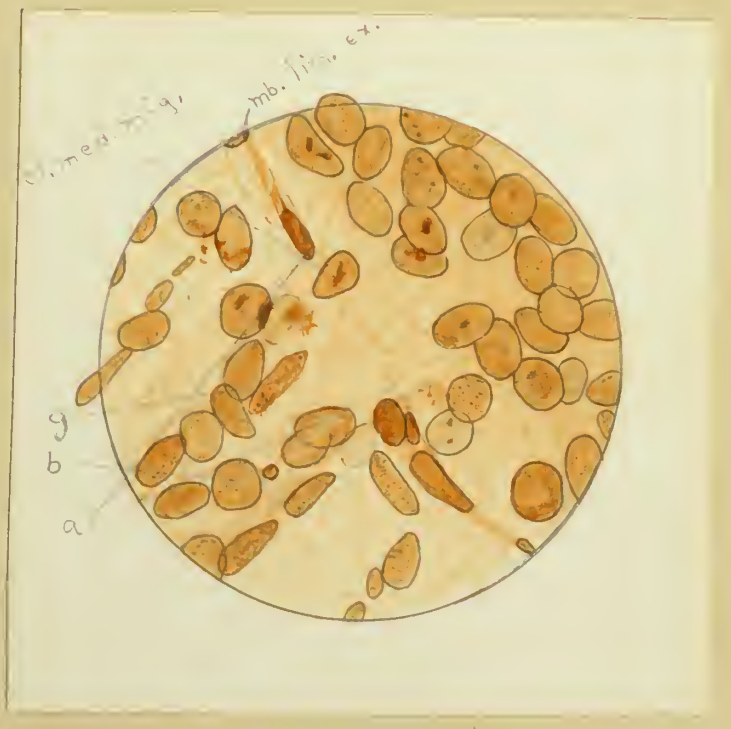
Figure 17.

Plate 8.

Figs. 18 & 19. Sections through the ventral roots of spinal nerves in pig embryo 11 m.m. long.
a = breach in external limiting membrane by the cells and fibres.

Pig Embr. 7 1/3 R

Figure 18.



Pig Embr 10 1/3 R

Figure 19.